

Final September 2008

VOLUME 9A

of The Rules Governing Medicinal Products in the European Union

– Guidelines on Pharmacovigilance for Medicinal Products for Human Use –

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INTRODUCTION

1. Legal Basis and Structure of Volume 9A (Human Pharmacovigilance)

Pharmacovigilance has been defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. Article 106 of Directive 2001/83/EC specifically requires the European Commission in consultation with the European Medicines Agency (EMA – “the Agency”), Member States and interested parties to draw up guidance on the collection, verification and presentation of adverse reaction reports in order to facilitate the exchange of information about human pharmacovigilance within the Community. Similarly, Article 26 of Regulation (EC) No 726/2004 includes a requirement for the Commission, in consultation with the Agency, Member States and interested parties to draw up a guide.

This guidance is required to include technical requirements for the electronic exchange of pharmacovigilance information in accordance with internationally agreed formats. In addition, the European Commission is also required to publish a reference to an internationally agreed medical terminology.

This Volume 9A has therefore been prepared by the European Commission in close consultation with the Agency, Member States and interested parties and is specifically related to human pharmacovigilance. It brings together general guidance on the requirements, procedures, roles and activities in this field, for both Marketing Authorisation Holders and Competent Authorities of medicinal products for human use; it incorporates international agreements reached within the framework of the International Conference on Harmonisation (ICH).

Volume 9A is presented in four parts:

Part I deals with Guidelines for Marketing Authorisation Holders;

Part II deals with Guidelines for Competent Authorities and the Agency;

Part III provides the Guidelines for the electronic exchange of pharmacovigilance in the EU; and

Part IV provides Guidelines on pharmacovigilance communication.

It should be noted, as with all guidance documents in rapidly evolving technical areas, that this guidance is intended to be regularly reviewed and updated, with publication on the European Commission’s website: <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>. This is particularly true of the detailed reporting requirements for individual member states and it should be noted that Annex 6 “Distribution Requirements and Address Lists for Data Submission” is currently under review by the Member States and is therefore likely to be updated in the near future.

2. Legal Framework for Pharmacovigilance

The legal framework for pharmacovigilance of medicinal products for human use in the European Union (EU) is given in Regulation (EC) No 726/2004¹ and Directive 2001/83/EC² on the Community code relating to medicinal products for human use, as last amended by Directive 2004/24/EC³ and by Directive 2004/27/EC⁴ (hereafter referred to simply as Directive 2001/83/EC). It should be noted that although Chapter 3 of Regulation (EC) No 726/2004 and Title IX of Directive 2001/83/EC contain the majority of pharmacovigilance provisions in the legislation, other measures directly relevant to the conduct of pharmacovigilance are found in other Chapters and Titles of those legislative texts.

The requirements explained in these guidelines are based on the ICH guidelines, where these exist, but may be further specified or contain additional requests in line with the legislation of the EU.

The pharmacovigilance obligations apply to all medicinal products authorised in the EU, including those authorised before 1 January 1995 and whatever procedure was used for their authorisation. For example, the obligations are the same for products authorised under Articles 10(1), 10(4), 10a, 13 to 16 and 16a to 16i of Directive 2001/83/EC ('generic', 'similar biological medicinal product', 'well-established use', 'homeopathic'⁵ and 'herbal' products respectively) as for products authorised under Article 6 of the same Directive. However, it should be noted that, pursuant to Article 16(3) of Directive 2001/83/EC, the pharmacovigilance title of that Directive does not apply to homeopathic medicinal products which are the subject of the simplified registration procedure (Article 14 (1) of Directive 2001/83/EC).

The legislation listed above describes the respective obligations of the Marketing Authorisation Holder and of the Competent Authorities to set up a system for pharmacovigilance in order to collect, collate and evaluate information about suspected adverse reactions. All relevant information should be shared between the Competent Authorities and the Marketing Authorisation Holder, in order to allow all parties involved in pharmacovigilance activities to assume their obligations and responsibilities. This requires an intensive exchange of information between the Marketing Authorisation Holder, the Competent Authorities of Member States and the Agency as well as procedures to avoid duplication, maintain confidentiality and ensure the quality of the systems and data.

Iceland, Liechtenstein and Norway have through the Agreement of the European Economic Area (EEA) adopted the complete Community acquis (i.e. the legislation at EU level, guidelines and judgements) on medicinal products, and are consequently parties to the Community procedures. Consequently, the following Guidelines do not only apply with regard to the Marketing Authorisation Holder's obligations towards Competent Authorities in Member States of the EU but also to those towards the States Iceland, Liechtenstein and Norway. Likewise they apply to the Competent Authorities in these States themselves.

The obligations concerned with the monitoring of adverse reactions occurring in clinical trials do not fall within the scope of pharmacovigilance activities, as described in these Guidelines. The legal framework for such obligations is Directive 2001/20/EC on the approximation of the laws, regulations and administrative provision of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use⁶. Part III of Volume 9A deals with technical aspects relating to adverse reaction/event reporting for pre- and post-authorisation phases. Furthermore, the requirements for non-interventional studies are described in Chapter I.7, the

¹ OJ L 136, 30.4.2004, p.1.

² OJ L 331, 28.11.2001, p. 67.

³ OJ L 136, 30.4.2004, p. 85.

⁴ OJ L 136, 30.4.2004, p. 34.

⁵ With the exception of those registered through the special, simplified registration procedure of Article 14(1) of Directive 2001/83/EC.

⁶ OJ L 121 1.5.2001 p.34

inclusion of clinical trials data in Periodic Safety Update Reports is described in Chapter I.6 and the notification of potential changes to the risk-benefit balance in Chapter I.8.

3. The Roles of the Various Parties

3.1 The Marketing Authorisation Holder

The Marketing Authorisation Holder must ensure that it has an appropriate system of pharmacovigilance and risk management in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary (see Part I).

3.2 The Competent Authorities

3.2.1 The Competent Authorities of the Member States

The authorities of the Member States are the Competent Authorities for medicinal products authorised nationally through national procedures, including the mutual recognition and decentralised procedure. The responsibilities for pharmacovigilance rest with the Competent Authorities of all the Member States in which the marketing authorisations are held. In addition the Member States are the supervisory authorities for centrally authorised products (see Chapter II.1).

3.2.2 The European Commission

For medicinal products authorised through the centralised procedure the European Commission is the Competent Authority. The European Commission is responsible for the adoption of Decisions on the basis of Committee for Medicinal Products for Human Use (CHMP) Opinions relating to medicinal products authorised through the centralised procedure and those products subject to the procedure of Articles 32, 33 and 34 of Directive 2001/83/EC. The European Commission also has responsibilities for the overall Community system of pharmacovigilance and for the legal framework (see Chapter II.1).

3.3 The EU Pharmacovigilance System

3.3.1 The Role of Competent Authorities of the Member States for Products Authorised Through National Procedures

In accordance with the legislation, each Member State has established a pharmacovigilance system for the collection and evaluation of information relevant to the risk-benefit balance of medicinal products. The Competent Authority continually monitors the safety profile of the products available on its territory and takes appropriate action where necessary and monitors the compliance of Marketing Authorisation Holders with their obligations with respect to pharmacovigilance. The Competent Authority should ensure that Marketing Authorisation Holders implement, when appropriate, Risk Management Plans to effectively monitor and manage risks associated with the safety of their products. Furthermore the Competent Authority should ensure that pharmacovigilance data are shared between Member States and the Agency via the data-processing network EudraVigilance (see Part II).

3.3.2 The Role of the Competent Authority of the Reference Member State for Products Authorised Through the Mutual Recognition or Decentralised Procedure

The responsibilities of pharmacovigilance rest with the Competent Authorities of all the Member States in which the marketing authorisations are held. For practical reasons, the Member States agree that the Reference Member State will normally take the lead for medicinal products authorised through the mutual recognition or decentralised procedures and responsibility for evaluating and producing Assessment Reports on safety concerns, in accordance with an agreed timetable. The Reference

Member State takes responsibility for the coordination of communication with the Marketing Authorisation Holder on such matters (see Chapter II.3) and for the monitoring of the compliance of the Marketing Authorisation Holder with his obligations with respect to pharmacovigilance. These arrangements do not replace the legal responsibilities of the Marketing Authorisation Holder with respect to individual Competent Authorities.

3.3.3 The Role of the Rapporteur for Products Authorised Through the Centralised Procedure

The Competent Authorities of the Member States are responsible for monitoring centrally authorised medicinal products in their respective territories. However, the pre-authorisation Rapporteur takes the lead in pharmacovigilance, unless otherwise decided by the CHMP. The Rapporteur is responsible for evaluating and producing Assessment Reports on safety concerns related to a centrally authorised product, in accordance with an agreed timetable (see Chapters II.2.A and II.2.B) and for the monitoring of the compliance of the Marketing Authorisation Holder with its obligations with respect to pharmacovigilance.

3.3.4 The Role of the Agency

The role of the secretariat of the European Medicines Agency (EMA – “the Agency”) is one of coordination of the supervision, under practical conditions of use, of medicinal products which have been authorised within the EU and the provision of advice on the measures necessary to ensure their safe and effective use, in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation.

The Agency’s scientific committee, the CHMP, aided by its Pharmacovigilance Working Party (PhVWP), is responsible for evaluating evidence and formulating Opinions on emerging safety concerns with centrally authorised products, based on the Rapporteur’s Assessment Report. The Agency secretariat is responsible for communicating with the Marketing Authorisation Holders of centrally authorised products on such concerns (see Chapter II.2) and for the co-ordination of issues relating to the monitoring of the compliance of the Marketing Authorisation Holder with its pharmacovigilance obligations (see Chapter I.2).

The role of the Agency secretariat is one of co-ordination in the case of referrals made to the CHMP for application of the procedures laid down in Articles 32, 33 and 34 of Directive 2001/83/EC. The CHMP, aided by the PhVWP, is responsible for evaluating evidence and formulating Opinions on matters referred to it (see Chapter II.5).

3.3.5 The Role of the CHMP Pharmacovigilance Working Party

The Mandate (see Appendix II.1.A) of the CHMP Pharmacovigilance Working Party (PhVWP) is to provide advice on the safety of medicinal products and the investigation of adverse reactions, in order to enable effective risk identification, assessment and management, in the pre- and post-authorisation phase (see Chapter I.3), leading to recommendations on harmonised and synchronised action at the request of the Competent Authorities and for centrally authorised products, and for products referred under Article 32, 33 and 34 of Directive 2001/83/EC at the request of the CHMP.

PART I: Guidelines for Marketing Authorisation Holders

1. General Principles

1.1 Legal Basis of the Marketing Authorisation Holder's Obligations for Pharmacovigilance

The legal basis for the Marketing Authorisation Holder's obligations for pharmacovigilance of medicinal products for human use in the EU is given in Regulation (EC) No 726/2004 and Directive 2001/83/EC.

1.2 Roles and Responsibilities of the Marketing Authorisation Holder and the Qualified Person Responsible for Pharmacovigilance

The Marketing Authorisation Holder should ensure that he has an appropriate system of pharmacovigilance in place in order to assume responsibility and liability for his products on the market and to ensure that appropriate action may be taken when necessary. The Marketing Authorisation Holder should therefore ensure that all information relevant to the risk-benefit balance of a medicinal product is reported to the Competent Authorities and the Agency fully and promptly in accordance with the legislation.

When submitting an application for a marketing authorisation, the Applicant, in preparation for the role and responsibilities as Marketing Authorisation Holder, should submit a description of the pharmacovigilance system (Article 8(3)(ia) of Directive 2001/83/EC) and submit proof that the services of a Qualified Person Responsible for Pharmacovigilance, hereafter referred to as the QPPV, are in place (Article 8(3)(n) of Directive 2001/83/EC) (see Chapter I.2).

The Marketing Authorisation Holder should have permanently and continuously at his disposal a QPPV, residing in the EU⁷.

The role of the QPPV is very important, and this Chapter therefore describes the role and responsibilities of the QPPV and also provides guidance for the Marketing Authorisation Holder on how to adequately support the QPPV.

Each company (i.e. Applicant/Marketing Authorisation Holder or group of Marketing Authorisation Holders using a common pharmacovigilance system) should appoint one QPPV responsible for overall pharmacovigilance for all medicinal products for which the company holds marketing authorisations within the EU (see also Chapter I.2).

National regulations in some Member States require a nominated individual in that country who has specific legal obligations in respect of pharmacovigilance at a national level. One such individual may also act as the QPPV for the whole EU. Alternatively, the QPPV for the EU may be a separate person, additional to requirements under the relevant national regulations.

The QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance in order to fulfil the responsibilities and tasks of the post. If the QPPV is not medically qualified, access to a medically qualified person should be available.

The name and 24-hour contact details of the QPPV and back-up procedures to ensure business continuity and continued fulfilment of pharmacovigilance obligations should be notified to the Competent Authorities of the Member States in which marketing authorisations are held or, for centrally authorised products, to the Competent Authorities of all Member States and to the Agency.

⁷ As explained in the Introduction, the EFTA States having signed EEA Agreement adopted the complete Community acquis on medicinal products, and therefore the QPPV may also reside in the EFTA States having signed the EEA Agreement.

1.2.1 The Role and Responsibilities of the Qualified Person Responsible for Pharmacovigilance

The QPPV is responsible for

- establishing and maintaining/managing the Marketing Authorisation Holder's pharmacovigilance system;
- having an overview of the safety profiles and any emerging safety concerns (see Glossary in Annex 1.2 for definition of safety concern) in relation to the medicinal products for which the Marketing Authorisation Holder holds authorisations;
- acting as a single contact point for the Competent Authorities on a 24-hour basis.

It is recognised that this important role of the QPPV may impose extensive tasks on the QPPV, depending on the size and nature of the pharmacovigilance system and the number and type of medicinal products for which the company holds authorisations. The QPPV may therefore delegate specific tasks, under supervision, to appropriately qualified and trained individuals, e.g. acting as safety experts for certain products, provided that the QPPV maintains system oversight and overview of the safety profiles of all products. Such delegation should be documented.

In case of absence, the QPPV should ensure that all responsibilities are undertaken by an adequately qualified person. This person should also reside in the EU (see Footnote 7).

The QPPV should have oversight of the pharmacovigilance system in terms of structure and performance and be in a position to ensure in particular the following system components and processes, either directly or through supervision:

- the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the Marketing Authorisation Holder, and to medical representatives, is collected and collated in order to be accessible at least at one point within the EU;
- the preparation for Competent Authorities of the Member States, where the medicinal product is authorised, of the reports referred to in Article 104 of Directive 2001/83/EC and in case of centrally authorised products the preparation for the Agency and Competent Authorities of the Member States of the reports referred to in Article 24 of Regulation (EC) No 726/2004. Detailed guidance for the preparation of these reports are included in:
 - Chapter I.4 on Individual Case Safety Reports (ICSRs),
 - Chapter I.6 on Periodic Safety Update Reports (PSURs), and
 - Chapter I.7 on reports on company-sponsored post-authorisation safety studies;
- the conduct of continuous overall pharmacovigilance evaluation during the post-authorisation period (see Chapter I.8);
- the ensuring that any request from the Competent Authorities for the provision of additional information necessary for the evaluation of the benefits and the risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned; and
- the provision to the Competent Authorities of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorisation studies and data from sources described in Chapter I.5.

The oversight referred to above should cover the functioning of the Marketing Authorisation Holder's pharmacovigilance system in all relevant aspects, including quality control and assurance procedures, standard operating procedures, database operations, contractual arrangements, compliance data (e.g. in relation to the quality, completeness and timeliness for expedited reporting and submission of Periodic Safety Update Reports), audit reports and training of personnel in relation to pharmacovigilance.

The QPPV should also act as the Marketing Authorisation Holder's contact point for pharmacovigilance inspections or should be made aware by the Marketing Authorisation Holder of any inspection, in order to be available as necessary.

1.2.2 Responsibilities of the Marketing Authorisation Holder in Relation to the Qualified Person Responsible for Pharmacovigilance

The Marketing Authorisation Holder should adequately support the QPPV and ensure that there are appropriate processes, resources, communication mechanisms and access to all sources of relevant information in place for the fulfilment of the QPPV's responsibilities and tasks.

The Marketing Authorisation Holder should ensure that there is full documentation covering all procedures and activities of the QPPV and that mechanisms are in place to ensure that the QPPV may receive or seek all relevant information. The Marketing Authorisation Holder should also implement mechanisms for the QPPV to be kept informed of emerging safety concerns and any other information relating to the evaluation of the risk-benefit balance. This should include information from ongoing or completed clinical trials and other studies the Marketing Authorisation Holder is aware of and which may be relevant to the safety of the medicinal product, as well as information from sources other than the specific Marketing Authorisation Holder, e.g. from those with whom the Marketing Authorisation Holder has contractual arrangements.

The Marketing Authorisation Holder should ensure that the QPPV has sufficient authority

- to implement changes to the Marketing Authorisation Holder's pharmacovigilance system in order to promote, maintain and improve compliance; and
- to provide input into Risk Management Plans (see Chapter I.3) and into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and, as appropriate, communication to Patients and Healthcare Professionals).

The Marketing Authorisation Holder should assess risks with potential impact on the pharmacovigilance system and plan for business contingency, including back-up procedures (e.g. in case of non-availability of personnel, adverse reaction database failure, failure of other hardware or software with impact on electronic reporting and data analysis).

1.3 Contractual Arrangements

A Marketing Authorisation Holder may transfer any or all of the pharmacovigilance tasks and functions, including the role of the QPPV, to another person(s) or organisation, but the ultimate responsibility for the fulfilment of all pharmacovigilance obligations and the quality and integrity of this always resides with the Marketing Authorisation Holder. In such cases, it is the responsibility of the Marketing Authorisation Holder to ensure that detailed and clear documented contractual arrangements for meeting pharmacovigilance obligations are in place between Marketing Authorisation Holder(s) and persons or organisations involved in the fulfilment of pharmacovigilance obligations and to provide the Competent Authorities and, if applicable the Agency, with information on such arrangements in line with the requirements set out in Chapter I.2. The contracted person(s) or organisation should implement quality assurance and quality control and accept to be audited by or behalf of the Marketing Authorisation Holder.

In cases of contractual arrangements between Marketing Authorisation Holders in relation to co-marketing of separately authorised medicinal products which are identical in all aspects apart from their invented names, these arrangements should include measures to avoid the duplicate submission of Individual Case Safety Reports (e.g. literature reports) to EudraVigilance.

2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections

2.1 Introduction

The rapid and effective identification and assessment of drug safety issues is dependent on early access to complete information. This is fundamental to Competent Authorities' and Marketing Authorisation Holders' ability to protect public health in taking appropriate action swiftly. Marketing Authorisation Holders and Competent Authorities have an obligation to implement medicines legislation and non-compliance with pharmacovigilance regulatory obligations could have a potentially serious health impact.

This Chapter sets out the framework for implementation, in the context of the revised pharmaceutical legislation, of the monitoring of compliance with pharmacovigilance obligations and of pharmacovigilance inspections. In the same context it sets out the information to be supplied in the application giving a detailed description of the pharmacovigilance system of the Marketing Authorisation Holder and proof that the Marketing Authorisation Holder has the services of a Qualified Person responsible for Pharmacovigilance (QPPV) and the necessary means for the notification of adverse reactions. This guidance is applicable for any medicinal product, whatever the marketing authorisation procedure used. The inspection process described focuses on centrally authorised products, however the principles are generally applicable.

The description of the risk management system, which includes product-specific pharmacovigilance activity, is not addressed in this Chapter but in [Chapter I.3](#).

2.1.1 Roles of the Marketing Authorisation Holder

The Marketing Authorisation Holders should ensure that they have an appropriate system of pharmacovigilance in place in order to assure responsibility for their products on the market and to ensure that appropriate action can be taken, when necessary. This includes the Marketing Authorisation Holder having at its disposal permanently and continuously an appropriately qualified person responsible for pharmacovigilance residing within the European Economic Area, and the establishment of a system of pharmacovigilance.

2.1.2 Roles of the Agency

The roles of the Agency are set out in [Regulation \(EC\) No 726/2004](#) and further described in this Volume 9A. Regarding the monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections, the following are of particular relevance:

- Article 57(1)(c) of Regulation (EC) No 726/2004 stating “coordination of the supervision, under practical conditions of use, of medicinal products which have been authorised within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation”;
- Article 57(1)(i) of Regulation (EC) No 726/2004 stating “coordinating the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations”.

2.1.3 Roles of the Competent Authorities in Member States

The roles of the Competent Authorities in Member States are set out in [Directive 2001/83/EC](#), in [Regulation \(EC\) No 726/2004](#) and further described in this Volume.

Title IX of Directive 2001/83/EC sets out requirements for pharmacovigilance.

2.1.4 Pharmacovigilance Inspections

The legal basis for the conduct of Pharmacovigilance inspections is set out in Article 111 of Directive 2001/83/EC and in Article 19(1) of Regulation (EC) 726/2004.

2.1.5 Detailed Description of the Pharmacovigilance System to Be Included in the Marketing Authorisation Application

The Applicant for a marketing authorisation is required (see Article 8(3)(ia) of Directive 2001/83/EC) to provide a detailed description of the system of pharmacovigilance and, where appropriate, of the risk management system which the Applicant will introduce. This Chapter addresses the detailed description of the pharmacovigilance system that should be supplied with the application dossier and supporting documentation that the Applicant should maintain and supply to the Competent Authorities on request. The description of the risk management system, which includes the product-specific pharmacovigilance activity, is addressed in Chapter I.3.

2.1.6 Proof of the Services of a QPPV and of the Necessary Means to Notify Adverse Reactions, to be Included in the Marketing Authorisation Application

The Applicant is required (Article 8(3)(n) of Directive 2001/83/EC) to provide proof that they have the services of a QPPV and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

2.2 Detailed Description of the Pharmacovigilance System

2.2.1 Location in the Marketing Authorisation Application and Update of the Detailed Description

The detailed description of the pharmacovigilance system, including the proof of the availability of the services of the QPPV and the proof that the Marketing Authorisation Holder has the necessary means for the collection and notification of any adverse reaction, should be provided in Module 1/section 1.8.1 of the application dossier.

The detailed description should comprise an overview of the pharmacovigilance system providing information on the key elements of that system. Where aspects of the system such as the organisational arrangements are particular to the product rather than the main system of the Marketing Authorisation Holder/company (Marketing Authorisation Holder or a group of Marketing Authorisation Holders sharing the same pharmacovigilance system) this should be indicated in a product-specific addendum.

The detailed description should be supported by documentation maintained by the company.

Updates to the information provided in the detailed description of the pharmacovigilance system should be made as type II variations.

2.2.2 Statement of the Marketing Authorisation Holder and the QPPV Regarding their Availability and the Means for the Notification of Adverse Reactions

The Applicant should provide a signed statement from the Marketing Authorisation Holder and the QPPV to the effect that the Applicant has their services available as QPPV and has the necessary means for the collection and notification of any adverse reaction occurring either in the Community or in a third country. This statement may make reference to the detailed description of the

pharmacovigilance system (see Chapter I.2, Section 2.3), indicate what is already in place, and confirm which items will be put in place before the product is placed on the market in the Community.

2.2.3 Elements of the Detailed Description of the Pharmacovigilance System

All Marketing Authorisation Holders are required to have an appropriate system of pharmacovigilance in place. The detailed description of the pharmacovigilance system should include the following elements, as applicable, and be set out in a structured manner consistent with this list. Additional important elements pertinent to a specific situation, should be added:

2.2.3.a) Qualified Person Responsible for Pharmacovigilance (QPPV)

- The name of the QPPV, located in the EEA. The business address and contact details should be provided in the Marketing Authorisation Application form. Companies might, for example, use a 24-hour telephone number through which the QPPV or their back-up can be reached, diverting it to the appropriate person according to availability.
- A summary Curriculum Vitae of the QPPV with the key information relevant to their role (main qualifications, training and experience).
- A summary of the job description of the QPPV.
- A description of the back-up procedure to apply in the absence of the QPPV.

2.2.3.b) Organisation

- Identification and location of the company units or other organisations where the principal EEA and global pharmacovigilance activities are undertaken (in particular those sites where the main databases are located, where Individual Case Safety Reports (ICSRs) are collated and reported and where PSURs (Periodic Safety Update Reports) are prepared and processed for reporting to the Competent Authorities). Identification of affiliates may be made in a general sense, rather than affiliate-by-affiliate.
- Identification of the point(s) in the Community at which pharmacovigilance data are accessible (to include access to ICSRs, PSURs and the global pharmacovigilance data).
- High-level organisation chart(s) providing an overview of the global and EEA pharmacovigilance units and organisations (identified above) and, illustrating the relationships between them, with affiliate/parent companies and contractors. The chart(s) should show the main reporting relationships with management and clearly show the position of the EEA QPPV within the organisation. Individual names of people should not be included. Licensing partnerships are usually product-specific and should be indicated in a product-specific addendum in the application for that product, unless a partnership is a consistent feature of the company's organisation across most products.
- A brief summary of the pharmacovigilance activities undertaken by each of the organisations/units identified above.
- Flow diagrams indicating the flow of safety reports of different sources and types. These should indicate how reports/information are processed and reported from the source, to the point of receipt by the Competent Authorities. These should be limited to the major processes identified in Volume 9A.

2.2.3.c) Documented Procedures

An essential element of any pharmacovigilance system is that there are clear, written procedures in place. The following list indicates topics that should usually be covered by these written procedures. The detailed description should indicate for which of these topics there are written procedures in place,

but should not list the procedure titles per se. A procedure may cover one or more of the topics or one topic may have one or more procedures depending on its complexity and the organisation of the company. Care should be taken to ensure that quality control and review are appropriately addressed in the various processes and reflected in the relevant procedures.

- The activities of the QPPV and the back-up procedure to apply in their absence;
- The collection, processing (including data entry and data management), quality control, coding, classification, medical review and reporting of ICSRs:
 - Reports of different types:
 - Organised data collection schemes (solicited), unsolicited, clinical trials, literature
 - The process should ensure that reports from different sources are captured:
 - EEA and third countries, healthcare professionals, sales and marketing personnel, other Marketing Authorisation Holder personnel, licensing partners, Competent Authorities, compassionate use, patients, others;
- The follow-up of reports for missing information and for information on the progress and outcome of the case(s);
- Detection of duplicate reports;
- Expedited reporting;
- Electronic reporting;
- Periodic Safety Update Reports (PSURs):
 - The preparation, processing, quality control, review (including medical review) and reporting;
- Global pharmacovigilance activities applying to all products: Continuous monitoring of the safety profile of authorised medicinal products (product-specific risk management systems and pharmacovigilance planning are covered in [Chapter I.3.](#)):
 - Signal detection and review,
 - Risk-benefit assessment;
 - Reporting and communication notifying Competent Authorities and healthcare professionals of changes to the risk-benefit balance of products, etc;
- Interaction between safety issues and product defects;
- Responses to requests for information from regulatory authorities;
- Handling of urgent safety restrictions and safety variations;
- Meeting commitments to Competent Authorities in relation to a marketing authorisation;
- Global pharmacovigilance activities applying to all products (signal detection, evaluation, reporting, communication etc.). (Product-specific risk management systems and pharmacovigilance planning are covered in [Chapter I.3.](#));
- Management and use of databases or other recording systems;
- Internal audit of the pharmacovigilance system;
- Training;
- Archiving.

The detailed description of the pharmacovigilance should indicate the processes for which written procedures are available. A list and copies of the global and EEA procedures should be available within two working days on request by the Competent Authorities. Any additional local procedures should be available to respond to specific requests.

2.2.3.d) Databases

A listing of the main databases used for pharmacovigilance purposes (e.g. compilation of safety reports, expedited/electronic reporting, signal detection, sharing and accessing global safety information) and brief functional descriptions of these should be provided including a statement regarding the validation status of the database systems.

A statement should be included regarding the compliance of the systems with the internationally agreed standards for electronic submission of adverse reaction reports as referred to in **Part III**.

A copy of the registration, of the QPPV, with the EudraVigilance system and identification of the process used for electronic reporting to the Competent Authorities.

There should be an indication of the responsibility for the operation of the databases and their location (with reference to the locations identified under **Chapter I.2, Section 2.3.b** above).

2.2.3.e) Contractual Arrangements with Other Persons or Organisations Involved in the Fulfilment of Pharmacovigilance Obligations

Links with other organisations such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. The company should identify the major subcontracting arrangements it has for the conduct of its pharmacovigilance activities and the main organisations to which it has subcontracted these (in particular where the role of the QPPV, the electronic reporting of ICSRs, the main databases, signal detection, or the compilation of PSURs is subcontracted).

A brief description of the nature of the agreements the company establishes with co-marketing partners and contractors for pharmacovigilance activities should be provided.

Co-licensing or co-marketing arrangements within the EEA should be identified and the distribution of the major responsibilities between the parties made clear.

Since co-licensing or co-marketing arrangements are mainly product-specific any information on these may be provided in a product-specific addendum, in the applicable Marketing Authorisation Application. Likewise if subcontracting is product-specific this should be indicated in a product-specific addendum.

2.2.3.f) Training

Staff should be appropriately trained for performing pharmacovigilance related activities. This includes not only staff within the pharmacovigilance units but also staff who may receive or process safety reports, such as sales personnel or clinical research staff. Provide a brief description of the training system and indicate where the training records, Curricula Vitae (CVs) and job descriptions are filed.

2.2.3.g) Documentation

Provide a brief description of the locations of the different types of pharmacovigilance source documents, including archiving arrangements. Reference can be made to the organisation charts provided under **Chapter I.2, Section 2.3.b** above.

2.2.3.h) Quality Management System

Provide a brief description of the quality management system, making cross-reference to the elements provided under the above Sections. Particular emphasis should be placed on organisational roles and

responsibilities for the activities and documentation, quality control and review, and for ensuring corrective and preventive action.

A brief description of the responsibilities for quality assurance auditing of the pharmacovigilance system, including auditing of sub-contractors, should be provided.

2.2.3.i) Supporting Documentation

The Marketing Authorisation Holder should ensure that the pharmacovigilance system is in place and documented.

An essential feature of a pharmacovigilance system is that it is clearly documented to ensure that the system functions properly, that the roles and responsibilities and required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system.

Documentation supporting the pharmacovigilance system (and its detailed description) may be required during the pre-authorisation period, or post-authorisation, for purposes such as assessment or inspection.

2.3 Monitoring of Compliance by the Competent Authorities

EEA Competent Authorities have been working for many years to facilitate Marketing Authorisation Holders in meeting pharmacovigilance regulatory obligations. This has included the development of guidelines, education programmes, responding to enquiries and the development of electronic reporting. Competent authorities should monitor Marketing Authorisation Holders for compliance with pharmacovigilance regulatory obligations. Furthermore, Competent Authorities exchange information in cases of non-compliance and will take appropriate regulatory action as required. It should be noted that enforcement action is within the competency of individual Member States. Article 84 of Regulation (EC) 726/2004 sets out the roles of the Member States, the Agency and the Commission with respect to the imposition of penalties for infringement of that Regulation or regulations adopted pursuant to it.

Set out below is an outline of how compliance monitoring should be performed. In this context compliance monitoring relates to activities that are separate to inspection activities and are carried out separately to them or as a prelude or follow-up to inspection. Where compliance monitoring raises concerns these should be highlighted to other Competent Authorities and in the case of centrally authorised products to the Agency, the Rapporteur/Co-Rapporteur, the CHMP, and the Pharmacovigilance Working Party as applicable. Deficiencies identified during compliance monitoring may lead to an inspection request.

Competent authorities will ensure that a system of pharmacovigilance is in place within Marketing Authorisation Holders through scrutiny of the detailed description of pharmacovigilance, procedures, safety reports and through pharmacovigilance inspections.

2.3.1 Qualified Person Responsible for Pharmacovigilance

Competent authorities will maintain a list of QPPVs within the EEA. This list will include business address and contact details (including out of hours contact). Where applicable this will include national contact points in the Member State concerned.

2.3.2 Availability of Pharmacovigilance Data

Competent authorities should monitor (e.g. by assessment of the detailed description of the pharmacovigilance system and when inspections are carried out) that pharmacovigilance data are

collated and accessible by the Marketing Authorisation Holder at least at one point within the Community.

2.3.3 Change in the Evaluation of the Risk-Benefit Balance of a Product

One of the key responsibilities of Marketing Authorisation Holders is to immediately notify the Competent Authorities of any change in the balance of risks and benefits of their products. Any failure to do so may pose a significant threat to public health. Any evidence of failure to notify such changes will result in consideration of enforcement action by the Competent Authorities.

2.3.4 Expedited Adverse Reaction Reporting

Requirements for expedited reporting of ICSRs are given in Chapter I.4. Non-compliance with expedited reporting may include complete failure to report, delayed reporting (i.e. submission beyond 15 days) and submission of reports of poor quality (particularly where evidence suggests that this results from inadequate company follow-up of individual cases). Failure to comply with electronic reporting requirements will be monitored.

Methods available to Competent Authorities for prospective monitoring of compliance with expedited reporting of adverse reactions could be:

- Monitoring adverse reaction reports received from Marketing Authorisation Holders against other sources to determine complete failure to report.
- Monitoring the time between receipt by Marketing Authorisation Holder and submission to Competent Authorities to detect late reporting.
- Monitoring the quality of reports. Submission of reports judged to be of poor quality may result in the follow-up procedures of Marketing Authorisation Holders being scrutinised.
- Monitoring that all adverse reactions that are kept electronically comply with the Note for Guidance on the Electronic Data Interchange (EDI) of ICSRs and Medicinal Product Reports (MPRs) in Pharmacovigilance in the Pre- and Post-Authorisation Phase in the EEA⁸.
- Checking of Periodic Safety Update Reports (PSURs) to detect under-reporting (e.g. of expedited reports).
- Checking interim and final reports of post-authorisation safety studies to ensure that all qualifying serious reports have been submitted within 15 days.
- At inspection there may be a review of a sample of reports on the Marketing Authorisation Holder database to assess the quality of data, determine whether the relevant reports have been expedited and are included on the EudraVigilance database, and to confirm that procedures are in place to follow up reports.

2.3.5 Periodic Safety Update Reports

PSURs are important pharmacovigilance documents. They provide an opportunity for Marketing Authorisation Holders to review the safety profile of their products and ensure that the Summary of Product Characteristics (SPC) and Package Leaflet are up to date. They also provide the Competent Authorities with a valuable source of pharmacovigilance data. For these reasons the Competent Authorities place great importance on compliance with periodic reporting. Non-compliance may include:

⁸ Doc.Ref. EMEA/115735/2004 latest version, available on EudraVigilance website <http://eudravigilance.emea.europa.eu>.

- Non-submission: Complete non-submission of PSURs, submission outside the correct cycle or outside the correct time frames (without previous submission of a type II variation), non-restart of the cycle of submission when necessary.
- Incorrect format of the document: Report not in accordance with **Chapter I.6**.
- Omission of information required by **Chapter I.6** particularly in the following sections of the report: Update of Regulatory Authority or Marketing Authorisation Holder Actions taken for Safety Reasons, Changes to Reference Safety Information, Patient Exposure, Presentation of Individual Case Histories.
- Poor quality reports: Poor documentation of adverse reactions or insufficient information provided to perform a thorough assessment in the Presentation of Individual Case Histories section, new safety signals not or poorly assessed in the Overall Safety Information section, misuse not highlighted, absence of use of standardised medical terminology (e.g. MedDRA).
- Company core data sheet (CCDS) or SPC: Where changes have been made to the CCDS or SPC since the submission of the last PSUR, the covering letter does not highlight the differences between the CCDS and the EU SPC.
- Previous requests from Competent Authorities not addressed: Submission of a report where previous requests from Competent Authorities have not been addressed (e.g. close monitoring of specific safety issues).

2.3.6 Information Requested by Competent Authorities

No fixed time frames are laid down in EU legislation or guidelines for responding to a request for information from Competent Authorities. This reflects the fact that the appropriate time frame will depend mainly on the urgency of the pharmacovigilance issue and its potential impact on public health. The Competent Authorities will ensure that all requests for information from Marketing Authorisation Holders have a clearly stipulated deadline and this deadline should be appropriate to the complexity and urgency of the issue. Competent Authorities will liaise with Marketing Authorisation Holders regarding the appropriate deadline, as required. Failure of Marketing Authorisation Holders to provide the necessary information/data within the deadline may be considered as non-compliance.

2.3.7 Submission of Safety Variations

EU legislation and guidelines do not specify deadlines for submission of safety variation applications. As with responding to requests for information from Competent Authorities, deadlines for submission of safety variations will depend on the urgency and potential public health impact of the pharmacovigilance issue. The Competent Authorities will ensure that requests for safety variations have a clearly stipulated deadline and this deadline should be appropriate to the complexity and urgency of the issue. The Competent Authorities will liaise with Marketing Authorisation Holders regarding the appropriate deadline, as required. Failure of Marketing Authorisation Holders to submit the variation application within the deadline may be considered as non-compliance.

2.3.8 CHMP Commitments in Respect of Centrally Authorised Products

EU legislation and guidelines do not specify deadlines for the submission of follow-up measures following the granting of a centralised marketing authorisation. The timeframe for submission of follow-up measures should be clearly stated in a letter of undertaking signed by the Applicant at the time of the CHMP Opinion.

Regulation (EC) No 726/2004 foresees a number of particular possibilities for marketing authorisations and post-marketing activities. Compliance with the provisions of these measures will be monitored. These include:

- Conditional marketing authorisations;

- Marketing authorisations under exceptional circumstances;

and the specific obligations or follow-up measures as applicable to these. Normal marketing authorisations may also include follow-up measures.

Non-compliance may include:

- Complete non-submission of data, including non-submission of specific obligations before the annual re-assessment;
- Submission of data after the deadline agreed in the letter of undertaking from the company (without previous agreement from the Competent Authority);
- Failure to implement a specific obligation;
- Failure to implement a follow-up measure;
- Poor quality of a report requested as a follow-up measure;
- Poor quality of a report requested as a specific obligation;
- Failure to implement an urgent provisional measure.

2.3.9 Post-Authorisation Safety Studies

Because of the objectives of safety studies there is considerable potential for safety signals to arise or changes in the balance of risks and benefits of products to be identified. Therefore, expedited reporting and submission to Competent Authorities of interim and final study reports from such studies has an important role in protecting public health. Where appropriate, Competent Authorities will scrutinise protocols prior to initiation of safety studies. Competent authorities should check that relevant adverse reaction reports from safety studies are expedited and monitor the submission of interim and final study reports. Guidance on post-authorisation safety studies is available in [Chapter I.7](#).

2.3.10 Provision of Additional Data on Studies

As part of their pharmacovigilance system, companies are required to have processes in place to screen all studies for information on safety or lack of efficacy and to report on this when required ([see also Chapters I.1 and I.8](#)). The Competent Authorities will monitor this by comparison of information received from different sources and in the course of inspections.

2.4 Pharmacovigilance Inspections

To ensure that Marketing Authorisation Holders comply with pharmacovigilance regulatory obligations and to facilitate compliance, Competent Authorities will conduct pharmacovigilance inspections. There should be collaboration between Competent Authorities to minimise duplication and maximise coverage. Inspections will be routine as well as targeted to Marketing Authorisation Holders suspected of being non-compliant. The results of an inspection will be routinely provided to the inspected Marketing Authorisation Holder who will be given the opportunity to comment on the findings. The results will be used to help Marketing Authorisation Holders improve compliance and may also be used as a basis for enforcement action. The scheduling and conduct of these inspections will be driven by routine programs and by risk analysis criteria. The inspection process described focuses on centrally authorised products, however the principles may be generally applicable.

2.4.1 Conduct of Inspections

The Competent Authority for inspection of the Marketing Authorisation Holder's pharmacovigilance system will be the Competent Authority of the Member State in whose territory the Marketing Authorisation Holder's QPPV is located. Where an additional facility (e.g. a database) in another

Member State requires inspection, the inspection will be carried out by the Competent Authority of the Member State in whose territory the facility is located.

In general, companies have a pharmacovigilance centre in the Community covering multiple products that are on the market, in the Community. These centres may also be the global pharmacovigilance centres, or the latter may be located in third countries. Where the global centres, databases etc. are located in third countries, the same Competent Authority as above will be responsible for purposes of inspection on behalf of the community, if such an inspection is considered necessary. Where relevant or on request, and in particular for product-specific issues, they may be assisted, or the inspection may be conducted, by an inspector and/or expert from the Rapporteur/Co-Rapporteur Member State (for centrally authorised products) or the Reference Member State (for mutual recognition procedures/decentralised procedures).

2.4.2 Routine Inspections

Routine inspections are carried out by the Competent Authority(ies) referred to in [Chapter I.2, Section 4.1](#). In general, it is anticipated that national inspection programmes will fulfil the need for routine inspections. They may be carried out on a repeated basis. The focus of these inspections is to determine that the Marketing Authorisation Holder has personnel, systems and facilities in place to meet their regulatory obligations for centrally authorised products. These inspections may be requested with one or more specific products selected as examples for which specific information can be traced and verified through the various processes, in order to provide practical evidence of the functioning of the pharmacovigilance system of the Marketing Authorisation Holder and their compliance with their regulatory obligations.

In cases where a Competent Authority has carried out, or intends, within the required timeframe, to carry out, an inspection covering the scope of that requested, this inspection will suffice and its results will be made available to the CHMP or applicable reviewing agency.

Such inspections may be specifically requested by the CHMP.

Where the pharmacovigilance system of a Marketing Authorisation Holder has not been inspected previously, the CHMP will request the relevant Competent Authority to carry out and report on an inspection of the system within 4 years of the placing on the market of the first centrally authorised product by that Marketing Authorisation Holder. Where the system has previously been inspected, re-inspection will take place at intervals. The timing of the first inspection and any further inspection will be determined on the basis of risk analysis criteria.

The CHMP, in conjunction with the Competent Authority referred to in [Chapter I.2, Section 4.1](#) and the applicable Pharmacovigilance and Inspectors' Working Parties, will determine a programme for inspection in relation to centrally authorised products. These inspections will be prioritised based on the potential risk to public health, the nature of the products, extent of use, number of products that the Marketing Authorisation Holder has on the EEA market, etc and risk factors such as those identified under [Chapter I.2, Section 4.3](#). This programme will be separate from any targeted inspection, but if a targeted inspection takes place it may replace the need for one under this programme dependent on its scope. The Competent Authorities of the Member States are responsible for determining their national inspection programmes.

2.4.3 Targeted Inspections

Targeted inspections may be conducted as and when the trigger is recognised and the CHMP and/or the Competent Authority determines that inspection is the appropriate course of action.

Targeted inspections may arise when one or more of the following arise:

- Triggers for the inspection are identified which do not relate to specific concerns about a product's safety or actual non-compliance, e.g.:
 - The Marketing Authorisation Holder has not previously been inspected;
 - The Marketing Authorisation Holder has placed their first product on the market in the EEA;
 - The Marketing Authorisation Holder has recently been or is involved in a merger or takeover process;
 - The Marketing Authorisation Holder has changed their system significantly (e.g. new database system, contracting out of reporting activities).
- Triggers for the inspection are identified which relate to specific concerns about a product's safety or actual non-compliance, e.g. significant issues relating to:
 - Delays in carrying out or failure to carry out specific obligations or follow-up measures relating to the monitoring of product safety, identified at the time of the marketing authorisation;
 - Delays in expedited or periodic reporting;
 - Incomplete reporting;
 - Submission of poor quality or incomplete PSURs;
 - Inconsistencies between reports and other information sources;
 - Change in risk-benefit balance;
 - Failure to communicate change in risk-benefit balance;
 - Previous inspection experience;
 - Information received from other authorities;
 - Poor follow-up to requests for information from the Competent Authorities;
 - Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the Competent Authorities or the Agency as applicable;
 - Product withdrawal with little or no advance notice to the EEA Competent Authorities.

The above are examples and other issues may trigger a targeted pharmacovigilance inspection. The presence of a trigger will not always lead to the conduct of an inspection.

2.4.4 Pharmacovigilance System Inspections

These inspections are designed to review the systems, personnel, facilities in place and their compliance with pharmacovigilance obligations. They may use products as examples to test the system. They may be routine or targeted.

2.4.5 Product-Specific Inspections

These inspections focus specifically on a given product and are usually targeted as a result of triggers that have been identified (see Chapter I.2, Section 4.3).

2.4.6 Requesting and Reporting of Inspections

Inspection requests are prepared by the Agency's inspection sector in conjunction with the Rapporteur/Co-Rapporteur and the relevant Competent Authority. They are presented to the CHMP for adoption and once adopted are carried out by the Competent Authority referred to in Chapter I.2, Section 4.1 on behalf of the Agency.

2.4.7 Inspections of Contractors and Licensing Partners

Any party carrying out pharmacovigilance activities in whole or in part on behalf of, or in conjunction with, the Marketing Authorisation Holder may be inspected in order to confirm their capability to support the Marketing Authorisation Holder's compliance with pharmacovigilance obligations.

2.4.8 Inspections in European Economic Area

These may be routine or targeted.

2.4.9 Inspections in Third Countries

These may be routine or targeted. They will be included in routine inspections when considered appropriate, particularly where the main pharmacovigilance centre and databases etc. are located outside the community, for the Marketing Authorisation Holder and centrally authorised product(s) in question. They will be included in targeted inspections whenever this is considered appropriate by the authority requesting the inspection.

2.4.10 Fees for Inspections Requested by the CHMP

An inspection fee(s) (and inspectors' expenses where applicable) will be charged in accordance with the **Council Regulation (EC) No 297/95** on fees, as amended and implementing rules applicable at the time.

2.4.11 Procedures for Coordination of Pharmacovigilance Inspection for Centrally Authorised Products

The Agency will establish procedures for the administration and review of inspection requests and reports in conjunction with the CHMP and relevant Pharmacovigilance and Inspectors' Working Parties.

These procedures will be adopted and published in line with the policies and procedures of the Agency on such documents.

2.4.12 Procedures for Pharmacovigilance Inspections

Procedures for pharmacovigilance inspection are prepared by representatives of the pharmacovigilance inspectors of the national Competent Authorities in association with representatives of the Pharmacovigilance Working Party and the Agency. The following procedures have been adopted and will be updated as needed:

- The Procedure for Coordinating Pharmacovigilance Inspections Requested by the CHMP (INS/PhV/1, latest version)⁹;
- The Procedure for Conducting Pharmacovigilance Inspections Requested by the CHMP (INS/PhV/2, latest version)¹⁰;
- The Procedure for Reporting Pharmacovigilance Inspections Requested by the CHMP (INS/PhV/3, latest version)¹¹.

⁹ Available on EMEA website <http://www.emea.europa.eu>.

¹⁰ Available on EMEA website <http://www.emea.europa.eu>.

¹¹ Available on EMEA website <http://www.emea.europa.eu>.

2.4.13 Unannounced Inspections

It is anticipated that the majority of inspections will be announced. However, on occasions, it may be appropriate to conduct unannounced inspections or to announce an inspection at short notice.

2.4.14 Inspection Reports

Each inspection will result in an inspection report, prepared in accordance with an agreed format. The inspection report will be made available to the CHMP. The inspection report will be made available to the Marketing Authorisation Holder. See Chapter I.2, Section 4.12 for the procedures.

2.4.15 Follow-up of Inspection Findings

Where an inspection reveals non-compliances the Marketing Authorisation Holder will be required to prepare a remedial action plan to correct the non-compliances and avoid their recurrence. The Marketing Authorisation Holder may be required to provide reports and where necessary evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial actions.

2.4.16 Sharing of inspection information

The national Competent Authorities and the European Commission, in co-operation with the Agency, will establish procedures for the sharing of information on inspections and their outcomes, in particular through the Pharmacovigilance Working Parties and the Inspection Services Groups.

2.5 Regulatory Action

Under EU legislation, to protect public health, Competent Authorities are obliged to implement pharmaceutical legislation and to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance regulatory obligations is detected, the necessary action will be judged on a case-by-case basis. What action is taken will depend on the potential negative public health impact of non-compliance but any instance of non-compliance may be referred for enforcement action. Action may be taken by the Agency, the Commission or the Competent Authorities of the Member States as appropriate in the context. Reference should also be made to legislation at EU and national level on penalties and sanctions and implementing procedures relating to these.

In addition, in the event of non-compliance, regulatory options include the following:

- **Education and Facilitation**
Marketing Authorisation Holders may be informed of non-compliance and advised on how this can be remedied.
- **Inspection**
Non-compliant Marketing Authorisation Holders may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved.
- **Warning**
Competent Authorities may issue a formal warning reminding Marketing Authorisation Holders of their pharmacovigilance regulatory obligations.
- **Naming non-compliant Marketing Authorisation Holders**
Competent Authorities will consider a policy of making public a list of Marketing Authorisation Holders found to be seriously or persistently non-compliant.
- **Urgent Safety Restriction**
In accordance with the guidance and rules set out elsewhere.
- **Variation of the Marketing Authorisation**

In accordance with the guidance and rules set out elsewhere.

- Suspension of the Marketing Authorisation

In accordance with the guidance and rules set out elsewhere.

- Revocation of the Marketing Authorisation

In accordance with the guidance and rules set out elsewhere.

3. Requirements for Risk Management Systems

3.1 Introduction

It is recognised that at the time of authorisation, information on the safety of a medicinal product is relatively limited. This is due to many factors including the small numbers of subjects in clinical trials, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes.

A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the risk-benefit is judged positive for the target population. However, not all actual or potential risks will have been identified when an initial authorisation is sought. In addition, there may be subsets of patients for whom the risk is greater than that for the target population as a whole.

Planning of pharmacovigilance activities will be improved if it were more closely based on product-specific issues identified from pre- or post-authorisation data and from pharmacological principles. Such planning will also guide the use of electronic data, which are routinely collected within health services to provide rapid investigation of predicted or emerging safety concerns.

The management of a single risk can be considered as having four steps, risk detection, risk assessment, risk minimisation and risk communication. However, a typical individual medicinal product will have multiple risks attached to it and individual risks will vary in terms of severity, and individual patient and public health impact. Therefore, the concept of risk management should also consider the combination of information on multiple risks with the aim of ensuring that the benefits exceed the risks by the greatest possible margin both for the individual patient and at the population level.

This Chapter¹² aims to provide guidance on how Marketing Authorisation Holders and Applicants should meet the requirements for a description of a risk management system that they will introduce for an individual medicinal product, or a series of medicinal products, in line with new Community legislation. This guidance also describes how such a risk management system can be presented to Competent Authorities in the form of a Risk Management Plan.

EU legislation requires Applicants/Marketing Authorisation Holders to provide Competent Authorities with a description of pharmacovigilance and risk management systems.

The requirements and format for the description of a pharmacovigilance system are covered in **Chapter I.2** and should be submitted accordingly.

Consideration should also be given to other relevant EU pharmacovigilance guidelines (see **Annex 3**).

The present Guideline provides guidance to Applicants and Marketing Authorisation Holders in the European Union on how to meet the requirements for a ‘detailed description of the risk management system’ (see **Chapter I.3, Section 2**) and the circumstances when it is appropriate (see **Chapter I.3, Sections 4 and 14**) to provide it. The risks addressed in this guidance are those related to non-clinical and clinical safety. Where the disposal of the product might pose a particular risk because of remaining active substance (e.g. patches) this should also be addressed. The Guideline is applicable to products in both the pre-authorisation and post-authorisation phase and whether the product was authorised through the centralised, decentralised or mutual recognition procedures. It incorporates the concepts of the International Conference on Harmonisation ICH-E2E Guideline.

¹² This guidance was first published in 2005 as Guideline on Risk Management Systems for Medicinal Products for Human Use (EMA/CHMP/96268/2005) on the EMA website.

Article 6 of Regulation (EC) No 726/2004 and Article 8 of Directive 2001/83/EC lay down the particulars and documents to be included in an application for the authorisation of a medicinal product for human use. More specifically and for the purpose of this guidance it requires in accordance with Article 8(3)(ia) of Directive 2001/83/EC the inclusion of *“a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce.”* This provision forms the legal basis for this guideline. Also relevant to the legal context for EU Risk Management Plans are the following legal provisions:

In the context of centrally authorised products Article 9(4) of Regulation (EC) No 726/2004 requires for a favourable opinion that the following shall be attached to the Opinion:

“b) details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including conditions under which the medicinal product may be made available to the patients, in accordance with the criteria in Title VI of Directive 2001/83/EC”;

“c) details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product”.

In addition to Article 9(4)(c) above, Article 127a of Directive 2001/83/EC states that *“When a medicinal product is to be authorised in accordance with Regulation (EC) 726/2004 and the Scientific Committee in its opinion refers to recommended conditions or restrictions with regard to the safe and effective use of the medicinal product [...], a decision addressed to the Member States shall be adopted in accordance with the procedure provided for in Article 33 and 34 of the Directive, for the implementation of those conditions or restrictions”.*

The legislation provides for additional information to be requested from Marketing Authorisation Holders.

Article 23 of Regulation (EC) No 726/2004 states *“[...] That qualified person shall reside in the Community and shall be responsible for the following:”*

“c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the risks and benefits of a medicinal product is answered fully and promptly, including the provision of information regarding the volume of sales or prescriptions for the medicinal product concerned [...]”;

“d) providing the competent authorities with any other information relevant to the evaluation of the risks and benefits of a medicinal product particularly information concerning post-authorisation safety studies”.

Similarly, for nationally authorised products, Article 103 of Directive 2001/83/EC states *“[...] That qualified person shall reside in the Community and shall be responsible for the following:”*

“c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned”;

“d) the provision to the competent authorities, of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorization safety studies”.

Article 26 of Regulation (EC) No 726/2004 states that *“[...] for a period of five years following the initial placing on the market in the Community, the Agency may request that the Marketing*

Authorisation Holder arrange for specific pharmacovigilance data to be collected from targeted groups of patients. [...]”.

Article 34 of Regulation (EC) No 1901/2006 on medicinal products for paediatric use states that “[...] Where there is a particular cause for concern, the competent authority shall require, as a condition of granting marketing authorisation, that a risk management system be set up or that specific post-marketing studies be performed and submitted for review. The risk management system shall comprise a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those interventions.”

The detailed description of a risk management system should be provided in the form of an EU Risk Management Plan (EU-RMP) in the situations described in [Chapter I.3, Section 4](#). It is strongly recommended that discussions with the Competent Authorities on the need for, and content of, an EU-RMP should take place in advance of submission.

3.2 Description of the Risk Management System

A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions. The legislation requires that a description of the risk management system should be submitted when appropriate. This requirement can be met by the submission of an EU-RMP in the circumstances detailed in [Chapter I.3, Sections 4 and 14](#).

The aim of a risk management system is to ensure that the benefits of a particular medicine (or a series of medicines) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. This can be done either by increasing the benefits or by reducing the risks but, by its definition, risk management focuses upon the risk reduction approach. Nevertheless, whenever possible, increases in benefits should also be considered and the characteristics of patients most likely to benefit from treatment should be better defined.

3.3 EU Risk Management Plan (EU-RMP)

The description of a risk management system should be submitted in the form of an EU-RMP. The EU-RMP contains two parts:

Part I:

- A Safety Specification,
- A Pharmacovigilance Plan; and

Part II:

- An evaluation of the need for risk minimisation activities;

and if there is a need for additional (i.e. non-routine) risk minimisation activities

- A risk minimisation plan.

Part I of the EU-RMP incorporates the concepts of ICH-E2E regarding the Safety Specification, which summarises the safety profile of the medicinal product at the particular point in time of its life-cycle, and the Pharmacovigilance Plan which is based on the Safety Specification. [Chapter I.3, Sections 6 and 7](#) of this guidance include relevant text from ICH-E2E with additional commentary on implementation within the EU. [Chapter I.3, Section 6.2.g](#) also details the particular EU requirements for the Safety Specification.

In Part II of the EU-RMP, on the basis of the Safety Specification, the Applicant/Marketing Authorisation Holder should consider carefully the need for risk minimisation activities to be introduced. Risk minimisation activities may be “routine” or “additional” (see Chapter I.3, Section 8). Within the “evaluation of the need for risk minimisation activities”, the Applicant/Marketing Authorisation Holder should discuss fully the use of routine risk minimisation activities and whether there is a need for additional risk minimisation activities. If only routine risk minimisation activities are required there is no need to submit a risk minimisation plan. If additional risk minimisation activities are thought necessary, the Applicant/Marketing Authorisation Holder should provide a risk minimisation plan within Part II of the EU-RMP. This risk minimisation plan should contain both the routine and additional activities for each safety concern. Every time the EU-RMP is updated (see Chapter I.3, Section 14) the Applicant/Marketing Authorisation Holder should reconsider its position vis-à-vis the need for risk minimisation activities and Part II should be updated accordingly.

3.4 Situations Requiring an EU-RMP

An EU-RMP may need to be submitted at any time of a product’s life-cycle – i.e. during both the pre-authorisation and post-authorisation phases. In particular an EU-RMP should be submitted:

- with the application for a new marketing authorisation for:
 - any product containing a new active substance;
 - a similar biological medicinal product;
 - a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product.
- with an application for a paediatric use marketing authorisation (PUMA);
- with an application involving a significant change in a marketing authorisation (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication, including a new paediatric indication) unless it has been agreed with the Competent Authority that submission is not required;
- on request from a Competent Authority (both pre-and post-authorisation);
- on the initiative of an Applicant/Marketing Authorisation Holder when they identify a safety concern with a medicinal product at any stage of its life cycle.

In some circumstances, products which are not in the above categories which are seeking a new authorisation via the centralised procedure may require an EU-RMP:

- Known active substances
- Hybrid medicinal products where the changes compared with the reference medicinal product suggest different risks
- Bibliographical applications
- Fixed combination applications.

For situations where the submission of an EU-RMP is not mandatory, the need for it should be discussed with the Competent Authority well in advance of the submission.

3.4.1 Marketing Authorisations via the Centralised Procedure

At any stage, but in particular during the pre-authorisation phase, an Applicant/Marketing Authorisation Holder may request advice on the need for, development or content of an EU-RMP through the scientific advice procedure.

Whether or not the scientific advice procedure has been used, discussion on the EU-RMP for a medicinal product seeking a new authorisation through the centralised procedure should take place at the pre-submission meeting.

For significant changes to an existing centralised marketing authorisation, the Marketing Authorisation Holder should discuss the need for an EU-RMP with the Agency at least two months in advance of the submission. When it is not mandatory that an EU-RMP is submitted and the Applicant/Marketing Authorisation Holder thinks it is unnecessary, the Applicant/Marketing Authorisation Holder should submit a brief justification of this along with the application which will form part of the formal assessment by the Rapporteur. However, it is strongly recommended that this is discussed with the Agency before submission of the application.

3.4.2 Marketing Authorisations via the Mutual Recognition or Decentralised Procedures

The Competent Authority of the Member State should be contacted regarding the timings of discussions on Risk Management Plans. Where there is a Reference Member State (RMS), the Competent Authority of this country should be consulted.

3.5 Location in the Application

An EU-RMP submitted at the time of an application for a Marketing Authorisation should be provided in Module 1.8.2 of the Marketing Authorisation Application in a stand-alone format allowing circulation to, and evaluation by pharmacovigilance and risk management experts. It should be accompanied by other relevant documents such as study protocols, where applicable.

Updates to the EU-RMP (see Chapter I.3, Section 14) should be presented preferably in a tab-separated dossier and in accordance with the appropriate headings and numberings of the EU-CTD format. This should be accompanied by a cover letter, detailing which sections of the EU-RMP have been changed, and study reports (if appropriate).

3.6 Safety Specification

The Safety Specification should be a summary of the important identified risks of a medicinal product, important potential risks, and important missing information. It should also address the populations potentially at risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the risk-benefit profile during the post-authorisation period. The Safety Specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan.

In the EU-RMP the Safety Specification will also form the basis of the evaluation of the need for risk minimisation activities and, where appropriate, the risk minimisation plan.

It is recommended that Applicants/Marketing Authorisation Holders follow the structure of elements provided below when compiling the Safety Specification. The elements of the Safety Specification that are included are only a guide. The Safety Specification can include additional elements, depending on the nature of the product and its development programme. Conversely, for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.

3.6.1 Non-clinical Part of the Safety Specification

Within the Safety Specification, this section should present non-clinical safety findings that have not been adequately addressed by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);
- General pharmacology (cardiovascular, including QT interval prolongation, nervous system);
- Drug interactions;
- Other toxicity-related information or data.

The relevance of the findings to the use in humans should be discussed. If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.

3.6.2 Clinical Part of the Safety Specification

3.6.2.a) Limitations of the Human Safety Database

Limitations of the safety database (e.g. related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

In order to assess the limitation of the human safety database, the size of the study population should be detailed using both numbers of patients and patient time (patient-years, patient-months) exposed to the drug. This should be stratified, for relevant population categories such as age and gender, type of study (e.g. randomised controlled trial, open clinical trial, observational study) and any other relevant variable, such as dose, indication and duration of treatment. Limitations of the database should also be presented in terms of the frequencies of adverse drug reactions detectable given the size of the database. The limitations of the database should also be discussed with regard to suspected long-term adverse reactions (e.g. malignancies) when it is unlikely that exposure data is of sufficient duration and latency.

Post-marketing (non-study) exposure:

Where marketing of the medicine has occurred, the applicant / Marketing Authorisation Holder should provide data on patients exposed post-marketing. Exposure data based on the number of kilogrammes of medicinal product sold divided by the average dose is only valid if the medicinal product is always taken at one dose level for a fixed length of time – which is not the situation with most medicinal products. In paediatric populations or mixed populations of different indications or age groups, use of this measure alone is inappropriate and other measures should be used.

A more accurate breakdown of drug exposure based on market research should be provided where possible. When deciding which measure to use for exposure data, it is important to consider the way a medicine is used. For example, for medicines used chronically, the appropriate measure may be patient years of use. However, when use is typically limited and utilisation is determined by pack size (e.g. a course of antibiotics), a simple count of packs sold may be more appropriate. The information should be stratified by relevant variables such as age, indication, dose and duration of treatment.

3.6.2.b) Populations Not Studied in the Pre-Authorisation Phase

The Safety Specification should discuss which populations have not been studied or have only been studied to a limited degree in the pre-authorisation phase. In particular, if paediatric development has

been limited to certain age categories, then the implications for other paediatric age groups should also be discussed. The implications, with respect to predicting the safety of the product in the marketplace, of all these populations with limited or no research should be explicitly discussed.

Limitations of the database should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population, in particular when exclusion criteria are not proposed as contraindications for the drug. In discussing differences between target populations and those exposed in clinical trials it should be noted that some differences may arise through trial setting (e.g. hospital or general practice) rather than through explicit inclusion/exclusion criteria.

Populations to be considered for discussion should include (but might not be limited to):

- Children (from birth to 18 years with consideration given to the different age categories as per ICH-E11¹³, or, if justified, to other developmentally meaningful groups);
- The elderly;
- Pregnant or lactating women;
- Patients with relevant co-morbidity such as hepatic or renal disorders;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying known and relevant genetic polymorphism;
- Patients of different racial and/or ethnic origins.

Post Marketing Experience:

For updates to the Safety Specification, specific reference should be made to how the realised pattern of exposure (including off-label use) has differed from that predicted and from the indication(s) and contraindications in the Summary of Product Characteristics.

Newly identified safety concerns should be mentioned, in particular any issue found in relation to a population not studied in the pre-approval phase should be discussed along with the implications for the Summary of Product Characteristics.

If regulatory action has been taken in relation to a safety concern, this should be mentioned.

3.6.2.c) Adverse Events/Adverse Reactions

This section should list the important identified and potential risks that require further characterisation or evaluation.

Identified risks that require further evaluation

More detailed information should be included on the most important identified adverse events/adverse reactions, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the medicinal product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These adverse events/adverse reactions should usually call for further evaluation as part of the Pharmacovigilance Plan (e.g. frequency in normal conditions of use, severity, outcome, at-risk groups).

Potential risks that require further evaluation

Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterise the association.

¹³ Available on EMEA website <http://www.emea.europa.eu>.

Presentation of risk data

When the information is available, detailed risk data should be presented according to the following format.

The frequency of important adverse reactions should be expressed taking into account the source of the data. For a product already on the market, the reporting rate based on the number of spontaneously reported adverse events/adverse reactions (in the numerator) and the sales data (in the denominator) is very likely to underestimate the rate of occurrence of an adverse reaction in an exposed population. When an accurate frequency is needed for an important adverse reaction, this should always be based on systematic studies (e.g. clinical trials or epidemiological studies) in which both the number of patients exposed to the medicinal product and the number of patients who experienced the respective adverse event/adverse reaction are known.

The denominator should be expressed using the appropriate measure: e.g. number of patients or in patient-time or equivalent units (courses of treatment, prescriptions, etc.) It should be stated clearly which frequency parameter is being used: e.g. incidence proportion (patient units in the denominator) or incidence rate (patient-time units in the denominator). Confidence intervals should be provided. When using patient-time, the underlying assumption is that the hazard function must be nearly constant over the follow-up time. Otherwise it should be split into relevant categories where the assumption of constancy holds. Where appropriate, the period of major risk should be identified. Adverse event/adverse reaction incidence rates should be presented for the whole population and for relevant population categories.

For important identified risks, the excess and relative incidence should be given. Excess incidence (in comparison to placebo and active comparator; if available) should be calculated based on the best available evidence (e.g. meta-analytic techniques) for each population (total controlled, total controlled plus open label extension, total study). Time to event data should be summarised using survival techniques which take appropriate account of informative censoring. Cumulative hazard functions may provide a simple visual comparison of the competing risks of different adverse reactions. These data can be stratified by substance (to investigate the difference in the adverse event profile between active and placebo), or by risk factors such as dose, gender or age.

The potential impact of the most important identified and important potential risks should be addressed using for example: strength of evidence, supporting plausibility, nature of evidence and potential public health burden, morbidity and case fatality. Recording this in a structured form will facilitate assessment of the potential significance of a safety concern. Classification of the safety concern by dose, time and risk factors is encouraged. The identification of susceptible patients should receive specific attention, possibly from analysis of cases. It is likely that the adverse reactions will require further evaluation as part of the Pharmacovigilance Plan.

3.6.2.d) Identified and Potential Interactions including Food-Drug and Drug-Drug Interactions

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed.

It should be stated which interactions require further investigation.

3.6.2.e) Epidemiology

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should take into account whenever possible

stratification by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, where feasible, (because the epidemiology of the indication(s) may vary across regions), but the emphasis should be on the epidemiology in the EU.

In addition, for important adverse events that may require further investigation, it is useful to review the incidence rate of these events among patients in whom the medicinal product is indicated (i.e. the background incidence rates). Information on risk factors for an adverse event would also be useful to include, if available. For example: if a medicinal product is intended for treating prostate cancer the target population is likely to be men over the age of 50 years. This population is also at increased risk of myocardial infarction. If it is suspected that the medicinal product might also cause myocardial infarction, it would be useful to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group, not on the medicinal product.

3.6.2.f) Pharmacological Class Effects

The Safety Specification should identify risks believed to be common to the pharmacological class.

If a risk which is common to the pharmacological class is not thought to be a safety concern with the medicinal product, this should be justified.

3.6.2.g) Additional EU Requirements

The Applicant/Marketing Authorisation Holder is requested to discuss the topics below. If the potential is thought to be significant, the topic should be identified as an important potential risk and means for reducing or minimising it discussed in the “evaluation of the need for risk minimisation activities”. In this context, “significant” means that there is a reasonable likelihood that it will occur. Where a particular topic is not relevant to the individual medicinal product, this should be stated along with the reason.

Potential for overdose

Special attention should be given in particular cases, e.g. where there is a narrow therapeutic margin, a medicinal product with significant toxicity and/or there is an increased risk of overdose in the target population.

Potential for transmission of infectious agents

The Applicant/Marketing Authorisation Holder should discuss the potential for the transmission of an infectious agent in line with [Chapter I.5](#).

Potential for misuse for illegal purposes

The potential for misuse for illegal purposes should be considered. If appropriate, the means of limiting this, e.g. by the use of colorants and/or flavourings in the dosage form, limited pack size and controlled distribution should be discussed in the RMP section “Evaluation of the Need for Risk Minimisation Activities”.

Potential for off-label use

The potential for off-label use should be discussed. This is particularly relevant where a medicinal product has an indication restricted to a subset of the population within a disease area or there are situations where the medicinal product must not be given for safety reasons. The potential for use in other disease areas should also be considered where this is likely.

Potential for off-label paediatric use

If the disease or disorder which is being treated or prevented is found in the paediatric population, and the product is not authorised in all paediatric age groups, the potential for off-label paediatric use in the non-authorised age groups should be discussed.

3.6.3 Summary

At the end of the Safety Specification a summary should be provided of the:

- Important identified risks;
- Important potential risks; and
- Important missing information.

Based on this summary the Applicant/Marketing Authorisation Holder should provide a Pharmacovigilance Plan and an evaluation of the need for risk minimisation activities (see Template in Annex 5.1.1).

3.7 Pharmacovigilance Plan

According to ICH-E2E, the Pharmacovigilance Plan should be based on the Safety Specification and propose actions to address the safety concerns identified. Early discussions between Competent Authorities and the Applicant or Marketing Authorisation Holder are recommended to identify whether, and which, additional pharmacovigilance activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable and the Pharmacovigilance Plan will not replace but rather complement the procedures currently used to detect safety signals.

3.7.1 Routine Pharmacovigilance

For medicinal products where no special concerns have arisen, routine pharmacovigilance should be sufficient for post-authorisation safety monitoring, without the need for additional actions (e.g. safety studies).

A description of routine pharmacovigilance activities is covered elsewhere in **Part I**, which should be consulted in developing the Pharmacovigilance Plan.

3.7.2 Additional Pharmacovigilance Activities and Action Plans

For medicinal products with important identified risks, important potential risks, or important missing information, additional activities designed to address these safety concerns should be considered.

Applicants/Marketing Authorisation Holders should also consider the situations when routine pharmacovigilance is likely to be inadequate. An example of this might be when a potential risk with an individual medicinal product has a significant background incidence in the target population(s), leading to difficulties in distinguishing between the effects of the medicinal product and the “normal” incidence. When any doubt exists about the need for additional pharmacovigilance activities, consultation with a Competent Authority should be considered.

The objective(s) of additional pharmacovigilance activities will normally differ according to the safety concern to be addressed. For important identified and potential risks, objectives may be to measure the incidence rate in a larger or a different population, to measure the rate ratio or rate difference in comparison to a reference medicinal product, to examine how the risk varies with different doses and durations of exposure, to identify risk factors or to assess a causal association. For important missing information, the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.

The threshold for investigating a safety concern further will depend upon the indication, the target population, and the likely impact on public health. For example, a safety concern with a vaccine might have a lower threshold for investigation than the same issue in a medicine used in the palliative treatment of metastatic cancer.

The **Table I.7.A** lists some of the epidemiological activities which might be considered for inclusion in a Pharmacovigilance Plan. Additional pharmacovigilance activities included in the Pharmacovigilance Plan should be designed and conducted according to the recommendations in the Guidelines for Good Pharmacoepidemiology Practices (GPP)¹⁴. For studies involving children, the **Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population** (see Annex 3.1.4) should be consulted. The responsibility for the scientific value of study protocols remains with Applicants or Marketing Authorisation Holders, even if they have been previously discussed with Competent Authorities.

3.7.3 Action Plan for Safety Concerns

Within the Pharmacovigilance Plan the action plan for each safety concern should be presented and justified according to the following structure (see also Annex 5.1.1):

- Safety concern
- Objective of proposed action(s)
- Action(s) proposed
- Rationale for proposed action(s)
- Monitoring by the Applicant/Marketing Authorisation Holder for safety concern and proposed action(s)
- Milestones for evaluation and reporting.

Protocols (draft or otherwise) for any formal studies should be provided. Details of the monitoring for the safety concern in a clinical trial could include: stopping rules, information on the drug safety monitoring board and when interim analyses will be carried out.

Although not explicitly included in this structure, it is also necessary in the EU-RMP to explain the decision making processes which will depend on the outcomes of the proposed actions. The possible consequences of the study outcomes should be discussed.

3.8 Evaluation of the Need for Risk Minimisation Activities

On the basis of the Safety Specification, the Applicant/Marketing Authorisation Holder should provide an evaluation of the need for risk minimisation activities.

For each safety concern, the Applicant/Marketing Authorisation Holder should assess whether any risk minimisation activities are needed. Some safety concerns may be adequately addressed by the proposed actions in the Pharmacovigilance Plan, but for others the risk may be of a particular nature and seriousness that risk minimisation activities are needed. It is possible that the risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by the careful use of labelling and packaging, i.e. routine risk minimisation activities. If an Applicant/Marketing Authorisation Holder is of the opinion that no additional risk minimisation activities beyond these are warranted, this should be discussed and, where appropriate, supporting evidence provided.

¹⁴ International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf. 2005; 14 (8): 589-595. Available on the ISPE website http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

However, for some risks, routine risk minimisation activities will not be sufficient and additional risk minimisation activities will be necessary. If these are required, they should be described in the risk minimisation plan (see Chapter I.3, Section 9) which should be included in Part II of the EU-RMP.

Within the evaluation of the need for risk minimisation activities, the Applicant/Marketing Authorisation Holder should also address the potential for medication errors (see Chapter I.3, Section 8.1) and state how this has been reduced in the final design of the pharmaceutical form, product information, packaging and, where appropriate, device.

As a rule, Applicants/Marketing Authorisation Holders should always consider the need for risk minimisation activities whenever the Safety Specification is updated in the light of new safety information on the medicinal product. In some circumstances, it may be appropriate to suggest that an additional risk minimisation activity be stopped because experience with the medicinal product suggests that it is no longer necessary for the safe and effective use.

3.8.1 Potential for Medication Errors

Applicants/Marketing Authorisation Holders are encouraged routinely to consider the likelihood of medication errors. In particular, they should assess prior to marketing, common sources of medication errors. During the development phase and during the design of the medicinal product for marketing, the Applicant needs to take into account potential reasons for medication error. The naming (taking into account the Guideline on the Acceptability of Invented Names for Human Medicinal Products Processed through the Centralised Procedure¹⁵), presentation (e.g. size, shape and colouring of the pharmaceutical form and packaging), instructions for use (e.g. regarding reconstitution, parenteral routes of administration, dose calculation) and labelling are among the items to be considered.

If a product has life-threatening potential when administered by an incorrect route, consideration should be given as to how such administration can be avoided. This is particularly important when it is common practice to administer the product at the same time as other medicinal products given by the hazardous route.

The need for visual (or physical) differentiation between strengths of the same medicinal product and between other medicinal products commonly administered or taken at the same time should be discussed. When a medicinal product is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error.

Consideration should be given to the prevention of accidental ingestion or other unintended use by children.

Medication errors identified during product development should be discussed and information on the errors, their potential cause(s) and possible remedies given. Where applicable an indication should be given of how these have been taken into account in the final product design.

If during the post-marketing period it becomes apparent that adverse reactions are occurring as a result of medication errors, this topic should be discussed in the updated EU-RMP and ways of limiting the errors proposed.

3.9 The Risk Minimisation Plan

The risk minimisation plan details the risk minimisation activities which will be taken to reduce the risks associated with an individual safety concern. When a risk minimisation plan is provided within an EU-RMP, the risk minimisation plan should include both routine and additional risk minimisation activities. A safety concern may have more than one risk minimisation activity attached to an

¹⁵ Doc.Ref. CPMP/328/98 latest version, available on EMEA website <http://www.emea.europa.eu>.

objective. For example, a possible plan for a known teratogen could have the objective of avoiding any patient taking the drug becoming pregnant. A routine risk minimisation activity might be to emphasise the need for effective contraception in the Summary of Product Characteristics and a recommendation that patients should have a negative pregnancy test before each prescription. One additional risk minimisation activity might be to develop an educational pack to provide information to the patients on the risks of the medicine and the need for contraception. It might also be an activity to limit the pack sizes to one month's supply of the medicine.

The risk minimisation plan should list the safety concerns for which risk minimisation activities are proposed. The risk minimisation activities, i.e. both routine and additional, related to that safety concern should be discussed. For each safety concern the following headings in the plan will mirror those for safety concerns listed in [Chapter I.3, Section 7.3](#). In addition, for each proposed additional risk minimisation activity, a section should be included detailing how the effectiveness of it as a measure to reduce risk will be assessed (see [Annex 5.1.1](#)).

3.10 Risk Minimisation Activities

It is difficult to provide precise guidance on which risk minimisation activity should be used in a given situation as each safety concern needs to be considered on a case-by-case basis. Some of the risk minimisation activities are described in the [Table I.3.A](#) at the end of this Chapter, but it is essential that appropriate specialised experts are consulted at all stages and Marketing Authorisation Applicants and Holders are also encouraged to discuss risk minimisation plans with the Competent Authorities early on.

3.10.1 Risk Communication

Accurate and timely communication of emerging data on risk is an essential part of pharmacovigilance. Risk communication is an important step in risk management as well as a risk minimisation activity. Patients and healthcare professionals need accurate and well communicated information about the risks associated with both the medicinal product, and the condition for which it is being used, so that an informed choice can be made about the most appropriate treatment. The product information in the form of the Summary of Product Characteristics and Patient Information Leaflets is an important means of informing prescribers and patients about the risks associated with a particular medicine but additional materials may be needed. A short list of established media for such communication is given in the [Table I.3.A](#) (under Additional Educational Material), but the target audience, levels of detail required to achieve effective results and the most appropriate forms of words will all vary with circumstances. Whereas Marketing Authorisation Holders may produce educational material to inform and educate Healthcare Professionals and Patients, the requirement to do this will only be included as a condition of the marketing authorisation when it is deemed necessary for the safe and effective use of the medicinal product.

Because of the importance of risk communication it is recommended that appropriate experts are consulted.

3.11 The Marketing Authorisation

Restrictions and conditions within the marketing authorisation may be used as a risk minimisation activity [Table I.3.A](#). When a marketing authorisation is granted, it will include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which the medicinal product may be made available to patients. These conditions may also be modified when the marketing authorisation is amended in the post-authorisation phase. This is commonly referred to as the “legal status” of a medicinal product. It may also restrict where the medicine can be administered (e.g. to a hospital) or by whom it can be prescribed (e.g. specialist). For medicines only available upon prescription, additional conditions may be imposed by classifying

medicines into those available only upon either a restricted medical prescription or a special medical prescription.

The CHMP or national Competent Authorities may also make recommendations on conditions or restrictions with regard to the safe and effective use of the medicinal product. In the case of the CHMP, these conditions or restrictions will usually only affect the Decision addressed to the Marketing Authorisation Applicant. However, in certain circumstances, the Commission may also adopt a Decision addressed to the Member States.

3.12 Ensuring the Effectiveness of Risk Minimisation Activities

The definition of risk management requires assessment of the effectiveness of the interventions forming part of the process. It is clearly desirable that activities which may involve substantial investment of effort and resources should be shown to achieve the desired effects. In addition, as a public health measure it is imperative that alternative methods be adopted should a particular risk minimisation strategy prove ineffective. Assessment of effectiveness will also increase understanding of which activities are most appropriate in addressing specific types of safety concerns.

3.12.1 Assessment of Risk Minimisation

Direct measurement of risk minimisation should be employed whenever feasible. Surrogate measures should be considered when this is not feasible or to provide interim assessments whilst awaiting direct risk minimisation measurements. For example, for measures based on the provision of information to professionals, descriptive studies or surveys which assess whether the information is being effectively communicated might be appropriate. The use of medical databases might also allow direct measures of how uniformly such advice was being adhered to by reviewing, for example, concomitant medication or the results of laboratory tests. Since such studies are likely to be required with increasing frequency, the availability of such databases will be an ever more important factor in risk management. If the prescribing databases are further linked to patient clinical outcome, a study of the adequacy of the prescribing process could be designed to evolve over time into a full risk reduction study.

It is clear that, even when risks are of a type which can be directly measured, ethical and practical considerations may prevent prospective comparison. It may be scientifically difficult to make direct comparison between a situation with and without the intervention to be assessed and may not be achievable in timescales which allow the lessons learned to be used to improve risk management. In particular this will occur when risks associated with long-term exposure or very rare events are to be reduced. For products where a risk minimisation plan has been introduced after some time on the market a comparison with historical data can be made. Notwithstanding the above, Applicants/Marketing Authorisation Holders should investigate new methodologies for monitoring and assessment.

3.13 Summary of Activities in the EU-RMP

The EU-RMP should contain an overall summary of the activities detailed for the medicinal product. This should be in two parts:

- Summary of activities for each important safety concern;
- Summary of all activities and their milestones.

The relationship between activities and safety concerns may be clarified by a cross-tabulation of the two categories showing which safety concerns are addressed by each activity (see Annex 5.1.1).

Summary of activities for each safety concern:

This should be a simple table, listing each safety concern and summarising the activities (both pharmacovigilance and, where appropriate, risk minimisation) which will be taken. Where

appropriate, it should provide a cross-reference to the actions in the Pharmacovigilance Plan and the risk minimisation activities for the individual safety concern.

Summary of all activities and their milestones:

This section of the EU-RMP for the product should be organised in terms of the actions or activities to be undertaken and their milestones. The reason for this is that one proposed activity (e.g. a prospective safety cohort study) could address more than one of the safety concerns. Timelines and milestones should be included in the summary with a timetable for the submission of findings. In developing these milestones one should consider:

- when it will be possible to detect an adverse reaction with a pre-defined frequency at a pre-defined confidence level. This frequency should be chosen such as to reflect an acceptable level of risk for patients and public health; or
- when it will be possible to assess with sufficient precision the effect of risk factors associated with the occurrence of an adverse reaction;
- when the results of ongoing or proposed safety studies are expected to be available;
- the seriousness and magnitude of the risk for which risk minimisation activities are being proposed. Evaluation of the effectiveness of the activities will need to be carried out earlier and more frequently if the risk is very serious.

3.14 Submission of Updated EU-RMP Documents

As additional information on the safety of a medicinal product becomes available, the Safety Specification and other sections of the EU-RMP should be updated accordingly. For example, spontaneous reports, clinical trials and pharmacoepidemiological studies may all give rise to safety signals which need to be investigated or the results from a study could provide new information to update the Safety Specification. It may be that, based on the new information, it can be concluded that the safety concern has been resolved and that no further actions are needed beyond routine pharmacovigilance. In other cases, additional activities may be proposed and new milestones should be developed.

The update should include assessment of the effectiveness of the risk minimisation activities within the RMP.

At each update, consideration should be given as to whether new risk minimisation activities are needed. This may be because of a new safety concern or with an existing safety concern because the data suggests that the current strategy is not effective.

Updated EU-RMPs are only required for medicinal products where an EU-RMP (or similar document) has already been submitted under the conditions in [Chapter I.3, Section 4](#) or required under the terms of the marketing authorisation.

The updated EU-RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR) unless other requirements have been laid down as a condition of the marketing authorisation. In addition, an updated EU-RMP should be submitted:

- when new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities;
- within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached or the results of a study becoming available;
- at the request of the Competent Authority.

A cover letter should be submitted with the updated EU-RMP briefly summarising the changes from the previous EU-RMP.

Where no changes to any part of the EU-RMP have occurred since the last submission, a letter stating this, and the date of the last EU-RMP submission should be sent. In this circumstance it is not necessary to re-submit the EU-RMP with the letter.

Periodic Safety Update Reports

A summary of any amendments made to the EU-RMP, prior to the data lock point of the Periodic Safety Update Report (PSUR), should be included in the PSUR (see Addendum to ICH-E2C Clinical Safety Data Management. Periodic Safety Update Reports for Marketed Drugs, Section 2.8.3 (see Annex 4)).

TABLE I.3.A: METHODS FOR RISK MINIMISATION

Risk minimisation activities can be divided into those where a reduction in risk is achieved primarily through the provision of information and education and those which seek to control the use of the medicine. When it is obvious that a risk minimisation activity will be needed post authorisation, consideration should be given to piloting the activity during the development phase to see the effectiveness and suitability. When this is done, the outcome should be provided in the risk minimisation plan under the appropriate action.
1. Provision of Information
Provision of information to Healthcare Professionals and/or Patients on the specific risks of a product and the measures on how to reduce them is an essential activity of risk management. This provision of information may be confined to information contained within the Summary of Product Characteristics (SPC) and Package Leaflet (routine risk management) or may be through the use of additional educational material (additional risk management). The need for additional material beyond the Summary of Product Characteristics and Package Leaflet will depend upon the risk and should be considered on a case-by-case basis. Experts in risk communication should be consulted as appropriate.
1.1 Additional Educational Material
The need for additional educational material and the form in which it should be provided will depend upon the specific safety concern. The aim of a specialised educational programme for healthcare professionals and/or patients is to: • Enhance understanding of the specific risk(s); • Enhance understanding of measures to reduce either the frequency or severity of adverse reactions; • Enhance early detection and treatment (if applicable) of an adverse reaction; • Enhance patient information, awareness and provide information on the need and use of additional precautions. The educational programme may include but is not limited to the following materials: • Direct Healthcare Professional Communications; • Physician's Guide to Prescribing; • Pharmacist's Guide to Dispensing; • Checklists for assessing comprehension, knowledge, attitudes, and/or desired safety behaviours about the risk(s). These should be tailored to the target audience (e.g. physicians, pharmacists or patients); • Checklists for actions before prescribing or dispensing; • Patient Information Brochures; • Specific training programmes. The choice of media may also need to be considered (written, audio or video) as well as the use of drawing/symbols to improve understanding. For medicines where the target population may include a larger proportion of visually impaired patients, the use of Braille or audio media should be given special consideration. Pre-testing materials in the target audience(s) is highly desirable to help ensure good comprehension and acceptance of the communication method and contents. A variety of testing methods such as readability testing, focus groups or surveys could be used. Specific training programmes may be considered in certain circumstances. However, it is unlikely that prescription/dispensing of the medicine can be limited to people who have undertaken such a programme.

The above educational materials should be in strict compliance with the contents of the SPC and the Package Leaflet and must be agreed with the Competent Authority.

2. Legal Status of a Medicine

It is possible that controlling the conditions under which a medicine may be made available could reduce the risks associated with its use or misuse. This might be achieved by control of either who may be permitted to prescribe or dispense a medicine or by controlling who, or the conditions under which a patient, may receive a medicine.

When a marketing authorisation is granted, it must include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which the medicinal product may be made available to Patients. This is commonly referred to as the “legal status” of a medicinal product. Typically it includes information on whether or not the medicinal product is subject to medical prescription. It may also restrict where the medicine can be administered (e.g. to a hospital) or by whom it can be prescribed (e.g. specialist).

For medicines only available upon prescription, additional conditions may be imposed by classifying medicines into those available only upon either a restricted medical prescription or a special medical prescription. When considering classification as subject to restricted medical prescription the following factors shall be taken into account:

- the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment;
- the medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere; or
- the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring prescription drawn up as required by a specialist and special supervision throughout the treatment.

In the case of an application for a marketing authorisation submitted in accordance with the Centralised procedure, the CHMP is responsible for recommending the legal status to the Commission. Although the use of legal status is not an activity that can be used directly by an Applicant for the purposes of risk reduction, the Applicant could request the Competent Authority to consider a particular legal status.

However, the definition of what constitutes a specialist is not uniform throughout the Member States so, in practice the provisions of the last indent are usually phrased in section 4.2 of the Summary of Product Characteristics as: “treatment by a physician experienced in the treatment of <the disease>”. Although restriction to use in a hospital environment may in practice ensure that the medicine is always prescribed by a specialist, this needs to be balanced against the inconvenience to patients if they need to attend a hospital for every prescription. Care also needs to be taken when considering where a medicine can be safely administered. For example the term “clinic” has different connotations depending upon the country. For this reason, the type of equipment needed may be specified rather than a location, e.g. “use in a setting where resuscitation equipment is available.”

For classification as subject to special medical prescription the following factors should be taken into account:

- the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971; or

- the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes; or - the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the previous indent as a precautionary measure. There is possibility of implementing further sub-categories at Member State level which permits the Member States to tailor the broad classifications described above to their national situation. The definitions and therefore also the implementation varies in those Member States where the sub-categories exist.
3. Control at Pharmacy Level The control of dispensing is another potential activity for risk management. Pharmacists who are well informed about the risks of a medicine can help educate the Patient and provide an additional level of protection.
4. Control of Prescription Size or Validity Limiting the validity of a prescription is another activity for risk management in the situation where decision to prescribe depends upon the result of a test which is only valid for a specific time. In some Member States it is possible to limit the validity of a prescription but not in others. Limiting the number of units prescribed is another risk minimisation activity. This can be useful if regular testing or review is needed. By limiting the number of units, the patient will need to see a Healthcare Professional at defined intervals increasing the opportunity for testing and reducing the length of time a patient is without review. If this strategy is adopted, it is a pre-requisite that the appropriate pack size is available and that supply issues are addressed. In extreme cases, making units available in only one pack size to try to link prescribing to the need for review may be considered. A small pack size can also be useful, especially if overdose is thought to be a major risk or if the potential for drugs to get into the general population needs to be controlled.
5. Informed Consent and other Patient Aspects In a clinical trial, patients are given information about the possible benefits and risks of the trial medication and any procedures associated with the trial. The Patient signs a form to say that they have been given the information, they understand it and agree to take part in the trial. This is known as informed consent. It has potential as a risk management activity to ensure that patients have been provided with appropriate information regarding the risks of the medicine and appropriate measures to reduce the risks. Use of informed consent outside the clinical trial area may not be possible in some Member States.
6. Restricted Access Programmes In high-risk situations, it may be necessary to restrict access to a medicinal product to those patients who agree to take part in a specific surveillance programme.

7. Patient Registries

Patient registries are often suggested as a means of risk management. They have been used (sometimes very successfully) in individual countries to record the results of tests, to ensure that the recommended conditions of use are being adhered to, and control access to a medicine. However, there are possible issues about who controls the registry and the confidentiality of medical data.

Whereas patient registries could be a very useful activity for pharmacovigilance studies to characterise risks, use as a means of controlling access is not currently possible in some Member States. It is strongly suggested that if a Marketing Authorisation Holder is contemplating the use of a patient registry, this should be discussed with the appropriate regulatory authority at a very early stage.

4. Requirements for Expedited Reporting of Individual Case Safety Reports

4.1 Introduction

The obligations of the Marketing Authorisation Holder for recording and reporting suspected adverse reactions associated with a medicinal product for which marketing authorisations are held are defined in Directive 2001/83/EC and Regulation (EC) No 726/2004. For suspected adverse reactions requiring expedited reporting, further explanation is provided in this Chapter. Reporting requirements in special situations, including obligations of the Applicant during the period between submission of the Marketing Authorisation application and granting of the Marketing Authorisation, are described in Chapter I.5.

For authorised medicinal products, independent of the authorisation procedure, adverse reactions received from Healthcare Professionals, either spontaneously or through post-authorisation studies, should be reported, regardless of whether or not the medicinal product was used in accordance with the authorised Summary of Product Characteristics (SPC) and/or any other conditions laid down for marketing of the product in accordance with applicable legal requirements. Adverse reactions identified from the worldwide-published scientific literature should also be reported. Electronic reporting of adverse reactions is mandatory, save in exceptional circumstances (see Chapter III.4).

The definitions of ‘suspected adverse reaction’, ‘serious adverse reaction’ and ‘expected/unexpected adverse reaction’ are provided in the Glossary (see Annex 1.1). In the context of pharmacovigilance, the term adverse reaction is considered as synonymous with suspected adverse reaction and adverse drug reaction.

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction and therefore should be reported in expedited manner (see Chapter I.5, Section 9). In addition, such cases should be considered for reporting as product defects if appropriate (see Compilation of Community Procedures on Inspections and Exchange of Information¹⁶).

When a Marketing Authorisation Holder receives an Individual Case Safety Report (ICSR) where the invented name of the medicinal product is not specified but the active substance is included in any of the medicinal products for which a marketing authorisation is held, the Marketing Authorisation Holder should assume that the report may relate to their product.

Spontaneous reports of adverse reactions received from Healthcare Professionals should be reported by the Marketing Authorisation Holder if:

- the Healthcare Professional has made a statement that a causal relationship between the event and the medicinal product is considered to be at least a reasonable possibility; or if
- the Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown; or if
- the Marketing Authorisation Holder considers that a causal relationship is at least a reasonable possibility.

If the Healthcare Professional has made an explicit statement that a causal relationship between the medicinal product and reaction has been excluded and the Marketing Authorisation Holder agrees with this, the event should not be reported.

When the Marketing Authorisation Holder is aware that a Healthcare Professional may have reported a reaction to one of their products directly to the Competent Authority of a Member State, the Marketing Authorisation Holder should still report the reaction, informing the Competent Authority that the

¹⁶ Doc.Ref. EMEA/INS/GMP/3351/03 latest version, available on EMEA website <http://www.emea.europa.eu>.

report may be a duplicate of a previous report. In this situation, it is essential for the Marketing Authorisation Holder to provide all the available details including all case identification numbers allocated to the case, in order to aid identification of the duplicate case. For further guidance on reporting of potential duplicates, refer to Section A.1.11 “Other case identifiers in previous transmission” of ICH-E2B(M) (see Annex 4).

The Marketing Authorisation Holder is expected to validate all adverse reactions reported by Healthcare Professionals to ensure, prior to reporting to the Competent Authorities, that the minimum information required is included in the report:

- An identifiable Healthcare Professional reporter (see Section A.2 “Primary source(s) of information” of ICH-E2B(M) (see Annex 4);
 - The reporter may be identified by name or initials, address or qualification (e.g. physician, dentist, pharmacist, nurse), taking into account EU legislation on data protection (Directive 95/46/EC, Regulation (EC) No 45/2001) and relevant national legislation (see also Chapter III.5, Section 4). Contact details for a Healthcare Professional should be available for the reporter to be considered as identifiable.
- An identifiable Patient (see Section B.1 “Patient characteristics” of ICH-E2B(M) (see Annex 4);
 - The Patient may be identified by initials, patient number, date of birth, age, age group or sex. The information should be as complete as possible, taking into account EU legislation on data protection (Directive 95/46/EC, Regulation (EC) No 45/2001) and relevant national legislation (see also Chapter III.5, Section 4).
- At least one suspected active substance/medicinal product (see Section B.4 “Drug(s) information” of ICH-E2B(M) (see Annex 4);
- At least one suspected adverse reaction (see Section B.2 “Reactions(s)/event(s)” of ICH-E2B(M) (see Annex 4).

For adverse reaction reports relating to biological products, the definite identification of the product with regard to its manufacturing is of particular importance. Therefore, Marketing Authorisation Holders should give advice to reporters to provide the name of the medicinal product (in accordance with Article 1(20) of Directive 2001/83/EC, see Annex 1.3) and the batch number and should follow-up the reports where this information is missing for completion.

Reports should be followed-up to obtain additional information relevant to the case as necessary, and relevant follow-up information should be reported to the Competent Authorities (see Chapter III.5, Section 3). All available clinical information relevant to the evaluation of the adverse reaction should be provided (see Chapter III.5, Section 1).

For reports on adverse reactions from Patients/Consumers, see Chapter I.4, Section 3.5.

If ICSRs, which do not qualify for expedited reporting as outlined in this Chapter, provide information that may lead to a change in the known risk-benefit balance for the product, this possible change should be notified to the Competent Authorities without delay.

4.2 Reporting Time Frames

The Marketing Authorisation Holder should transmit all ICSRs requiring expedited reporting promptly and no later than 15 calendar days from receipt. This applies to initial and follow-up information.

The date the Marketing Authorisation Holder becomes aware of a case which fulfils the minimum information (see Chapter I.4, Section 1) should be considered day 0. The same applies if new information on the case is received by the Marketing Authorisation Holder, i.e. the reporting time clock begins again for the submission of the follow-up report from the day the Marketing Authorisation Holder receives relevant follow-up information (see also Chapter III.5, Section 3).

The clock for expedited reporting starts (day 0) as soon as the minimum information (see Chapter I.4, Section 1), has been brought to the attention of any personnel of the Marketing Authorisation Holder or an organisation having a contractual arrangement with the Marketing Authorisation Holder, including medical representatives.

For individual cases described in the worldwide scientific literature, the clock starts (day 0) with awareness of a publication containing the minimum information (see Chapter I.4, Section 1) by any personnel of the Marketing Authorisation Holder or an organisation having a contractual arrangement with the Marketing Authorisation Holder, including medical representatives. For further guidance see Chapter III.7.

Contractual arrangements may be made with a person or organisation to perform literature searches and/or report relevant individual cases to Competent Authorities. If another person or organisation is performing these tasks, explicit procedures and detailed agreements should exist between the Marketing Authorisation Holder and this person or organisation to ensure that the Marketing Authorisation Holder is promptly made aware of any individual cases described in the worldwide scientific literature to ensure that the Marketing Authorisation Holder can comply with their reporting obligations.

In general, where the Marketing Authorisation Holder has set up contractual arrangements with a person or organisation for e.g. the marketing of, or research on a medicinal product authorised to this Marketing Authorisation Holder, the clock starts as soon as any personnel of the Marketing Authorisation Holder or the other person/organisation receives the minimum information that constitutes a reportable case. Explicit procedures and detailed agreements should exist between the Marketing Authorisation Holder and the person/organisation to ensure that the Marketing Authorisation Holder can comply with his reporting obligations (see Chapter I.1).

4.3 Requirements by Reporting Source

4.3.1 Spontaneous Reports from Healthcare Professionals

a) Individual Case Safety Reports on adverse reactions occurring within the EU

For all medicinal products, independently of the authorisation procedure, the Marketing Authorisation Holder should report, on an expedited basis, all serious adverse reactions occurring within the EU, and brought to their attention by a Healthcare Professional, to the Competent Authority of the Member State on whose territory the incident occurred.

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction and therefore should be reported in expedited manner (see Chapter I.5).

For medicinal products authorised through the mutual recognition or decentralised procedures and for medicinal products which have been the subject of a referral procedure, the Marketing Authorisation Holder is responsible for ensuring that all serious adverse reactions received from Healthcare Professionals or Competent Authorities within the EU are reported to the Reference Member State. To avoid duplicate reporting, the Reference Member State/Rapporteur Member State should not re-transmit these ICSRs to EudraVigilance if they did not occur within its territory (see Chapter II.3).

Non-serious adverse reactions occurring within the EU should only be reported in an expedited manner on request and otherwise in accordance with Chapter I.6 on Periodic Safety Update Reports. For centrally authorised products and periodic transmission of such cases into EudraVigilance see Chapter III.11, Section 7.

For an overview on the expedited reporting requirements in Member States, see Annexes 6.1.1 and 6.1.2.

b) Individual Case Safety Reports on adverse reactions occurring outside the EU

For all medicinal products, independent of the authorisation procedure, the Marketing Authorisation Holder should report on an expedited basis, all unexpected serious adverse reactions and any suspected transmission via a medicinal product of an infectious agent occurring in the territory of a non-EU country, and initially reported (or confirmed) by a Healthcare Professional, to the Agency and to all Member States where the medicinal product is authorised.

Serious unexpected adverse reactions and any suspected transmission via a medicinal product of an infectious agent initially reported by a Healthcare Professional and subsequently transmitted by a regulatory authority outside the EU to the Marketing Authorisation Holder are also subject to expedited reporting to the Competent Authorities of the EU by the Marketing Authorisation Holder.

Although not a legal requirement, Marketing Authorisation Holders are encouraged to also report all expected serious adverse reactions occurring outside the EU on an expedited basis to the Agency, provided that reporting takes place electronically in accordance with ICH-E2B(M) (see Chapter III.11, Section 3).

Non-serious adverse reactions occurring outside the EU should only be reported in expedited manner on request and otherwise in accordance with Chapter I.6 on Periodic Safety Update Reports.

For reporting of non-serious adverse reactions with centrally authorised products and periodic transmission of reports occurring outside the EU to EudraVigilance, see Chapter III.11, Section 7.

For an overview on the expedited reporting requirements in Member States, see Annex 6.1.3.

Expedited Reporting Requirements (shaded in grey: reporting encouraged but not a legal requirement)

Marketing Authorisation Type	Origin	Adverse Reaction Type	Destination	Time line
Centralised	EU	All serious adverse reactions, including any suspected transmission via a medicinal product of an infectious agent	To Member State where adverse reaction occurred	15 days
Mutual recognition or decentralised, or subject to referral	EU	All serious adverse reactions, including any suspected transmission via a medicinal product of an infectious agent	To Member State where adverse reaction occurred and to Reference/Rapporteur Member State ¹⁷	15 days
Purely national	EU	All serious adverse reactions, including any suspected transmission via a medicinal product of an infectious agent	To Member State where adverse reaction occurred	15 days
Centralised	Non-EU	All serious unexpected adverse reactions and any suspected transmission via a medicinal product of an infectious agent	To all Member States and to Agency	15 days
Centralised	Non-EU	All serious adverse reactions and any suspected transmission via a medicinal product of an infectious agent	To the Agency	15 days
National, including mutual recognition, decentralised, or subject to referral	Non-EU	All serious unexpected adverse reactions and any suspected transmission via a medicinal product of an infectious agent	To all Member States where product is authorised and to the Agency	15 days
National, including mutual recognition, decentralised, or subject to referral	Non-EU	All serious adverse reactions and any suspected transmission via a medicinal product of an infectious agent	To the Agency	15 days

4.3.2 Reports Published in the Worldwide Literature

Individual case reports from the worldwide literature in accordance with the provisions of **Chapter I.4, Section 1** are considered to be reports of which the Marketing Authorisation Holder can reasonably be expected to be aware and have knowledge of.

The Marketing Authorisation Holder is therefore expected to maintain awareness of possible publications by accessing a widely used systematic literature review and reference database (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week. In addition, company

¹⁷ To avoid duplicate reporting, the Reference/Rapporteur Member State should not forward the adverse reaction to EudraVigilance if the adverse reaction did not occur within its territory. The adverse reaction should be reported by the Member State in whose territory the adverse reaction occurred.

offices in each Member State are required to be aware of publications in their local journals and bring them to the attention of the QPPV as appropriate.

Cases of adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed to identify individual cases which might qualify for expedited reporting.

As required by legislation, the Marketing Authorisation Holder should report within 15 days published serious adverse reactions associated with the use of the active substance(s) of their medicinal products, as relevant to the categories identified in **Chapter I.4, Section 3.1**. The procedure for handling of adverse reaction reports published in the worldwide literature is described in **Chapter III.7**.

If the medicinal product source and/or the invented name is not specified and ownership of the product cannot be excluded on the basis of the active substance(s), formulation or route of administration, the Marketing Authorisation Holder should assume that it is one of their products the publication refers to, although the report should indicate that the specific product source and/or the invented name was not identified.

If multiple medicinal products are mentioned in the publication, a report should be submitted only by the Marketing Authorisation Holder(s) of the product(s) which is (are) identified by the publication's author(s) as having at least a possible causal associated with the reaction.

4.3.3 Information on Adverse Reactions from the Internet

The Marketing Authorisation Holder should regularly screen websites under their management or responsibility, for potential reports on adverse reactions. The Marketing Authorisation Holder is not expected to screen external websites for information on adverse reactions. However, if a Marketing Authorisation Holder becomes aware of an adverse reaction on any other website the Marketing Authorisation Holder should review the case and determine whether it should be reported in expedited manner in accordance with **Chapter I.4, Sections 3.1 and 3.5**.

The Marketing Authorisation Holder should consider utilising their websites to facilitate adverse reaction collection, e.g. by providing adverse reaction forms for reporting or by providing appropriate contact details for direct communication. In relation to such reported adverse reactions, identifiability of the reporter and Patient refers to the existence of actual people (see **Chapter I.4, Section 3.1**)

4.3.4 Reports from Organised Data Collection Systems

Reporting requirements for cases derived from organised data collection systems (which include clinical trials, post-authorisation studies, registries, post-authorisation named-patient use programmes, other patient support and disease management programmes, surveys of Patients or Healthcare Providers, and information gathering on efficacy or patient compliance) differ depending on whether they are derived from interventional or non-interventional studies.

a) Interventional Studies

Interventional studies fall under the provisions of Directive 2001/20/EC on clinical trials and adverse reactions should be reported in line with that Directive and associated guidance, in particular the Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use (**ENTR/CT3, Volume 10 of The Rules Governing Medicinal Products in the EU, Chapter II¹⁸**), which includes guidance on unblinding, and the Detailed Guidance on the European Database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module) (**ENTR/CT4, Volume 10 of The Rules Governing**

¹⁸ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

Medicinal Products in the EU, Chapter II). For reporting of adverse reactions in the Periodic Safety Update Reports (PSURs), see Chapter I.6.

b) Non-interventional Studies

Post-authorisation studies that are non-interventional are not covered by the provisions of Directive 2001/20/EC but by Directive 2001/83/EC and Regulation (EC) No. 726/2004 (see Annex 1.1 for the definition of a non-interventional trial). Serious adverse reactions arising from such studies should be reported on an expedited basis according to the same criteria and timelines as adverse reactions reported spontaneously by Healthcare Professionals (see Chapter I.4, Section 1); this includes any suspected transmission via a medicinal product of an infectious agent. For an overview on the expedited reporting requirements in Member States, see Annexes 6.1.1, 6.1.2 and 6.1.3. All adverse reactions, i.e. also non-serious ones, should be included in the final study report. For reporting of adverse reactions in the Periodic Safety Update Reports (PSURs), see Chapter I.6. For further information on post-authorisation safety studies see Chapter I.7.

4.3.5 Reports from Patients and Other Consumers

When information is received directly from a Patient /Consumer suggesting that an adverse reaction may have occurred, the Marketing Authorisation Holder should attempt to obtain the Patient's consent to contact the Healthcare Professional involved for further information. When such a report has been confirmed by the Healthcare Professional, it should be documented as a spontaneous report from a Healthcare Professional and reported according to Chapter I.4, Sections 1 and 3.1. When a Consumer submits medical documentation that supports the occurrence of the adverse reaction, this should be considered sufficient to report the individual case if it provides the minimum information (see Chapter I.4, Section 1). For requirements to reflect Consumer reports in Periodic Safety Update Reports see Chapter I.6, Section 3.7.

For requirements in relation to reporting of outcomes of use of medicinal products during pregnancy, originating from Consumers, see Chapter I.5, Section 4.

Member States may have additional requirements in place with regard to reports from Consumers, which need to be followed by the Marketing Authorisation Holder (see Annexes 6.1.1, 6.1.2 and 6.1.3). Medically unconfirmed adverse reactions should not be reported to the Agency/EudraVigilance on expedited basis.

4.3.6 Reports from Other Non-Medical Sources

If a Marketing Authorisation Holder becomes aware of a case report from non-medical sources other than those mentioned in Chapter I.4, Section 3.5, e.g. the lay press or other media, every attempt should be made to obtain the minimum information that constitutes an individual case (see Chapter I.4, Section 1) and to follow-up the case as for reports from a Patient/Consumer (see Chapter I.4, Section 3.5).

4.4 Data Elements for the Report

The principles in the ICH-E2D Guideline and ICH-E2B(M) Guideline (see Annex 4) should be followed. Detailed aspects related to the preparation of ICSRs and the applicable data elements are defined in Part III.

For the minimum information constituting a case and for the standards relating to the electronic transmission of an ICSR, see Chapter I.4, Section 1 and Chapter III.2.

It is essential for the Marketing Authorisation Holder to provide as many data elements as possible for cases of adverse reactions to facilitate assessment (see Chapter III.5, Sections 1 and 2). The Marketing

Authorisation Holder is expected to follow-up all reports of serious adverse reactions to their medicinal product(s) to obtain comprehensive information where available. Additional information not available at the time of the initial report should be provided in the form of follow-up reports (see Chapter I.4, Section 1 and Chapter III.5, Section 3).

The suspect, interacting and/or concomitant active substance(s)/invented name of the suspect product(s) should be reported in accordance with ICH-E2B(M) (see Annex 4) and as outlined in Chapter III.5, Section 1. The Marketing Authorisation Holder should report ICSRs to the Competent Authorities of Member States and EudraVigilance in English (see also Chapter III.11, Section 5). In addition to the English summary, the original verbatim in the local language may be maintained in the field B.5.1 “Case narrative including clinical course, therapeutic measures, outcome and additional relevant information” of ICH-E2B(M), if considered necessary.

The Marketing Authorisation Holder may comment on the causal relationship between the suspect product(s) and the reaction(s) reported and should provide the criteria on which he has made the assessment in field B.4.k.18 “Relatedness of drug to reaction(s)/event(s)” of ICH-E2B(M).

In situations where ICSRs impact on the known risk-benefit balance of a medicinal product, the Marketing Authorisation Holder should indicate in a separate letter to the Competent Authorities and, if applicable, to the Agency what action is proposed in relation to the marketing authorisation, the Summary of Product Characteristics and Patient Information Leaflet. This should in addition be recorded in field B.5.4 “Sender’s comments” of ICH-E2B(M).

4.5 Method of Reporting

Electronic reporting of adverse reactions is mandatory, save in exceptional circumstances. The requirements for electronic transmission of ICSRs to be followed are explained in accordance with Part III.

5. Requirements for Reporting in Special Situations

5.1 Introduction

Adverse reactions should be reported according to the requirements outlined in Chapter I.4, regardless of whether or not the medicinal product was used in accordance with the authorised Summary of Product Characteristics (SPC) and/or any other conditions laid down for the marketing of the product.

In addition to routine expedited and periodic reporting requirements as laid out in Chapters I.4 and I.6, the Marketing Authorisation Holder should be aware of the following additional reporting requirements relating to worldwide experience with the medicinal product:

- Reporting in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation;
- Reporting following suspension or withdrawal of the marketing authorisation for safety of commercial reasons;
- Reporting of outcomes of use of a medicinal product during pregnancy;
- Reporting of adverse reactions during breastfeeding;
- Reporting of data on use of medicinal products in children;
- Reporting from compassionate/named-patient use;
- Reporting of lack of efficacy;
- Reporting of suspected transmission of infectious agents;
- Reporting in relation to overdose, abuse and misuse;
- Reporting of medication errors;
- Reporting in the event of a public health emergency.

5.2 Reporting in the Period between the Submission of the Marketing Authorisation Application and the Granting of the Marketing Authorisation

In the period between submission of the marketing authorisation application and the authorisation, information that could impact on the risk-benefit balance may become available to the Applicant (see also Chapter I, Section 5.1.1 of Volume 2A (Notice to Applicants) of The Rules Governing Medicinal Products in the European Union¹⁹). It is the responsibility of the Applicant to ensure that this information is immediately submitted to the Competent Authorities of the Member States where the application is under assessment (including Reference Member State and all Concerned Member States for products assessed under the mutual recognition or decentralised procedures). For centralised applications, information should also be provided to the Agency, the Rapporteur and Co-Rapporteur (see Chapter II.3, Section 4.1 and Chapter II.2.A).

5.3 Reporting Following Suspension or Withdrawal of the Marketing Authorisation for Safety or Commercial Reasons

Reporting requirements remain following suspension of the marketing authorisation of a medicinal product (see Chapters I.4 and I.6). Where a marketing authorisation is withdrawn or revoked, the former Marketing Authorisation Holder is encouraged to continue to report in line with Chapter I.4 to e.g. facilitate review of delayed onset adverse reactions and retrospectively notified cases. It may be appropriate to continue submission of PSURs after withdrawal or revocation of the marketing authorisation. An agreement should be made on a case-by-case basis with the Competent Authorities and, where applicable, the Agency.

¹⁹ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

5.4 Reporting of Outcomes of Use of a Medicinal Product During Pregnancy

The Marketing Authorisation Holder should follow-up all reports from Healthcare Professionals relating to pregnancies where the foetus may have been exposed to one of his medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure). Where reports originate from Consumers, reasonable attempts should be made to follow-up via the Patient's Healthcare Professional. When a Consumer submits medical documentation that supports the occurrence of a suspected adverse reaction, this should be considered sufficient to report the case if it provides the minimum information (see Chapter I.4, Section 1).

When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering the possibility of foetal exposure (i.e. medicinal products taken before conception need to be considered) (see Annex 3.1.3).

Individual cases with an abnormal outcome in association with a medicinal product should be reported on an expedited basis, following the reporting requirements outlined in Chapter I.4 and in accordance with the Guideline on Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data (see Annex 3.1.3.) and the ICH-E2B(M) Guidelines (see Annex 4).

This refers especially to:

- Reports of congenital anomalies in the foetus/child;
- Reports of foetal death and spontaneous abortion; and
- Reports of adverse reactions in the neonate that are classified as serious.

Other cases, i.e. reports of termination of pregnancy without information on congenital malformation and reports of pregnancy exposure without outcome data, should not normally be reported on an expedited basis.

In certain circumstances, the Marketing Authorisation Holder may be requested to treat any reports of pregnancy exposure as cases requiring expedited reporting, e.g. pregnancy exposure to products contraindicated in pregnancy because of a high teratogenic potential.

Information on exposure to medicinal products during pregnancy should include dates of exposure and, as far as possible, details of the period of gestation at the time of exposure, specified by the method of assessment and expressed as weeks and/or days. This information is necessary to establish a possible causal relationship between the adverse event(s) reported and exposure to the product.

It is also important to collect information on pregnancies, which have a normal outcome. Not infrequently, pregnant women or Healthcare Professionals will contact either the Marketing Authorisation Holder or Competent Authorities requesting information on the teratogenic potential of a medicinal product and/or experience of use during pregnancy (see Annex 3.1.3).

Expedited reports together with other reports on outcome of exposure during pregnancy should also be included in the Periodic Safety Update Report (PSUR) (see Chapter I.6) together with aggregated data on the overall exposure and details of normal/abnormal outcomes. Reports from prospective registries should also be included and evaluated in the PSUR.

If, at any time, the Marketing Authorisation Holder identifies, or becomes aware of, a signal of a possible teratogenic effect (e.g. through a cluster of similar abnormal outcomes) all Competent Authorities where a marketing authorisation is held, and also the Agency in the case of centrally authorised medicinal products, should be informed on an expedited basis. This also applies to possible signals arising from Consumer reports for which medical confirmation has not (yet) been obtained.

5.5 Reporting of Adverse Reactions during Breastfeeding

Adverse reactions suspected in infants following exposure to a medicinal product from breastfeeding, should be reported in accordance with [Chapter I.4](#).

5.6 Reporting of Data on Use of Medicinal Products in Children

Collection and evaluation of data on exposure of children to medicinal products and associated risks is an important task and specific guidance is therefore included in the [Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population \(see Annex 3.1.4\)](#). Exposure of children should also be considered and addressed in the Risk Management Plan ([see Chapter I.3](#)).

5.7 Reporting from Compassionate/Named-Patient Use

Compassionate or named-patient use of a medicine should be strictly controlled by the company responsible for providing the medicine and should ideally be the subject of a protocol.

Such a protocol should ensure that the Patient is registered and adequately informed about the nature of the medicine and that both the prescriber and the Patient are provided with the available information on the properties of the medicine with the aim of maximising the likelihood of safe use. The protocol should encourage the prescriber to report any adverse reactions to the company, and to the Competent Authority, where required nationally.

Companies should continuously monitor the risk-benefit balance of medicines used on compassionate or named-patient basis (subject to protocol or not) and follow the requirements for reporting to the appropriate Competent Authorities. As a minimum, the requirements laid down in [Chapter I.4, Section 1](#) apply.

For inclusion of experience from compassionate or named-patient use in Periodic Safety Update Reports, [see Chapter I.6](#).

5.8 Reporting of Lack of Efficacy

Reports of lack of efficacy should not normally be reported on expedited basis, but should be discussed in the relevant Periodic Safety Update Report ([see Chapter I.6](#)). However, in certain circumstances reports of lack of efficacy should be treated as expedited cases for reporting purposes. Medicinal products used for the treatment of life-threatening diseases, vaccines and contraceptives are examples of classes of medicinal products where lack of efficacy should be considered as cases requiring expedited reporting. Judgement should be used in reporting, considering if other cases qualify for reporting.

For example, antibiotics used in life-threatening situations where the medicinal product was not in fact appropriate for the infective agent should not be reported. However, a life-threatening infection where the lack of efficacy seems to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible should be reported on an expedited basis

For vaccines, cases of lack of efficacy should be reported, in particular with a view to possible signals of reduced immunogenicity in a sub-group of vaccinees, waning immunity and strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of efficacy as suspected by a healthcare professional may constitute a signal of strain replacement. Such signals may need prompt action and further investigation through post-authorisation safety studies as appropriate. Internationally agreed case definitions should be used as available.

5.9 Reporting of Suspected Transmission of Infectious Agents

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product is also considered a serious adverse reaction and all such cases should be reported in expedited manner in accordance with the criteria outlined in [Chapter I.4](#), whether they occur within or outside the EU.

For cases occurring outside the EU, the legislation includes this reporting requirement specifically to ensure that such cases are appropriately reported and to avoid failure to report due to interpretation of such cases as expected (e.g. given the manufacturing process). For cases occurring within the EU, the legal requirement to report any such transmission in expedited manner is addressed by the reporting requirements for all (i.e. expected and unexpected) serious adverse reactions as [Chapter I.4](#).

For electronic reporting, such cases should to be classified as serious in field A.1.5.1, and field A.1.5.2. “Seriousness criteria” should be set to “Other medically important condition (see ICH-E2B(M) in Annex 4).

The requirement to apply MedDRA coding ([see Annex 4](#)) is also relevant to the reporting of cases of suspected transmission of an infectious agent.

Because any suspected transmission of an infectious agent via a medicinal product is considered a serious adverse reaction, it should be assessed under the category of medically important in the absence of other seriousness criteria.

Any organism, virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

A transmission of an infectious agent may be suspected from clinical signs or symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. As in the case of suspected adverse reactions and adverse reactions, the terms suspected transmission and transmission are considered synonymous.

Emphasis should be on the detection of infections/infectious agents known to be potentially transmitted via a medicinal product, but the occurrence of unknown agents should never be excluded. In the context of evaluating suspected transmission of an infectious agent via a medicinal product, care will have to be taken to discriminate, whenever possible, between

- adverse reactions caused by a product manufactured as specified;
- adverse reactions caused by a product with confirmed contamination;
- adverse reactions caused by a medication error, including distribution, storage, prescribing and administration error;
- adverse reactions caused by a product designed in a way that it may insufficiently prevent medication errors or contamination during administration;
- adverse reactions caused by the injection of a product, e.g. injection-site reactions;
- adverse reactions caused by a product in an immunosuppressed patient/vaccinee;
- adverse reactions caused by a product in close contacts of the patient/vaccinee.

MedDRA coding also applies in this context.

Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned medicinal product increases the evidence for transmission of an infectious agent.

The requirement to report the suspected transmission of an infectious agent via a medicinal product also applies to vaccines, including live attenuated vaccines. For the latter, e.g. shedding, transmission of the attenuated agent to close contacts and reversion to virulence may cause harm to vaccinees

and/or their close contacts. Pregnant women and the foetus might be at particular risk. Furthermore, as with other biological medicinal products, certain batches of a vaccine may be contaminated and cause adverse reactions in vaccinees.

Signals arising from case reports on suspected transmission of an infectious agent should be investigated as for other adverse reactions.

Where a quality defect is suspected or confirmed, the procedures laid down in the [Compilation of Community Procedures on Inspections and Exchange of Information](#)²⁰ should also be followed. Any contamination of a medicinal product should be considered serious and is likely to be classified as a Class 1 or Class 2 Product Defect.

The potential for transmission of an infectious agent via a medicinal product should also be addressed in the Risk Management Plan (see [Chapter I.3](#)).

In the case of medicinal products derived from human blood or human plasma, haemovigilance procedures also apply, in accordance with [Directive 2002/98/EC](#).

Medicinal products should also comply with the [Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Products](#)²¹.

5.10 Reporting in Relation to Overdose, Abuse and Misuse

The Marketing Authorisation Holder should collect any available information on overdose, abuse and misuse related to his products. Reports of overdose, abuse and misuse should be routinely followed up to ensure that information is as complete as possible with regard to early symptoms, treatment and outcome. The Marketing Authorisation Holder should report cases of overdose, abuse and misuse that lead to serious adverse reactions on an expedited basis in accordance with the requirements in [Chapter I.4](#). This includes cases of intended suicide. The Marketing Authorisation Holder should continuously monitor and evaluate the potential impact of overdose, abuse and misuse on the overall risk-benefit balance of the medicinal product. The potential for overdose, abuse and misuse and the associated risks should also be addressed in the Periodic Safety Update Reports (see [Chapter I.6](#)) and the Risk Management Plan (see [Chapter I.3](#)).

5.11 Reporting of Medication Errors

The Marketing Authorisation Holder should report cases of medication errors that are associated with serious adverse reactions on an expedited basis in accordance with the requirements in [Chapter I.4](#), and as required by national requirements. Cases not associated with adverse reactions and near misses should only be reported in accordance with national requirements. Cumulative information on medication errors, resulting in adverse reaction or not, should be discussed in the section of the Periodic Safety Update Report on the overall safety evaluation (see [Chapter I.6](#)). The potential for medication errors and their prevention should be addressed in the Risk Management Plan (see [Chapter I.3](#)).

For reporting of medication errors due to confusion of invented names in relation to centrally authorised products, see the [Guideline on the Acceptability of Invented Names for Human Medicinal Products Processed through the Centralised Procedure](#)²².

²⁰ Doc.Ref. EMEA/INS/GMP/3351/03 latest version, available on EMEA website <http://www.emea.europa.eu>.

²¹ Doc.Ref. EMEA/410/01 latest version, available on EMEA website <http://www.emea.europa.eu>.

²² Doc.Ref. EMEA/CPMP/328/98, latest version available on EMEA website <http://www.emea.europa.eu>.

5.12 Reporting in the Event of a Public Health Emergency

A public health emergency is a public health threat duly recognised either by the World Health Organization (WHO) or the Community in the framework of Decision No. 2119/98/EC of the European Parliament and of the Council. In the event of a public health emergency, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and appropriately notified.

For anti-influenza products used in a pandemic, the following documents are available on the EMEA website <http://www.emea.europa.eu>:

- EMEA Pandemic Influenza Crisis Management Plan for the Evaluation and Maintenance of Pandemic Influenza Vaccines and Antivirals (EMEA/214301/2006, latest version);
- Guideline on Influenza Vaccines Prepared from Viruses with the Potential to Cause a Pandemic and Intended for Use Outside of the Core Dossier Context (EMEA/CHMP/VWP/263499/2006, latest version);
- CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/32706/2007, latest version).

6. Requirements for Periodic Safety Update Reports

6.1 Introduction

A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a medicinal product to Competent Authorities at defined time points post-authorisation. At these times, Marketing Authorisation Holders are expected to provide succinct summary information together with a critical evaluation of the risk-benefit balance of the product in the light of new or changing information. This evaluation should ascertain whether further investigations need to be carried out and whether changes should be made to the marketing authorisation and product information.

Regulation (EC) No 726/2004 and Directive 2001/83/EC establish the periodicity for submission of PSURs, unless other requirements are laid down as a condition for the granting of the marketing authorisation. This Chapter is consistent with ICH-E2C and the Addendum to ICH-E2C (now ICH-E2C(R), [see Annex 4](#)).

It should be noted that electronic periodic submission of Individual Case Safety Reports (ICSRs) for centrally authorised products, described in [Chapter III.11, Section 7](#), is a process that is independent of PSUR submission.

Once a medicinal product is authorised in the EU, even if it is not marketed, the Marketing Authorisation Holder is required to submit PSURs at 6-monthly intervals. When launch dates are planned, this information should be reflected in the upcoming PSUR.

Once marketed, 6-monthly PSUR submissions should be continued following initial placing on the market in the EU and until two full years of marketing experience in the EU has been gained. Then, PSURs should be submitted once a year for the following two years and thereafter at 3-yearly intervals.

PSURs should also be submitted upon request of a Competent Authority or the Agency at any time after granting of the marketing authorisation.

Moreover, review of the periodicity is also part of the Risk Management Plan and its assessment ([see Chapter I.3](#)).

There may be situations where exceptionally the submission of 6-monthly and subsequent yearly PSURs may be re-started, or where other amendments of the periodicity are required. This is further explained in [Chapter I.6, Section 2.4.c](#).

For medicinal products authorised through the centralised procedure, PSURs should be submitted to the Competent Authorities of all Member States and to the Agency in accordance with Regulation (EC) No 726/2004 Article 24. For medicinal products authorised nationally, PSURs should be submitted to the Competent Authorities in accordance with Directive 2001/83/EC, Article 104 ([see Distribution Requirements and Address Lists for PSURs in Annex 6.2](#)).

If the Marketing Authorisation Holder considers, on the basis of the data included in the PSUR, that amendment of the Summary of Product Characteristics (SPC) is necessary, a variation application should be submitted with the PSUR, or where this is not possible, a timetable for submission should be proposed at the time of PSUR submission.

For products authorised through the centralised, mutual recognition or decentralised procedures, amendments to the PSUR submission periodicity should be agreed via a type II variation. For nationally authorised products, amendments to the PSUR submission periodicity should be agreed according to the national requirements.

For nationally authorised products, including those authorised through the mutual recognition or decentralised procedures, initiatives have been taken by the national Competent Authorities to synchronise PSUR submission schedules for products containing the same active substance. For many active substances, harmonised “virtual” birth dates, so-called EU Harmonised Birth Dates (EU HBDs) and related harmonised data lock points for the following PSURs have been agreed between the relevant Marketing Authorisation Holders for originator products and national Competent Authorities. These harmonised birth dates and related data lock points are published by the Heads of Medicines Agencies²³. Marketing Authorisation Holders for generic products are encouraged to use the same PSUR submission schedules as those agreed for originator products.

6.2 General Principles

6.2.1 General Scope of Information

The main focus of the PSUR should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSUR. For this purpose, analysis of adverse reaction reports, an overview of cumulative data, safety data from studies and other relevant safety information, as well as follow-up of any Risk Management Plan (see Chapter I.3) should be adequately addressed in the PSUR. Reports of lack of efficacy (see Chapter I.5, Section 8), specifically for medicinal products used in the treatment of life-threatening conditions and for certain other medicinal products, e.g. contraceptives and vaccines, may represent a significant hazard and in that sense may give rise to a safety concern. These types of cases should be discussed within the PSUR (see Chapter I.6, Section 3.9.a). Moreover, data from pregnancy experience and outcome should also be discussed.

An increase in the frequency of Individual Case Safety Reports (ICSRs) for known adverse reactions is considered as relevant new information. Although increased reporting should be discussed in the PSUR, it is not possible to provide specific guidance as to what constitutes increased reporting or what method should be used for quantifying this. The Marketing Authorisation Holder should provide details of the methods that have been used. Judgement should be used in such situations to determine whether the data reflect a meaningful change in occurrence of adverse reactions or in the safety profile and whether an explanation can be proposed for such a change (e.g. population exposed, duration of exposure).

6.2.2 One Periodic Safety Update Report for Products Containing an Active Substance Authorised to One Marketing Authorisation Holder

It is recommended that information on all indications, dosage forms, routes of administration and regimens for a given active substance for medicinal products authorised to one Marketing Authorisation Holder should be included in a single PSUR, with a single data lock point common for all aspects of product use to facilitate a consistent, broad-based examination of the safety information for the active substance(s) in a single document.

When relevant and possible, data relating to a particular indication, dosage form, route of administration or dosing regimen should be presented in separate sections within the body of the PSUR and any safety concerns addressed accordingly without preparing a separate PSUR (e.g. a section dedicated on paediatric use summarising safety as well as exposure information).

In exceptional cases, the Agency, the Competent Authorities or the Marketing Authorisation Holder may consider it appropriate to have a separate PSUR. In such cases, agreement should be obtained at the time of authorisation or during the post-authorisation phase, as applicable. Examples include:

²³ Available on Heads of Medicines Agencies website <http://heads.medagencies.com>.

- Products authorised through line extensions to existing medicinal products (e.g. an active substance in two or more different formulations for systemic versus topical administration) with cross-reference between PSURs, if appropriate (see Chapter I.6, Section 6.2.4.c);
- Fixed combinations, where options include either a separate PSUR for the combination with cross-reference to the single-substance PSUR(s) or inclusion of the fixed combination data within one of the single-substance PSURs.

If a subsequent marketing authorisation is granted to a Marketing Authorisation Holder for a product which contains the same active substance as one previously granted to the same Marketing Authorisation Holder, the data lock points used for the PSURs for the first product should normally be used for the following joint PSURs covering the first and all subsequent products.

In addition, in order to put in place measures facilitating work sharing of PSUR assessment among Competent Authorities, harmonisation of birth dates, renewal dates and/or PSUR submission schedules for medicinal products containing the same active substances may be proposed by the Marketing Authorisation Holder or the Competent Authorities. In this context, submission of a type II variation to amend the schedule is not required, if the Marketing Authorisation Holder follows the harmonised PSUR submission schedule.

6.2.3 Products Authorised to More Than One Marketing Authorisation Holder

Where a product is authorised to more than one Marketing Authorisation Holder, in the case of multiple applications, submission of common PSURs is acceptable provided that the products remain identical in all respects apart from their invented names and that the PSURs are submitted separately by each Marketing Authorisation Holder. The data lock point should be based on the birth date used for the first authorised product. The submission cover letter should confirm that the data in these PSURs are identical.

Generic products should preferably have the same PSUR submission periodicity as the corresponding originator product (see Chapter I.6, Section 6.2.4.c). It is generally considered acceptable that Marketing Authorisation Holders for generic products collaborate on the preparation of PSURs. However, each Marketing Authorisation Holder remains responsible for the appropriate submission of PSURs for their products. Where common PSURs are submitted, the Marketing Authorisation Holders should confirm in writing that the data in these PSURs are identical.

Marketing Authorisation Holders who have contractual arrangements in place but opt not to submit common PSURs, should ensure that all data which may meaningfully contribute to the safety analysis and influence any proposed or effected changes in the Product Information of the medicinal product authorised to the reporting Marketing Authorisation Holder, should be included, with the source indicated, and discussed in the PSUR, even if it is known that they are included in another Marketing Authorisation Holder's PSUR.

6.2.4 Frequency of Review and Reporting

6.2.4.a) Regular and Ad Hoc Submission of Periodic Safety Update Reports

In accordance with the regular periodicity for PSUR submission, PSURs are required to be prepared and submitted:

- before initial placing on the EU market:
 - immediately upon request from a Competent Authority or the Agency; and
 - at least every 6 months after authorisation;

- after initial placing on the EU market:
 - 6-monthly PSUR submissions should be continued until two full years of marketing experience in the EU has been gained;
 - yearly PSURs for the following two years; and
 - thereafter PSURs should be submitted at 3-yearly intervals;
 - in addition, PSURs should be submitted immediately upon request from a Competent Authority or, for centrally authorised products, from the Agency.

The first PSUR should have a data lock point within 6 months after granting of the marketing authorisation.

The date of initial placing on the EU market is the date of launch, for the first time, in any Member State.

Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the data lock point.

Because the renewal is an independent process, it does not change the data lock point and submission schedule for the PSURs. It should be noted that re-assessment of the risk-benefit balance at the time of renewal is an opportunity to review and, if necessary, change the periodicity PSUR, or to request a second renewal.

When yearly or 3-yearly PSURs are due for submission, multiple 6-monthly or yearly PSURs are acceptable, provided that the Marketing Authorisation Holder submits a PSUR Summary Bridging Report, the content of which is described in [Chapter I.6, Section 4](#). It should be noted that in such cases, the Marketing Authorisation Holder should not send 6-monthly or yearly PSURs 60 days after the data lock points of these 6-monthly or yearly PSURs, but should send them only at the required due date (yearly or 3-yearly).

If a time gap occurs between the data lock point of a regular PSUR and a request from a Competent Authority (e.g. renewal, Risk-Benefit Review, ad hoc PSUR request), a PSUR Addendum Report should also be submitted (see [Chapter I.6, Section 5](#)). For a PSUR that spans longer time intervals, e.g. 3 years, an Addendum Report would only be considered appropriate if the time since preparation of the 3-year PSUR and the locally required report is greater than 6 months.

For PSURs requested for immediate submission by a Competent Authority or the Agency on an ad hoc basis, the Marketing Authorisation Holder should liaise with the Competent Authority/the Agency to agree the PSUR submission date, depending on the urgency of the issue.

Exceptionally, a Marketing Authorisation Holder may make a special request to the Competent Authority for 30 additional calendar days to submit a PSUR. Ideally, this request should be made before the data lock point. The Competent Authority should respond as rapidly as possible. The basis for such a request should be justified and could include:

- a large number of case reports for the reporting period, provided that there is no new significant safety concern;
- safety concerns raised by Competent Authorities in the previous PSUR for which the Marketing Authorisation Holder is preparing additional or further analysis in the next PSUR; and/or
- safety concerns identified by the Marketing Authorisation Holder that might require additional or further analysis.

The Marketing Authorisation Holder should make such a request only for the specific PSUR in question and not for subsequent PSURs. Subsequent PSURs will generally be expected to be submitted on the appropriate date in line with their original periodicity.

6.2.4.b) Submission of Periodic Safety Update Reports for Renewal of Marketing Authorisations

The Guideline on the Processing of Renewals in the Centralised Procedure and the Guideline on the Processing of Renewals in the Mutual Recognition and Decentralised Procedures define the different requirements to be respected for the purpose of data submission as part of the renewal application (for both Guidelines see Volume 2C of The Rules Governing Medicinal Products in the European Union²⁴).

The Marketing Authorisation Holder should submit safety data with the renewal application at least 6 months before the expiry date of the marketing authorisation in the EU. For the submission of safety data as part of the application for renewal of the marketing authorisation, the PSUR concept should be used. The Marketing Authorisation Holder should lock the data no more than 60 days before submitting the PSUR.

The data lock point for submission of safety information should be at 4 years and 4 months following the marketing authorisation date. Renewal applications may be submitted earlier than 6 months before the expiry date of the marketing authorisation in any Member State, in order to facilitate synchronisation of the PSUR submission schedule as well as harmonisation of renewal dates.

For the purpose of the renewal application, the Marketing Authorisation Holder should submit:

- the PSUR, or the PSUR plus a PSUR Addendum Report (see Chapter I.6, Section 5) or plus line-listings and/or summary tabulations, or only a PSUR Addendum Report, or only line-listings and/or summary tabulations (see Chapter I.6, Sections 2.4.d and 2.6.c), covering the period since the data lock point of the last PSUR (e.g. for the first renewal, the safety data of this PSUR or Addendum Report together with the PSURs previously submitted should cover a period of 4 years and 4 months since the marketing authorisation); and
- a PSUR Summary Bridging Report, bridging all PSURs (including those already submitted) covering the period of 4 years and 4 months. Alternatively, the information which corresponds by its content with the PSUR Summary Bridging Report may be included in the Clinical Overview, to be submitted with the renewal application. It is accepted that previously submitted PSURs should not be re-submitted, provided that a list of original submission dates is appended to the Summary Bridging Report.

If at the time of the first renewal, the Competent Authority or the Agency concludes that an additional renewal is needed, this conclusion may also include a requirement for an additional period of 6-monthly or yearly PSURs. The second renewal application should discuss PSURs data covering a five-year period since the data lock point of the PSUR(s) submitted with the first renewal application.

Because the renewal is an independent process, it does not change the periodicity and submission dates for PSURs due as part of pharmacovigilance reporting requirements. It should be noted that re-assessment of the risk-benefit balance at the time of renewal is an opportunity to review and, if necessary, change the PSUR periodicity, or to request a second renewal.

The Marketing Authorisation Holder may discuss the requirements for PSURs for the renewal applications with the relevant Competent Authorities of the Member States and/or the Agency, and agree on the appropriate PSUR documentation required.

6.2.4.c) Circumstances Where the Periodicity May Be Amended

Submission of PSURs is part of the normal conditions of marketing authorisations and pharmacovigilance obligations of the Marketing Authorisation Holder. The periodicity of PSUR

²⁴ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

submission may be amended, as required by the Competent Authority or proposed by the Marketing Authorisation Holder. This may result in more or less frequent submission of PSURs. However, submission of PSURs at a lower frequency than once every 3 years is not possible.

Where an amendment is proposed, the Applicant/Marketing Authorisation Holder should submit, as part of the application for a marketing authorisation, a reasoned request for the amendment, which, if granted, becomes part of the conditions of authorisation. If a Marketing Authorisation Holder applies for such an amendment following authorisation, such an application should follow the procedures for a type II variation.

Circumstances where less frequent submission of PSURs may be appropriate include:

- Products authorised through line-extensions to existing medicinal products;
- Newly authorised generic medicinal products.

A priori, a line-extension triggers the restart of the regular PSUR periodicity, unless a different periodicity has been agreed as a condition for the granting of the marketing authorisation (Article 104(6) of Directive 2001/83/EC).

However, in many cases, there will be no need to restart the regular PSUR periodicity following the line-extension, as data for the newly authorised product may be addressed in the PSURs submitted according to the existing submission schedule. A justification for continuing the existing submission schedule should be provided by the Marketing Authorisation Holder as part of the line-extension application, and the conditions for the authorisation will include any amendment of the periodicity, if required, as part of the outcome of the application evaluation.

Where separate PSURs for the product approved through the line-extension are considered appropriate, these should be submitted in accordance with the authorisation date of the newly approved product by starting the regular PSUR periodicity, while the PSUR submission for the previously authorised product(s) continues according to the existing submission schedule. These requirements should be reflected in the conditions for the authorisation. If/when separate PSURs are no longer considered necessary, data relevant to the product approved through the line-extension should be incorporated in a single PSUR covering all related products.

The addition of a paediatric indication for an existing medicinal product is an example of a line-extension which would result in re-starting the regular PSUR periodicity following the authorisation date of the newly approved product (see Annex 3.1.4).

For newly authorised generic products or products authorised on the basis of informed consent applications, application for submission of PSURs on a 3-yearly basis may be included in the authorisation application. PSURs for such products should preferably have the same data lock points as the corresponding originator product (see Chapter I.6, Section 2.4.c). Such applications will be assessed on a case-by-case basis by the Competent Authority.

Circumstances where more frequent PSUR submission may be required include:

- variations introducing new indications, populations, dosage forms and routes of administrations;
- an active substance which is a different salt/ester or derivative (with the same therapeutic moiety);
- the presence of an excipient without an established safety profile; and
- a Risk Management Plan in place for a corresponding originator product requiring specific monitoring of a safety concern.

In some circumstances, e.g. for biological products, a change in the manufacturing process may require close monitoring of possible clinical impact in terms of safety. Therefore, the conditions under

which the related variation of the marketing authorisation is granted, may include a re-start of the regular PSUR periodicity.

If the Competent Authority considers it appropriate to amend the PSUR periodicity and submission schedule, this should be clearly communicated to the Marketing Authorisation Holder.

6.2.4.d) Preparation of Periodic Safety Update Report according to the International Birth Dates

Medicinal products, which are also authorised outside the EU, will have an International Birth Date (IBD).

The IBD is the date of first marketing authorisation of a medicinal product granted to the Marketing Authorisation Holder (or a contractual partner of the Marketing Authorisation Holder) anywhere in the world. For practical reasons, the IBD may be defined as the last day of the month in which this first authorisation date falls.

The EU Birth Date (EBD) is the date of first marketing authorisation granted for the medicinal product in any EU Member State to the Marketing Authorisation Holder (see Glossary in Annex 1.1).

In order to harmonise PSUR submissions internationally, the Marketing Authorisation Holder may use the IBD to determine the dates of the datalock points for the PSUR submission schedule, provided that the first datalock point falls within the 6 months following the EBD.

After initial placing of the product on the EU market, the Marketing Authorisation Holder should submit at least four PSURs covering 6 months each, in order to ensure that two full years of experience with the product on the EU market are covered through provision of 6-monthly PSURs, while keeping the data lock point according to the IBD or EBD.

For purely nationally authorised medicinal products that are marketed in Member States, the Marketing Authorisation Holder may wish to synchronise national birth dates with the IBD. Although such a process may be difficult (e.g. multiple applications for variations might be required), such a step may be feasible and should be discussed with the Competent Authorities. If feasible, this may be implemented by notification.

For nationally authorised products, including those authorised through the mutual recognition or decentralised procedures, where national birth dates are used to determine the submissions of PSURs, the Marketing Authorisation Holders and Competent Authorities may liaise and designate an EU HBD which may be the IBD (see Chapter I.6, Section 1). After such harmonisation of the birth date, the first PSUR to be submitted in the EU should be based on the EU HBD and should cover a period in accordance with the life cycle of the product in the EU (6 months, 1 year or 3 years). When PSURs have previously been submitted in Member States based on different national birth dates, Competent Authorities should accept that there may be an overlap between the last PSUR based on a national birth date and the first PSUR based on the EU HBD.

6.2.5 Reference Safety Information

An objective of a PSUR is to establish whether information recorded during the reporting period is in accordance with previous knowledge of the medicinal product's safety, and to indicate whether changes should be made to the Product Information or the Risk Management Plan. Reference information is needed to carry out this comparison.

Having one reference safety document would facilitate a practical, efficient and consistent approach to the safety evaluation and make the PSUR a unique report also accepted in other regions of the world.

It is common practice for Marketing Authorisation Holders to prepare their own Company Core Data Sheet (CCDS), which includes material relating to safety, indications, dosing, pharmacology and other information concerning the product. A practical option for the purpose of the PSUR is for each Marketing Authorisation Holder to use, as a reference, the safety information contained within the CCDS, which is referred to as Company Core Safety Information (CCSI).

For the purposes of PSURs, the CCSI forms the basis for determining whether an adverse reaction is already listed or is still unlisted (listed and unlisted are terms that are introduced to distinguish them from the usual terminology of expectedness, which is used in association with the authorised Product Information). The EU Summary of Product Characteristics (SPC) or national SPC authorised by a Member State continues to be the reference document upon which expectedness is based for the purpose of expedited post-authorisation safety reporting in the EU.

It is important to highlight meaningful differences between the CCSI and the EU or national SPC in the cover letter accompanying the submission of the PSUR. The EU or national SPC should also be provided.

For 6-monthly and yearly PSURs the version of the CCSI in effect at the beginning of the period covered by the PSUR should be used as the reference information.

However, there may be valid reasons to use the CCSI in effect at the end of the period:

When producing a PSUR covering a period of more than one year or a PSUR Summary Bridging Report, it is often impractical to base the analysis of listedness on the CCSI that was in effect at the beginning of the period. There may be considerable variation in listedness over the reporting period. Therefore, the latest CCSI in effect at the end of the period may be used for PSURs covering a longer period. For PSURs covering a period of more than one year, when listedness is assessed at the time of PSUR preparation after the data lock point, it is generally considered appropriate to use the version of the CCSI in place at the end of the reporting period as the reference document, as long as that choice is made clear in the PSUR.

Whether the CCSI valid at the beginning or at the end of the period covered in the PSUR is used, the Marketing Authorisation Holder should ensure that all changes to the CCSI made over this period are described in the relevant section of the PSUR entitled “Changes to the Reference Safety Information” (see Chapter I.6, Section 3.5).

Marketing Authorisation Holders assessing listedness at case entry or on an ongoing basis throughout the reporting period should include the current version of the CCSI and comment on the reasons for any change in listedness assessment over time. In both cases, changes added since the previous PSUR should be explained in the PSUR sections “Changes to Reference Safety Information” (see Chapter I.6, Section 3.5) and/or “Overall Safety Evaluation” (see Chapter I.6, Section 3.10).

The Reference Safety Information to be used for PSURs for generic medicinal products based on EU HBD should consist of the common safety information that is included in all current SPCs of the concerned generic medicinal product, as authorised in the EU Member States at the time of the data lock point. In addition, a summary of the other safety information that was not included in all SPCs should be submitted. The Marketing Authorisation Holder should indicate in the PSUR which changes to the Reference Safety Information as used are considered necessary on the basis of the data examined in the PSUR.

6.2.6 Presentation of Data on Individual Cases

6.2.6.a) Sources of Information

Generally, adverse reaction data from the following sources are potentially available to the Marketing Authorisation Holder and should be included in the PSUR:

- Adverse reaction reports notified directly to the Marketing Authorisation Holder (or through schemes under its control):
 - Spontaneous reports from Healthcare Professionals;
 - Reports from Marketing Authorisation Holder-sponsored studies or named-patient/compassionate use;
 - Reports from Patients and other Consumers (not medically confirmed).
- Literature
- Adverse reaction reports received from regulatory authorities worldwide:
 - Spontaneous and non-spontaneous reports from Healthcare Professionals;
 - Reports from Patients and other Consumers (not medically confirmed).
- Other sources of data including:
 - Exchange of reports on adverse reactions in the framework of contractual arrangements (e.g. licensors-licensees agreements);
 - Data from special registries;
 - Reports from poison control centres;
 - Epidemiological databases.

6.2.6.b) Description of the Adverse Reaction

The reaction terms used in the PSUR should be in accordance with the MedDRA terminology (see Annex 3.2.1).

Whenever possible, the original reporter's reaction terms should be used to describe the adverse reaction.

However, when the original reporter's terms are not medically appropriate or meaningful, the Marketing Authorisation Holder should use the best alternative compatible reaction terms from MedDRA to ensure the most accurate representation possible of the original terms. Under such circumstances, the following should be borne in mind:

- In order to be able to make it available on request, the “verbatim” information supplied by the original reporter should be kept on file (in the original language and/or as a medically valid English translation, if applicable).
- In the absence of a diagnosis by the original reporter, a suggested diagnosis for a symptom complex may be made by the Marketing Authorisation Holder and used to describe the case, in addition to presenting the reported individual signs, symptoms and laboratory data.
- If the Marketing Authorisation Holder disagrees with a diagnosis that is provided by the original reporter, such disagreement may be indicated within the line-listing of cases (see Chapter I.6, Section 2.6.c).
- The Marketing Authorisation Holder should report and try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the original reporter.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms or diagnosis could be presented in the line-listing: first, the reaction as originally reported; second, when it differs, the Marketing Authorisation Holder's medical interpretation (identified by asterisk or other means).

6.2.6.c) Line listings and/or Summary Tabulations

Depending on their type or source, available adverse reaction cases should be presented as line-listings and/or as summary tabulations (see Table below).

A line-listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help Competent Authorities identify cases which they may wish to examine more completely by requesting full case reports.

The Marketing Authorisation Holder should prepare line-listings of consistent structure and content for cases directly reported to him (or under his control), including those from persons and organisations with whom the Marketing Authorisation Holder has set up contractual arrangements, as well as those received from worldwide regulatory authorities (see Chapter I.6, Section 2.6.a). They should usually do the same for published cases (usually well documented; if not, follow-up with the author may be possible). However, inclusion of individual cases from second- or third-hand sources, such as persons or organisations with whom the Marketing Authorisation Holder has contractual arrangements and special registries (see Chapter I.6, Section 2.6.a) may not be possible without standardisation of data elements, or appropriate due to the paucity of information, and may represent unnecessary re-entry/re-processing of such information by the Marketing Authorisation Holder. Therefore, summary tabulations or possibly a narrative review of these data are considered acceptable under these circumstances.

In addition to individual case line-listings, summary tabulations of adverse reaction terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in the line-listings (e.g. all serious adverse reaction and all non-serious unlisted adverse reaction), and also on other cases for which line-listings are not requested (e.g. non-serious listed adverse reactions). Details are found in Chapter I.6, Sections 3.7.a and 3.7.b.

Presentation of individual case histories in the PSUR:

Source	Type of Case	Only Summary Tabulation	Line-Listing and Summary Tabulation
1. Direct Reports to MAH			
▪ Spontaneous reporting*	serious		yes
	non-serious unlisted		yes
▪ Post-authorisation safety studies and other studies	non-serious listed		yes**
▪ Compassionate use programmes	serious / attributable to drug by investigator or sponsor		yes
	serious		yes
2. Literature	serious		yes
	non-serious unlisted		yes
3. Other sources			
▪ Regulatory authorities	serious		yes
▪ Contractual partners***	serious	yes	
▪ Registries	serious	yes	
▪ Poison control centres	serious	yes	
▪ Epidemiological databases	serious	yes	

* Medically unconfirmed reports should be provided as an annex to the PSUR as a line-listing.

** Line-listing should be provided as an annex to the PSUR.

*** For the purpose of this Table, the term contractual partners does not refer to persons and organisations to whom the MAH has transferred pharmacovigilance tasks and functions. Such persons and organisations are included in “Direct Reports to MAH”.

6.3 Model for a Periodic Safety Update Report (PSUR)

The following Sections are organised as a model PSUR. In each of these Sections, guidance is provided on what should be included.

6.3.1 PSUR section “Executive Summary”

The Marketing Authorisation Holder should prepare a brief overview of each PSUR in the form of an Executive Summary to provide the reader with a description of the most important information. The Executive Summary should be placed at the beginning of the PSUR immediately after the title page and should include a summary of:

- The worldwide marketing authorisation status (including a list of countries where the product is authorised/marketed and the authorised indications;
- Other relevant regulatory information related to the period covered by the PSUR (e.g. any urgent safety restriction should be highlighted);
- Exposure data;
- Number of new case reports received during the period covered by the PSUR and the cumulative numbers;
- Particular issues and safety concerns investigated;
- Overall findings of the PSUR;
- Conclusions.

When the Marketing Authorisation Holder has performed a review of one or several specific safety concern(s), this should be stated in this Executive Summary (as well as the nature of safety concerns that have been reviewed).

6.3.2 PSUR section “Introduction”

The Marketing Authorisation Holder should briefly introduce the product so that the PSUR “stands alone” but is also placed in perspective relative to previous PSURs and circumstances.

Reference should be made not only to product(s) covered by the PSUR but also those excluded.

Exclusions should be explained; for example, they may be covered in a separate PSUR (e.g. for a combination product).

If it is known that a PSUR on the same product(s) will be submitted by another Marketing Authorisation Holder and some of whose data are included in the PSUR (see Chapter I.6, Section 2.3), the possibility of data duplication should be noted.

6.3.3 PSUR section “Worldwide Marketing Authorisation Status”

This section of the PSUR provides cumulative information.

The following information should be provided for any indication, usually as a table, for all countries where a regulatory decision about marketing has been made related to the following:

- Dates of marketing authorisation and subsequent renewal (where PSURs are common for identical products with different invented names, or in the case of generic medicinal products, the list of the dates should cover all products separately);
- Any qualifications surrounding the authorisation, such as limits on indications if relevant to safety;
- Treatment indications and special populations covered by the market authorisation, when relevant;

- Lack of approval, including explanation, by worldwide regulatory authorities;
- Withdrawal by the company of an application for authorisation submission if related to safety or efficacy;
- Dates of launch (where PSURs are common for identical products with different invented names or in the case of generics, the listing of the dates should cover separately all products);
- Dates when the marketing authorisation has been revoked/withdrawn or dates when the marketing or marketing authorisation has been suspended either by a regulatory authority or voluntarily by the Marketing Authorisation Holder;
- Invented name(s).

Typically, indications for use, populations treated (e.g. children vs. adults) and dosage forms will be the same in many or even most countries where the product is authorised. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures.

If more convenient and useful, separate regulatory status tables for different product uses or forms should be utilised.

Country entries should be listed in chronological order of regulatory authorisations.

Annex 5.2.2 provides an example, with fictitious data for an antibiotic, of how such a table might be organised. The product was initially developed as a solid oral dosage form for out-patient treatment of various infections.

6.3.4 PSUR section “Update of Regulatory Authority or Marketing Authorisation Holder Actions taken for Safety Reasons”

This section should include details on the following types of worldwide actions relating to safety that were taken during the period covered by the PSUR and between data lock point and PSUR submission:

- Marketing authorisation withdrawal, revocation or suspension;
- Failure to obtain a marketing authorisation renewal;
- Restrictions on distribution;
- Clinical trial suspension;
- Dosage modification;
- Changes in target population or indications;
- Formulation changes;
- Urgent safety restrictions.

The safety-related reasons that led to these actions should be described and documentation appended when appropriate; any communication with Healthcare Professionals (e.g. Direct Healthcare Professional Communication (DHPC), commonly called “Dear Doctor Letter” (DDL)) as a result of such action should also be described with copies appended. For practical reasons, only a single DHPC in the English language, or together with an English summary of the information distributed in one or more countries should be appended.

6.3.5 PSUR section “Changes to Reference Safety Information”

For 6-monthly and yearly PSURs, the version of the CCDS with its CCSI coming into effect at the beginning of the period covered by the report should normally be used as the reference information. For a PSUR covering a period of over one year, the latest CCSI in effect at the end of the period may be used (see Chapter I.6, Section 2.5).

The CCSI used as reference should be numbered, dated and appended to the PSUR and include the date of the last revision. Changes to the CCSI, such as new contraindications, precautions, warnings, adverse reactions or interactions, already made during the period covered by the PSUR, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next PSUR and the next period (see also Chapter I.6, Section 2.5).

With the exception of emergency situations, it may take some time before intended modifications are introduced in the Product Information. Therefore, during that period the amended reference document (CCSI) may contain more “listed” information than the existing Product Information in many countries.

When meaningful differences exist between the CCSI and the EU/Member State’s Summary of Product Characteristics (SPC) (or the official data sheets/Product Information documents approved in a country), a brief comment should be prepared by the Marketing Authorisation Holder, describing the local differences and their consequences on the overall safety evaluation and on the actions proposed or initiated. This commentary may be provided in the cover letter accompanying the local submission of the PSUR.

6.3.6 PSUR section “Patient Exposure”

Estimating patient exposure data for marketed medicinal products often relies on gross approximations of in-house or purchased sales data or volume to determine patient exposure. This is not always reliable or available for all products. For example, hospital-based (in-patient exposure) data from the major monitoring sources are frequently unavailable. It may also be difficult to obtain accurate data for medicinal products of which generic presentations are in use. For non-prescription products, use is often on an as-required basis, and individual packages are frequently used by multiple family members of different ages and weights.

Where possible, an estimate of patient exposure should cover the same period as the interim safety data. While it is recognised that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate. An explanation and justification should be presented if the number of patients is impossible to estimate. In its place, other measures of exposure, such as patient-days, number of prescriptions or number of dosage units are considered appropriate; the method used should be explained. Given the difficulty of estimating cases, patient exposure should preferably be provided as person-time of exposure (days, months, years). The Marketing Authorisation Holder should be consistent in its method of calculation across PSURs for the same product. If a change in the method is appropriate, then both methods and calculations should be shown in the PSUR introducing the change. If these or other more precise measures are not available, bulk sales (tonnage) may be used. The concept of a Defined Daily Dose may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially paediatric vs. adult) should be provided. Paediatric population exposure should be broken down according to age groups. An estimate of use outside the terms of the marketing authorisation should be provided along with the method used to provide the estimate. Pregnancy exposure should also be estimated specially in the case of pregnancy registries using the same data lock point as the PSUR.

When an observed pattern of case reports indicates a potential problem, details by country (with locally recommended daily dose) or other breakdowns (e.g. indication, dosage form) should be presented if available.

When adverse reaction data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made.

When exposure data are based on information from a period that does not fully cover the period of the PSUR, the Marketing Authorisation Holder may extrapolate using the available data. If this is done it should be clearly indicated what data were used and why it is valid to extrapolate for the PSUR period in question (e.g. stable sales over a long period of time, seasonality of use of the product).

In a PSUR Summary Bridging Report, exposure should be presented including the full reporting period and explaining any differences in this estimation from the simple sum of exposure estimates included in the separate PSURs covered by the PSUR Summary Bridging Report. In addition, cumulative exposure estimates should be presented (for further guidance see explanations provided in the Risk Management Plan Template in [Annex 5.1.1](#)).

6.3.7 PSUR section “Presentation of Individual Case Histories”

This section should contain a description and analysis of selected cases containing new or relevant safety information and grouped preferably by medically relevant headings/MedDRA System Organ Classes (SOCs).

A description of the criteria used to select cases for presentation should be provided.

Follow-up data on individual cases may be obtained subsequent to their inclusion in a PSUR. If such information is relevant to the interpretation of the case (e.g. significant impact on the case description or analysis), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description. Cases where follow-up information is not considered to have any impact on the overall assessment of the case and has not led to relevant coding changes for the case, do not need to be discussed in the body text of the PSUR.

However, such cases should always be presented in cumulative tables and analyses if relevant.

With regard to the literature, Marketing Authorisation Holders should monitor standard, recognised medical and scientific journals for safety information relevant to their products and/or make use of one or more literature search/summary services for that purpose.

Published cases received from other sources (e.g. spontaneous reporting, studies) should only be included once and literature citation should be provided regardless of the “primary” source.

With regards to spontaneous reports that originate from Patients/Consumers, Marketing Authorisation Holders should:

- ensure review of data from Patients/Consumers or other non-healthcare professionals;
- include analysis of this data if associated with a safety concern in the PSUR section “Overall Safety Evaluation” (clearly identifying such reports by their source); and
- provide the data as a line-listing and summary tabulation (if considered appropriate).

6.3.7.a) “Cases Presented as Line-Listings”

The types of cases referenced below should be included in the line-listings. Attempts should be made to avoid duplicate reporting of cases from literature and regulatory sources.

- All serious adverse reactions and non-serious unlisted adverse reactions from spontaneous reporting;
- All serious adverse reactions (attributable to the medicinal product by either investigator or sponsor) available from post-authorisation safety studies (PASS) and other studies (including those which are part of the Risk Management Plan) or named-patient/compassionate use;
- All serious adverse reactions, and non-serious unlisted adverse reactions from the literature;
- All serious adverse reactions transmitted to the Marketing Authorisation Holder by worldwide regulatory authorities.

In addition, the types of cases referenced below should be included as line-listings in the form of an annex to the PSUR:

- All non-serious listed adverse reactions from spontaneous reporting ;
- All serious and non-serious (listed and unlisted) adverse reactions reported by Patients/Consumers and other non-healthcare professionals (not medically confirmed).

Suspected transmission via a medicinal product of any infectious agent should be considered as a serious adverse reaction (see Chapter I.5, Section 9).

Line-listing(s) (see Annex 5.2.3 for Template) should include each Patient only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed according to the most serious adverse reactions (sign, symptom or diagnosis), as judged by the Marketing Authorisation Holder.

It is possible that the same Patient may experience different adverse reactions on different occasions (e.g. weeks apart during a clinical trial). Such experiences should be treated as separate reports. Under such circumstances, the same Patient might then be included in a line-listing more than once, and the line-listings should be cross-referenced when possible. Line-Listings should be organised (tabulated) by body system (MedDRA System Organ Classes (SOCs)).

Where common PSURs are submitted, the line-listings should still reflect the invented name of the medicinal product (or the active substance name if the invented name of the medicinal products is not available) as reported by the original reporter.

The following headings should usually be included in the line-listings (see Annex 5.2.3):

- Marketing Authorisation Holder case reference number;
- Country in which the case occurred;
- Source (e.g. clinical trial, literature, spontaneous, regulatory authority);
- Age and sex of the Patient;
- Daily dose of the suspected medicinal product (and, when relevant, dosage form or route);
- Date of onset of the adverse reaction(s). If not available, best estimate of time to onset from therapy initiation. For adverse reactions known to occur after cessation of therapy, estimate of time lag if possible (may go in comments section);
- Dates of treatment. If not available, best estimate of treatment duration;
- Description of adverse reaction(s) as reported, and when necessary as interpreted by the Marketing Authorisation Holder (English translation when necessary) (see Chapter I.6, Section 2.6.b);
- Patient outcome (at case level) (e.g. resolved, fatal, improved, sequelae, unknown). This should indicate the consequences of the adverse reaction(s) for the Patient, using the worst of the different outcomes for multiple reactions
- Comments, if relevant (e.g. causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect medicinal product(s); dechallenge/rechallenge results if available). It should be used only for information that helps to clarify individual cases.

Depending on the product or circumstances, it may be useful or practical to have more than one line-listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

6.3.7.b) “Cases Presented as Summary Tabulations”

An aggregate summary for each of the line-listings should usually be presented. These tabulations usually contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g. by source of report). See Annex 5.2.4 for a sample data presentation on serious reactions.

The terms used in these tables should ordinarily be those used by the Marketing Authorisation Holder to describe the case (see Chapter I.6, Section 2.6.b).

Data on serious reactions from other sources (see Chapter I.6, Section 2.6.a) should normally be presented as a summary tabulation. If useful, the tabulations may, for example, be sorted by source of information or country.

When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description rather than a formal table is considered suitable.

As previously described, the data in summary tabulations should be interval data, as should the line-listings from which they are derived. However, for adverse reactions that are both serious and unlisted, a cumulative figure (i.e. all cases reported to date) should be provided in the table(s) or as a narrative.

6.3.7.c) “Marketing Authorisation Holder’s Analysis of Individual Case Histories”

This section may be used for brief comments on the data concerning individual cases. For example, discussion may be presented on particular serious or unanticipated findings (their nature, medical significance, mechanism, reporting frequency, etc.). The focus here should be on individual case discussion and should not be confused with the global assessment in the PSUR section “Overall Safety Evaluation” (see Chapter I.6, Section 3.10).

6.3.8 PSUR section “Studies”

All studies (non-clinical, clinical and epidemiological) yielding safety information (this includes lack of efficacy data) with a potential impact on product information, studies specifically planned, in progress and those published that address safety concerns should be included with a discussion of any interim or final results. The Marketing Authorisation Holder should not routinely catalogue or describe all the studies. Studies that are part of the Risk Management Plan should be mentioned (see Chapter I.6, Section 3.9.c).

6.3.8.a) “Newly Analysed Studies”

All relevant studies containing important safety information and newly analysed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations. Reference should be made to the Risk Management Plan, where applicable. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to non-clinical and clinical study reports. Copies of full study reports should be appended, e.g. in case of post-authorisation safety studies and for other studies with a significant safety finding only if deemed appropriate.

6.3.8.b) “Targeted New Safety Studies”

New studies specifically planned or conducted to examine a safety concern (actual or hypothetical) should be described (e.g. objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analysed, the final results should be presented in a subsequent PSUR as described in [Chapter I.6, Section 3.8.a](#).

Copies of full reports should be appended in the case of post-authorisation safety studies and for other studies with a significant safety finding only if deemed appropriate.

Planned studies should be discussed in the Risk Management Plan ([see Chapter I.3](#)) and if relevant in the related PSUR section ([see Chapter I.6, Section 3.9.c](#)).

6.3.8.c) “Published Studies”

Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarised and publication reference(s) provided.

6.3.8.d) “Other Studies”

The Marketing Authorisation Holder should provide any relevant information from the data collected by pregnancy exposure registries and a discussion of the positive and negative experience of use of the medical product during pregnancy.

6.3.9 PSUR section “Other information”

6.3.9.a) “Efficacy-related Information”

For products used in prevention (e.g. vaccines) or in treatment of serious or life-threatening diseases (e.g. antibiotics and antiviral products) or products used in healthy Consumers (e.g. contraceptives), medically relevant lack of efficacy reports, which may represent a significant hazard, should be described and explained.

Where appropriate, all other medically relevant reports of lack of efficacy should be discussed in this section.

6.3.9.b) “Late-breaking Information”

Any important, new information received after the database was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the PSUR section “Overall Safety Evaluation” ([see Chapter I.6, Section 3.10](#)).

6.3.9.c) “Risk Management Plan”

When a specific Risk Management Plan is in place, it should be discussed. In this case, the status of the Risk Management Plan and its amendments prior to the data lock point should be presented together with all available study results.

The assessment of the effectiveness of the risk management system should be presented ([see Chapter I.3](#)).

6.3.9.d) “Risk-Benefit Analysis Report”

When a more comprehensive safety or risk-benefit analysis (e.g. all indications reviewed) has been conducted separately, a summary of the analysis should be included in this section.

6.3.10 PSUR section “Overall Safety Evaluation”

The Marketing Authorisation Holder should provide a concise analysis of the data presented, taking into account any late-breaking information (see Chapter I.6, Section 3.9.b), and followed by the Marketing Authorisation Holder’s assessment of the significance of the data collected during the period. Discussion and analysis of the “Overall Safety Evaluation” should be organised by SOC rather than by listedness or seriousness; the latter properties should still be covered under each SOC. Although related terms may be found in different SOCs, they should be reviewed together for clinical relevance.

Standardised MedDRA Queries (SMQs) may be used for signal detection and the use of SMQs is recommended in order to retrieve and review cases of interest where signals are identified from adverse reaction databases²⁵.

The Marketing Authorisation Holder should also review the cumulative experience and highlight any new information on:

- A change in characteristics of listed reactions, e.g. severity, outcome, target population;
- Serious unlisted adverse reactions, placing into perspective the cumulative reports;
- Non-serious unlisted adverse reactions;
- An increased reporting frequency of listed adverse reactions, including comments on whether it is believed the data reflect a meaningful change in adverse reactions occurrence.

This section should also explicitly address any new safety concern on the following (lack of significant new information should be mentioned for each):

- Interactions;
- Experience with overdose, deliberate or accidental, and its treatment;
- Abuse or misuse;
- Positive or negative experiences during pregnancy or lactation;
- Experience in special patient groups (e.g. children, elderly, organ impaired, a qualitative description of off-label use should be given);
- Effects of long-term treatment;
- Patient/Consumer and other non-healthcare professional reports (see Chapter I.6, Section 3.7), if appropriate;
- Prescription errors/medication errors, including those associated with invented names or with the presentation of the medicinal products, that have safety implications, if available.

A subsection of the PSUR should deal with use of the medicinal product in children if the product has a paediatric indication, if there is evidence of significant off-label use in children or if there are adverse reactions reported in the paediatric population. Data from completed or ongoing clinical trials should be presented separately from spontaneous reports (see Annex 3.1.4).

6.3.11 PSUR section “Conclusion”

The “Conclusion” should address the overall risk-benefit balance in the context of the data presented in the PSUR and:

- indicate which safety data are not in accordance with previous cumulative experience and the reference safety information (CCSI);
- specify and justify any action recommended or initiated.

²⁵ Council for International Organizations of Medical Sciences (CIOMS). Development and rational use of Standardised MedDRA Queries (SMQs). Geneva: CIOMS; 2004. Available on CIOMS website <http://www.cioms.ch/>.

The need to amend the SPC should be addressed in the cover letter from the Marketing Authorisation Holder, where consistency between the CCSI and the SPC is cross-checked and any comment or planned action is proposed.

Having made a decision to amend the SPC, the Marketing Authorisation Holder should submit a variation application at the same time as the PSUR or, where this is not possible, state a proposed timetable for submission.

6.4 Contents of the PSUR Summary Bridging Report

The PSUR Summary Bridging Report should not contain any new data but should provide a brief summary bridging two or more PSURs, or PSURs and PSUR Addendum Reports (e.g. two consecutive 6-monthly PSURs for a yearly PSUR or six consecutive 6-monthly PSURs to compile 3-year PSUR data). It is intended to assist Competent Authorities with a helpful overview of the appended PSURs. The PSUR data should not be repeated but cross-referenced to individual PSURs. The format of the Summary Bridging Report should be identical to that of the usual PSUR, but the content should consist of summary highlights and an overview of data from the attached PSURs to which it refers.

A Summary Bridging Report should contain the following:

- Introduction (a brief description of the purpose of the document specifying the time periods covered and cross-referencing any appended PSURs);
- Worldwide marketing authorisation status (number of countries which have approved the product);
- Update on regulatory authority or Marketing Authorisation Holder-initiated actions for safety reasons (an integrated summary of actions taken if appropriate);
- Changes to the CCSI (significant changes over the entire period);
- Exposure data (estimation of the total number of patients exposed in the time period);
- Individual case histories (brief statement outlining the total number of cases presented in the series of PSURs). When there is an important specific safety concern that has not been adequately discussed in one or more PSURs, it is considered appropriate to include a cumulative line-listing or summary tabulation for the types of cases of concern presenting adverse reactions ordered by SOC, seriousness and listedness covering the period of the Summary Bridging Report and pointing out any differences from prior listings or tabulations. In this case, there should be a clear understanding that the tables should be generated from live databases, which change over time as cases are updated. These tables should then reflect the most up-to-date data available at the time they are generated. It is recognised that the case counts in these summary tables may differ somewhat from the contents of the individual tables in the appended PSURs. A general statement describing the differences should be provided);
- Studies (a brief summary of important targeted clinical safety studies);
- Other information (only highly significant safety information received after the data lock point);
- Overview of the safety concerns and Conclusion (unresolved key issues).

In addition, the cover letter accompanying the Summary Bridging Report should also contain information highlighting any significant differences between the approved SPC and the current CCSI.

6.5 Contents of the PSUR Addendum Report

A PSUR Addendum Report is an update to the most recently completed PSUR when a Competent Authority requests or requires a safety update outside the usual IBD-based PSUR submission schedule. An Addendum Report should be provided when more than 3 months for a 6-monthly or yearly PSUR, and more than 6 months for a PSUR covering a longer period have elapsed since the

data lock point of the most recent PSUR. It may also be appropriate to provide an Addendum Report to the PSUR Summary Bridging Report (see Chapter I.6, Section 4).

The Addendum Report should summarise the safety data received between the data lock point of the most recent PSUR and the Competent Authority's requested cut-off date. It is not intended that the Addendum Report should provide an in-depth analysis of the additional cases, as these should be included in the next regularly scheduled PSUR. Depending on the circumstances and the volume of additional data since the last scheduled report, an Addendum Report may follow the PSUR format or a simplified presentation.

The proposed simplified presentation should include the following sections, containing any new information or changes beyond the most recent PSUR to which the Addendum Report refers:

- Introduction (purpose; cross-reference to most recent PSUR);
- Changes to the CCSI (including a copy of the most recent CCSI document if it differs from the one in the PSUR);
- Significant worldwide regulatory authorities' actions relevant to safety;
- Line-listing(s) and/or summary tabulations;
- Conclusions (brief overview).

7. Company-Sponsored Post-Authorisation Safety Studies

7.1 Introduction

There is a continuous need to monitor the safety of medicinal products as they are used in clinical practice. Spontaneous reporting schemes provide important early signals of safety concerns and also provide a means of continuous surveillance. Formal studies to evaluate safety may also be necessary, particularly in the confirmation, characterisation and quantification of safety concerns identified at an earlier stage of product development or during post-authorisation use (see Chapter I.8). Such studies may also be useful in identifying previously unsuspected adverse reactions or in confirming the safety profile of a medicinal product under normal conditions of use. In accordance with legal requirements, post-authorisation safety studies (PASS) may be required by Competent Authorities either as a commitment at the time of authorisation or in the post-authorisation phase to further assess a signal. In either case, such studies will be considered as a relevant part of the Risk Management Plan (see Chapter I.3).

This Chapter of Volume 9A applies to the conduct of studies sponsored by the pharmaceutical industry, which evaluate the safety of products with a marketing authorisation for human use. They encompass all studies carried out to evaluate the safety of authorised medicinal products and for which a Marketing Authorisation Holder takes responsibility for their initiation, management and/or financing. This includes studies where the medicine is provided by the Marketing Authorisation Holder and those where it is prescribed in the normal way, both in general practice and in the hospital setting. A study follows a protocol, which defines the study population and the design for its conduct and analysis. Therefore, in this context, databases searches to count e.g. number of adverse events or number of prescriptions are not considered studies.

The present guidance provides a framework whereby a variety of data collection methods may be used to evaluate the safety of authorised medicinal products. Whilst it is recognised that the study design used needs to be tailored to particular products and safety concerns, this guidance defines the essential principles to be applied in a variety of situations. The study methods in this field continue to develop and therefore there will be a need to regularly review guidance to ensure that it reflects advances made in the assessment of product safety (see Table I.7.A at the end of this Chapter).

A post-authorisation safety study is defined in Article 1(15) of Directive 2001/83/EC as “pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product”. The definition of non-interventional trial is provided in Article 21 of Directive 2001/20/EC: “A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within the current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data”.

In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice. Based on these definitions a fundamental distinction can be made between non-interventional (observational) and interventional post-authorisation safety studies. The latter are considered clinical trials falling under the scope of the Directive 2001/20/EC.

If the definition of non-interventional is not met, the study should be considered as interventional. For instance, studies exploring new indications, new routes of administration or new combinations, after a product has been authorised, should be considered as interventional. In such cases, Directive 2001/20/EC and the related guidance should be followed (see Volume 10 of The Rules Governing

Medicinal Products in the European Union²⁶). The guidance on Good Clinical Practice does not apply to non-interventional post-authorisation studies.

The guidance below relates principally to those non-interventional post-authorisation studies where there is a known safety issue under investigation and/or where the numbers of patients to be included in the study will add significantly to the existing safety data for the product(s).

A safety concern may be unexpectedly identified in the course of performing a study on an authorised medicinal product that would normally fall outside the scope of this guidance. In that case, the Marketing Authorisation Holder and specifically the QPPV are expected to inform the relevant Competent Authorities immediately and to provide a brief report on progress at intervals and at study end as requested by the Authorities.

If there is doubt as to whether or not a study comes under the scope of the present guidance, the company should discuss the intended protocol with the relevant Competent Authorities of the Member State(s) in which the study is to be conducted (see Chapter I.7, Section 4.1).

In addition to the guidance below, Marketing Authorisation Holders should consider the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE)²⁷.

7.2 Objectives of Post-Authorisation Safety Studies

Post-authorisation safety studies may be conducted for the purpose of identifying previously unrecognised safety concerns (hypothesis-generation), investigating potential and identified risks (hypothesis-testing in order to substantiate a causal association), or confirming the known safety profile of a medicinal product under normal conditions of use. They may also be conducted to quantify established adverse reactions and to identify risk factors.

Situations where studies may be appropriate include:

- a medicinal product with a novel chemical structure or novel mode of action;
- where there is uncertainty as to the clinical relevance of a toxic effect in animals;
- where there is uncertainty as to the safety profile;
- where there is a need to better quantify adverse events identified in clinical trials and elucidate risk factors;
- where there is a need to confirm or refute safety concerns suggested by other sources (e.g. spontaneous reporting);
- where there is a concern regarding the use of the medicinal product (e.g. to quantify the off-label use); and
- when there is a need to evaluate the effectiveness of a risk minimisation measure.

A variety of designs may be appropriate including observational cohort studies, case-control studies or registries (see Table I.7.A). Clinical trials involving systematic allocation of treatment (e.g. randomisation) may also be used to evaluate the safety of authorised products. Such clinical trials should comply with the requirements of Directive 2001/20/EC.

The design to be used will depend on the objectives of the study, which must be clearly defined in the study protocol. Any specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods. A reference to the Risk Management Plan should be made in the protocol when such a Plan exists.

²⁶ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

²⁷ Available on ISPE website <http://www.pharmacoepi.org/index.cfm>.

For protocol development consideration should be given to the elements described in **Table I.7.B** at the end of this Chapter.

7.3 Responsibilities for the Conduct of Post-Authorisation Safety Studies

The Marketing Authorisation Holder who initiates, manages and/or finances the study is responsible for its conduct and should meet the pharmacovigilance obligations concerning PASS. The study should be supervised by a designated monitor(s) or monitoring organisation and the names of the monitors should be recorded in the study documents. In case the Marketing Authorisation Holder does not directly conduct the study, detailed and clear contractual agreements for meeting pharmacovigilance obligations should be documented (see **Chapter I.1**).

The QPPV at EU level and/or, where applicable, the nominated person responsible for pharmacovigilance at national level, should be involved in the review of protocols for all post-authorisation safety studies, in order to ensure compliance with pharmacovigilance requirements.

7.4 Liaison with Competent Authorities

7.4.1 Evaluation of the Protocol

Marketing Authorisation Holders proposing to perform a post-authorisation safety study should send the protocol to the Competent Authority of the Member State(s) in whose territory the study is to be performed. In case of products authorised through the mutual recognition or decentralised procedures, the protocol should also be sent to the Reference Member State and, in case of centrally authorised products, to the Agency, the Rapporteur and Co-Rapporteur. National legal requirements or guidelines should be taken into account in those Member States where these exist, and Directive 2001/20/EC should be followed when the study qualifies as a clinical trial.

Two different situations can be envisaged depending on whether or not the study has been requested by the Competent Authorities:

a) Studies requested by Competent Authorities

The contact point will depend on the procedure by which the product has been authorised in the EU:

- For centrally authorised products, the Agency will normally be the contact point. The (Co-)Rapporteur will initially review the draft protocol for approval by the CHMP. The draft protocol may also be discussed at PhVWP level if so requested by CHMP.
- For products authorised through the mutual recognition or decentralised procedure, the Reference Member State will normally be the contact point and the initial reviewer of the draft protocol. A further discussion may take place at PhVWP level.
- For purely nationally authorised medicinal products, the Competent Authority of the Member State requesting the study and the Competent Authority of each Member State where the study is to be conducted will be the contact points. However, when the need for the study has been discussed at PhVWP level, a Lead Member State may be nominated who will act as the contact point and initial reviewer for the draft protocol. Further discussions may take place at PhVWP level when the study is to be conducted in several Member States or the product is used in several Member States.

Meetings will be organised as appropriate between the designated (Co-) Rapporteur or Reference/Lead Member State and the Marketing Authorisation Holder in order to agree upon a protocol and a timetable. When the Marketing Authorisation Holder considers that the protocol requires a major amendment, this should be reported to the (Co-)Rapporteur or Reference/Lead Member State who will consider its appropriateness and the need for further evaluation at CHMP and/or PhVWP level. Refinements of exposure and/or case definitions will normally not require notification.

When the same or a similar study is also requested by other Competent Authorities, e.g. countries outside the EU for centrally authorised or other Member States for nationally authorised products, an effort should be made by the Marketing Authorisation Holder to reach agreement on a common protocol.

b) Studies performed at Marketing Authorisation Holder's initiative

When the study has commenced, the Marketing Authorisation Holder should inform the relevant Competent Authorities of all Member States where the study is being conducted, as well as the Agency and (Co-)Rapporteur for centrally authorised products and the Reference Member State for products authorised through the mutual recognition or decentralised procedures. Any major amendment to the protocol should be reported to the relevant Authorities accompanied by a justification for it. Refinements of exposure and/or case definitions will normally not require notification.

7.4.2 Reporting of Adverse Reactions

For post-authorisation safety studies that qualify as clinical trials, the reporting criteria laid down in Directive 2001/20/EC and related guidance (see Volume 10 of the Rules Governing Medicinal Products in the EU²⁸) should be followed as well as the requirements established for Periodic Safety Update Reports (PSURs) (see Chapter I.6).

For non-interventional post-authorisation safety studies, conducted inside and outside the EU, the usual regulatory requirements for reporting of adverse reactions should be fulfilled according to Chapters I.4. and I.6 (in conjunction with Part III for electronic exchange of pharmacovigilance information).

This means that

- reports of all serious adverse reactions arising from such studies within the EU should be reported on an expedited basis (i.e. within 15 days), to the Competent Authority of the Member State on whose territory the incident occurred, and in addition, for products authorised through the mutual recognition or decentralised procedures and for products which have been the subject of a referral procedure, to the Reference Member State. These reports should also be included in the PSURs (see Chapter I.6);
- reports of all unexpected serious adverse reactions arising from such studies outside the EU should be reported on an expedited basis to the Agency and to all Member States where the medicinal product is authorised. These reports should also be included in the PSURs (see Chapter I.6);
- reports on expected serious occurring outside the EU should be reported in accordance with Chapter I.6 on PSURs;

All adverse reactions/events including those which are considered non-serious, should be summarised in the final study report in frequency tables.

Marketing Authorisation Holders should ensure that they are notified by the investigator of serious adverse reactions and, if specified in the study protocol, of events (those not suspected by the investigator or the Marketing Authorisation Holder to be adverse reactions).

In certain study designs, such as case-control or retrospective cohort studies (see Data Sources in Table I.7.A), in which it is not feasible or appropriate to make an assessment of causality between medical events recorded and the medicinal products at individual case level, expedited reporting of Individual Case Safety Reports (ICSRs) is not required. In case of doubt, the Marketing Authorisation

²⁸ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

Holder should clarify the reporting requirements through the contact point referred to in **Chapter I.7, Section 4.1.a**, according to the authorisation procedure of the product.

7.4.3 Progress and Final Study Reports

a) Studies requested by Competent Authorities

Marketing Authorisation Holders should provide a study progress report annually, or more frequently as requested by the Competent Authorities (e.g. according to the Risk Management Plan milestones) or on their own initiative. If the study is discontinued, a final report should also be submitted, which will include the reasons for stopping the study.

The content of the progress report should follow a logical sequence and should include all the available data which is judged relevant for the progress of the study; e.g. number of patients who have entered the study according to their status (exposure, outcome, etc.), problems encountered and deviations from the expected plan. After review of the report, Competent Authorities may request additional information.

A final study report should be submitted according to an agreed timetable (e.g. Risk Management Plan milestones). For the content of the final report consideration should be given to the recommendations laid down in **Table I.7.C at the end of this Chapter**. The findings of the study should be made public, preferably through scientific journals.

Both progress and final reports should be sent to the Competent Authorities of the Member States in which the study is being conducted and to the Competent Authority that requested the study. In case of products authorised through the mutual recognition or decentralised procedures, these reports should also be sent to the Reference Member State and, in case of centrally authorised products, to the Agency, the Rapporteur and Co-Rapporteur. For evaluation of such reports, the same procedure as for evaluation of the protocol should be followed (see **Chapter I.7, Section 4.1**).

For post-authorisation safety studies that qualify as clinical trials, the criteria laid down in Directive 2001/20/EC and related guidance (see **Volume 10 of the Rules Governing Medicinal Products in the EU²⁹**) should be followed, in addition to the requirements established in the present guidance.

b) Studies performed at the Marketing Authorisation Holder's initiative

Progress and final reports should be included or updated in the corresponding PSUR and/or Risk Management Plan. When a safety concern is raised, a report should be submitted immediately to the relevant Competent Authorities (including the Agency and (Co-) Rapporteur for centrally authorised products and the Reference Member State for products authorised through the mutual recognition or decentralised procedures). The findings of the study should be made public, preferably through scientific journals.

For post-authorisation safety studies that qualify as clinical trials, the criteria laid down in Directive 2001/20/EC and related guidance (see **Volume 10 of the Rules Governing Medicinal Products in the EU³⁰**) should be followed, in addition to the requirements established in this guidance provided in Volume 9A.

7.5 Promotion of Medicinal Products

Post-authorisation studies should not be planned or conducted for the purposes of promoting the use of medicinal products.

²⁹ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

³⁰ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

Company sales and marketing representatives should not be involved in studies in such a way that it could be seen as a promotional exercise, such as in the recruitment of patients and physicians.

7.6 Participation of Healthcare Professionals

Subject to the Healthcare Professional's terms of service, payment should be restricted to compensation of the Healthcare Professional for any additional time and expenses incurred.

No additional payment or inducement for a Healthcare Professional to participate in a post-authorisation safety study should be offered or given.

7.7 Ethical Issues

Post-authorisation safety studies that qualify as clinical trials fall within the scope of Directive 2001/20/EC. For non-interventional post-authorisation safety studies, the Marketing Authorisation Holders and investigators should follow relevant national legislation in those Member States where this exists, in addition to the guidance given here.

The highest possible standards of professional conduct and confidentiality must always be maintained and legislation on data protection followed (see Directive 95/46/EC). The Patient's right to confidentiality is paramount. The Patient's personal identifiers should be replaced by a code in the study documents, and only authorised persons should have access to identifiable personal details if data verification procedures demand inspection of such details. Responsibility for the retrieval of information from personal medical records lies with the Healthcare Professional(s) responsible for the Patient's care. Such information from medical records should be provided to the Marketing Authorisation Holder, who is thereafter responsible for the handling of such information.

It is recommended that non-interventional post-authorisation safety studies are referred to an Ethics Committee. Studies conducted entirely using records not containing any personal identifiers (e.g. anonymised records) may not require an ethical review of individual study protocols. National guidelines in this respect should be followed where they exist.

According to European data protection legislation, explicit consent is required when the study plans to collect data containing personal identifiers, though some exceptions are envisaged.

7.8 Procedure for Complaints

A post-authorisation safety study, the objective, design or conduct of which gives cause for concern (e.g. using the study as a promotional activity), should be referred to the relevant Competent Authorities, and, if appropriate, to other bodies within Member States which are deemed to have the matter within their remit.

TABLE I.7.A: EPIDEMIOLOGICAL METHODS FOR POST-AUTHORISATION SAFETY STUDIES

Spontaneous reporting schemes are valuable tools for providing safety signals in a continuous manner. In many situations, however, such passive surveillance should be complemented with more formal approaches in order to increase the sensitivity for risk identification or to confirm, characterise or quantify possible safety concerns. These more formal approaches are included under the term ‘post-authorisation safety studies’.	
1.	Study Designs
Post-authorisation safety studies may adopt different designs depending on their objectives. A brief description of the fundamental types of studies, as well as the types of data resources available, is provided hereafter. However, this table is not intended to be exhaustive and should be complemented with other widely available information sources (1-4). The ICH-E2E Guideline has been followed to a great extent in order to provide a harmonised view on this topic.	
1.1	Methods for Active Surveillance
Active surveillance, in contrast to passive surveillance, seeks to ascertain more completely the number of adverse events in a given population via a continuous organised process. An example of active surveillance is the follow-up of patients treated with a particular medicinal product through a risk management system. Patients who fill a prescription for this product may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.	
1.1.1	Sentinel Sites
Active surveillance may be achieved by reviewing medical records or interviewing patients and/or physicians/pharmacists in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites may provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, collection of information on the use of a medicinal product, such as the potential for abuse, may be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those medicinal products used mainly in institutional settings such as hospitals, nursing homes, and haemodialysis centres. Institutional settings may have a greater frequency of use for certain products and may provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerised laboratory reports in certain clinical settings may provide an efficient active surveillance system.	
1.1.2	Intensive Monitoring Schemes
Intensive monitoring is a system of record collation in designated areas, e.g. hospital units or by specific Healthcare Professionals in community practice. In such cases, the data collection may be undertaken by monitors who attend ward rounds, where they gather information concerning undesirable or unintended events thought by the attending physician to be causally related to the medication. Monitoring may also be focused on certain major events that tend to be drug-related such as jaundice, renal failure, haematological disorders, bleeding. The major strength of such systems is that the monitors may document important information about the events and exposure to medicinal products. The major limitation is the need to maintain a trained monitoring team over time.	

1.1.3 Prescription Event Monitoring

Prescription event monitoring is a method of active pharmacovigilance surveillance. In prescription event monitoring, patients may be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire (5-6). Limitations of prescription event monitoring include incomplete physician response and limited scope to study products which are used exclusively in hospitals. More detailed information on adverse events from a large number of physicians and/or patients may be collected.

1.1.4 Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic may be a disease or an outcome (disease registry) or a specific exposure (exposure or drug registry). Both types of registries, which only differ by the type of patient data of interest, may collect a battery of information using standardised questionnaires in a prospective fashion.

Disease/outcome registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations may help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients within the registry with another condition, or from outside the registry.

Exposure registries address populations exposed to medicinal products of interest (e.g. registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a medicinal product has a special impact on this group of patients. Some exposure registries address exposures to medicinal products in specific populations, such as pregnant women. Patients may be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires. Single cohort studies may measure incidence, but, without a comparison group, cannot provide proof of association. However, they may be useful for signal amplification particularly for rare outcomes. This type of registry may be very valuable when examining the safety of an orphan drug indicated for a specific condition.

1.2 Comparative Observational Studies

Traditional epidemiological methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

1.2.1 Cross-sectional Study (Survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed, which limits its use for aetiologic research unless the exposures do not change over time. These studies are best used to examine the prevalence of a disease at one time-point or to examine trends over time, when data for serial time-points can be captured. These studies may also be used to examine the crude association between exposure and outcome in ecologic analyses.

1.2.2 Cohort Study

In a cohort study, a population-at-risk for an event of interest is followed over time for the occurrence of that event. Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a medicinal product at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving exposure to medicinal product(s), comparison cohorts of interest are selected on the basis of medication use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events may also be investigated using the same data source in a cohort study. However, it may be difficult to recruit sufficient numbers of patients who are exposed to a product of interest (such as an orphan drug) or to study very rare outcomes. The identification of patients for cohort studies may come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies may be used to examine safety concerns in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist. Cohort studies may be prospective or retrospective depending on when the outcome of interest occurs in relation to the commencement of the research: If the outcome occurs after the research begins, it would be prospective; if the outcome had already occurred when the investigation began, it would be retrospective.

1.2.3 Case-control Study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure to the medicinal product among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease among the exposed as compared to the non-exposed. Patients may be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a medicinal product (or products) and one specific rare adverse event, as well as to identify risk factors for adverse events (or actually, effect-modifiers). Risk factors may include conditions such as renal and hepatic dysfunction, which might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study may also provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated. As in cohort studies, case-control studies may be prospective or retrospective (see 1.2.2. of this Table).

When the source population within which the case-control study is conducted is a well-defined cohort, it is then possible to select a random sample from it to form the control series. The name “nested case-control study” has been coined to designate those studies in which the control sampling is density-based (e.g. the control series represents the person-time distribution of exposure in the source population). The case-cohort is also a variant in which the control sampling is performed on those persons who make up the source population regardless of the duration of time they may have contributed to it (4).

A case-control approach could also be set up as a permanent scheme to identify and quantify risks (case-control surveillance). This strategy has been followed for rare diseases with a relevant aetiology fraction attributed to medicinal products, including blood dyscrasias or serious skin disorders.

1.2.4 Other Novel Designs

Some novel designs have been described to assess the association between intermittent exposures and short-term events, including the case-series (7), the case-crossover (8) and the case-time-control (9) studies. In these designs only cases are used and the control information is obtained from past person-time experience of the cases themselves. One of the important strengths of these designs is that those confounding variables that do not change within individuals are automatically matched.

1.3 Clinical Trials

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing may also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the medicinal product in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies may include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolise medicinal products differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

In performing clinical trials Directive 2001/20/EC and related guidance (Volume 10 of the Rules Governing Medicinal Products in the EU³¹) should be followed.

1.3.1 Large Simple Trials

A Large Simple Trial is a specific form of clinical trial where large numbers of patients are randomised to treatment but data collection and monitoring is kept to the absolute minimum consistent with the aims of the study (10). This design is best used in pharmacovigilance to elucidate the risk-benefit profile of a medicinal product outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event.

These studies qualify as clinical trials and are subject to Directive 2001/20/EC and related guidance (Volume 10 of the Rules Governing Medicinal Products in the EU³²).

1.4 Other Studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with exposures to medicinal products. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of medicinal products in specified populations.

1.4.1 Occurrence of Disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that

³¹ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

³² Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, may be used to assist in putting spontaneous reports into perspective (1). For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

1.4.2 Drug Utilisation Study

Drug utilisation studies (DUS) describe how a medicinal product is marketed, prescribed and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication and other characteristics. DUS may be used to determine if a product is being used in these populations. From these studies, denominator data may be derived for use in determining rates of adverse reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of medicinal products, as well as to develop estimates of the economic burden of adverse reactions. DUS may be used to examine the relationship between recommended and actual clinical practice. These studies may help to determine whether a medicinal product has potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies may include a lack of clinical outcome data or information of the indication for use of a product.

2. Data Sources

Pharmacoepidemiological studies may be performed using a variety of data sources. Traditionally, field studies were required for retrieving the necessary data on exposure, outcomes, potential confounders and other variables, through interview of appropriate subjects (e.g. patients, relatives) or by consulting the paper-based medical records. However, the advent of automated healthcare databases has remarkably increased the efficiency of pharmacoepidemiologic research. There are two main types of automated databases, those that contain comprehensive medical information, including prescriptions, diagnosis, referral letters and discharge reports, and those mainly created for administrative purposes, which require a record-linkage between pharmacy claims and medical claims databases. These datasets may include millions of patients and allow for large studies. They may not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data, and paper-based medical records should be consulted to ascertain and validate test results and medical diagnoses. Depending on the outcome of interest, the validation may require either a case-by-case approach or just the review of a random sample of cases. Other key aspects may require validation where appropriate. There are many databases in place for potential use in pharmacoepidemiological studies or in their validation phase.

Marketing Authorisation Holders should select the best data source according to validity (e.g. completeness of relevant information, possibility of outcome validation) and efficiency criteria (e.g. time span to provide results). External validity should also be taken into account: As far as feasible the data source chosen to perform the study should include the population in which the safety concern has been raised. In case another population is involved, the Marketing Authorisation Holder should evaluate the differences that may exist in the relevant variables (e.g. age, sex, pattern of use of the medicinal product) and the potential impact on the results. In the statistical analysis, the potential effect of modification of such variables should be explored.

With any data source used, the privacy and confidentiality regulations that apply to personal data should be followed.

References:

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TABLE I.7.B: ELEMENTS TO BE CONSIDERED IN THE PROTOCOL OF POST-AUTHORISATION SAFETY STUDIES AS APPROPRIATE

(Based on the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology³³.)

A	A descriptive title and version identifier (e.g. date)
B	The names, titles, degrees, addresses and affiliations of all responsible parties, including the principal investigator, co-investigators and a list of all collaborating primary institutions and other relevant study sites
C	The name and address of the Marketing Authorisation Holder
D	An abstract of the protocol
E	The proposed study tasks, milestones and timelines
F	A statement of research objectives, specific aims and rationale <i>Research objectives describe the knowledge or information to be gained from the study. Specific aims list the measurements to be made and any hypotheses to be tested. The protocol should distinguish between a priori research hypotheses and hypotheses that are generated based on knowledge of the source data. The rationale explains how achievement of the specific aims will further the research objectives.</i>

³³ Available on ISPE website <http://www.pharmacoepi.org/index.cfm>.

G	A critical review of the literature to evaluate pertinent information and gaps in knowledge <i>The literature review should describe specific gaps in knowledge that the study is intended to fill. The literature review might encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The literature review should also cite the findings of similar studies and the expected contribution of the current study.</i>
H	A description of the research methods, including: 1. The overall research design, strategy and reasons for choosing the proposed study design <i>Research designs include case-control, cohort, cross-sectional, nested case-control or hybrid designs.</i> 2. The population or sample to be studied <i>The population is defined in terms of persons, place, time period and selection criteria. The rationale for the inclusion and exclusion criteria and their impact on the number of subjects available for analysis should be described. If any sampling from a base population is undertaken, details of sampling methods should be provided.</i> 3. The strategies and data sources for determining exposures, health outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers, using validated measurements whenever possible <i>Data sources might include questionnaires, hospital discharge files, abstracts of primary clinical records, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews or exposure/disease registries.</i> 4. Clear operational definitions of health outcomes, exposures and other measured risk factors as well as selection criteria and comparison groups <i>An operational definition is one that can be implemented independently using the data available in the proposed study. For example, "PCP episode" is not an operational definition, whereas a better description would be "hospitalisation with a primary discharge diagnosis of ICD-9-CM code 136.3".</i> 5. Projected study size, statistical precision and the basis for their determination <i>Describe the relation between the specific aims of the study and the projected study size in relation to each outcome.</i> 6. Methods used in assembling the study data <i>This should include a description of or reference to any pre-testing procedures for research instruments and any manuals and formal training to be provided to interviewers, abstractors, coders or data entry personnel.</i> 7. Procedures for data management <i>Describe data management and statistical software programmes and hardware to be used in the study.</i> 8. Methods for data analysis <i>Data analysis includes all the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, to impute values or to modify raw data. Data analysis comprises comparisons and methods for analysing and presenting results, categorisations as well as procedures to control sources of bias and their influence on results, e.g. possible impact of biases due to selection,</i>

	<i>misclassification, confounding and missing data. The statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or effect, for instance, should be presented. Any sensitivity analyses undertaken should also be described.</i> 9. A description of quality assurance and quality control procedures for all phases of the study <i>Mechanisms to ensure data quality and integrity should be described, including, abstraction of original documents. As appropriate, include certification and/or qualifications of any supporting laboratory or research groups.</i> 10. Limitations of the study design, data sources and analytic methods <i>At a minimum, issues relating to confounding, misclassification, selection, generalisability and random error should be considered. The likely success of efforts taken to reduce errors should be discussed.</i>
I	A description of plans for protecting human subjects <i>This section should include information about whether study subjects will be placed at risk as a result of the study, provisions for maintaining confidentiality of information on study subjects and potential circumstances and safeguards under which identifiable personal information may be provided to entities outside the study. Conditions under which the study would be terminated (stopping rules) should be described. Procedures for monitoring results should be described; for prospective studies consider using a Data Safety Monitoring Board (DSMB) for this purpose.</i>
J	Management and reporting of adverse events/adverse reactions <i>This section should include the procedures for collecting, management and reporting of individual cases of adverse events or adverse reactions, as appropriate. If an exemption to the individual case reporting has been granted by the Competent Authorities, a mention should be made in this section along with a justification (the waiver must be attached as an annex).</i>
K	A description of plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication <i>There is an ethical obligation to disseminate findings of potential scientific or public health importance (e.g. results pertaining to the safety of a marketed medicinal product).</i>
L	Resources required to conduct the study <i>Describe time, personnel and equipment required to conduct the study, including a brief description of the role of each of the personnel assigned to the research project.</i>
M	Bibliographic references
N	Dated amendments to the protocol <i>Significant deviations from the protocol, such as any changes in the population or sample that were implemented after the beginning of the study, should be documented in writing. Any changes made after data analysis has begun should be documented as such and the rationale provided.</i>

O	Annexes <i>For any additional or complementary information on specific aspects not addressed in the body text (e.g. questionnaires, case report forms).</i>
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TABLE I.7.C: ELEMENTS TO BE CONSIDERED IN THE FINAL STUDY REPORT

(Based on the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology³⁴.)

1	A descriptive title
2	An abstract
3	Purpose (objectives) of the research, as stated in the protocol
4	The names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators
5	Name and address of the Marketing Authorisation Holder
6	Dates on which the study was initiated and completed
7	Introduction with background, purpose and specific aims of the study
8	A description of the research methods, including: a) Source population and selection of study subjects; b) Data collection methods and, if questionnaires or surveys are involved, complete copies (including skip patterns); c) Transformations, calculations or operations on the data; d) Statistical methods used in data analyses.
9	A description of circumstances that may have affected the quality or integrity of the data <i>Describe the limitations of study approach and the methods used to address them (e.g. response rates, missing or incomplete data).</i>
10	Analysis of the data <i>Include sufficient tables, graphs and illustrations to present the pertinent data and to reflect the analyses performed.</i>
11	Management and reporting of adverse events/adverse reactions
12	A statement of the conclusions drawn from the analyses of the data

³⁴ Available on ISPE website <http://www.pharmacoepi.org/index.cfm>.

13	A discussion of the implication of study results <i>Cite prior research in support of and in contrast to present findings. Discuss possible biases and limitations in present research.</i>
14	References

8. Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action

8.1 Introduction

Granting of a marketing authorisation for a medicinal product indicates that it is considered to have a satisfactory risk-benefit balance under the conditions defined in the Summary of Product Characteristics (SPC) and in accordance with the Risk Management Plan (where applicable) (see Chapter I.3), on the basis of the information available at that time.

During the post-authorisation period, larger and more diverse populations than those during the development phase of the product are likely to be exposed. New information on the benefits and risks of the product will be generated, and evaluation of this information and any safety concerns should be an on-going process, both by the Marketing Authorisation Holder and the Competent Authorities.

Both the Marketing Authorisation Holder and the Competent Authorities must keep abreast of all relevant information in order to fulfil the following responsibilities:

- Ensuring that all sources of information are screened regularly to identify any potential signals;
- Ensuring that appropriate action is taken in response to new evidence which impacts on the known risk-benefit balance;
- Keeping the Competent Authorities, Healthcare Professionals and Patients informed.

This Chapter

- outlines the responsibilities of Marketing Authorisation Holders in signal detection;
- provides the principles on which an assessment of the risk-benefit balance should be based; and
- outlines the steps that may be taken by Marketing Authorisation Holders in order to address a change in the risk-benefit balance.

8.2 Signal Detection and Evaluation

Signals of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions may arise from any source including preclinical and clinical data (e.g. spontaneous reports from Healthcare Professionals or Consumers; epidemiological studies; clinical trials), published scientific and lay literature. Standardised MedDRA Queries (SMQs) may be used for signal detection and the use of SMQs is recommended in order to retrieve and review cases of interest where signals are identified from adverse reaction databases.³⁵ Rarely, even a single report of an unexpected adverse reaction may contain sufficient information to raise a signal on or establish a causal association with the suspected medicinal product and impact on the risk-benefit balance.

The responsibilities of the Marketing Authorisation Holder, and in particular of the QPPV, are provided in Chapter I.1, Section 2. It is the responsibility of the QPPV to provide the Competent Authority with any information relevant to the evaluation of benefits and risks afforded by a medicinal product, including appropriate information on post-authorisation safety studies.

The Marketing Authorisation Holder should immediately inform the Competent Authorities in all Member States where the product is authorised and additionally, for centrally authorised products, the Agency of any prohibition or restriction imposed by the Competent/regulatory authorities of any country in the world in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product.

³⁵ Council for International Organizations of Medical Sciences (CIOMS). Development and rational use of Standardised MedDRA Queries (SMQs). Geneva: CIOMS; 2004. Available on CIOMS website <http://www.cioms.ch/>.

The Marketing Authorisation Holder and the Competent Authority should agree on the appropriate scope and timelines for evaluation, taking account of the authorisation procedure (see Chapters II.2.A and II.3) and agreed responsibilities for review. The Marketing Authorisation Holder should provide a comprehensive evaluation of the issue and the risks in the context of the benefits at the earliest opportunity and no later than the agreed date specified in the written communications between the Competent Authority and the Marketing Authorisation Holder. It should be sent to the Competent Authorities in all Member States where the medicinal product is authorised, and additionally to the Agency in the case of centrally authorised products.

8.3 Principles of Risk-Benefit Assessment

Overall risk-benefit assessment should take into account and balance all the benefits and risks referred to below. Risk-benefit assessment should be conducted separately in the context of each indication and population, which may impact on the conclusions and actions.

8.3.1 Assessment of Benefits

When a new or changing risk is identified, it is important to re-evaluate the benefit of the medicinal product using all available data. The benefit of a medicinal product can be seen as the decrease in disease burden associated with its use. Benefit is composed of many parameters including: the extent to which the medicinal product cures or improves the underlying condition or relieves the symptoms; the response rate and duration and quality of life. In the case of prophylactic medicinal products, the benefit may be considered as the reduction of the expected severity or incidence of the disease. With diagnostics, the benefit will be defined in terms of sensitivity and specificity or, in other words, false negative and false positive rates. Any available information on misuse of the product and on the level of compliance in clinical practice, which may have an impact on the evaluation of its benefits, should also be considered. The quality and degree of the evidence of benefit should be taken into account. Benefit should, as far as possible, be expressed in quantitative terms in a way that makes it comparable to the risks.

8.3.2 Assessment of Risks

Assessment of risk involves a stepwise process requiring identification, confirmation, characterisation (including identification of risk factors), and quantification of the risk in the exposed population. Overall assessment of risk should consider all available sources of information, including:

- Spontaneous adverse reaction reports;
- Adverse reaction data from studies which may or may not be company-sponsored;
- In vitro and in vivo laboratory experiments;
- Epidemiological data (see Table I.7.A);
- Registries, for example of congenital anomaly/birth defects;
- Data published in the worldwide scientific literature or presented as abstracts, posters or communications;
- Investigations on pharmaceutical quality, and
- Data on sales and product usage.

Important issues, which should be addressed in the assessment of adverse reactions, include evidence of causal association, seriousness, absolute and relative frequency and presence of risk factors, which may allow preventive measures. The quality and degree of evidence of risk should be taken into account. In the assessment of risks and consideration of regulatory action, it is important to note that rarely even a single case report may establish a causal association with the suspected medicinal product and impact on the risk-benefit balance. Risk assessment should also take account of the potential for overdose, misuse, abuse, off-label use and medication errors.

When new safety concerns are identified, which, could have an impact on the overall risk-benefit balance of a medicinal product, the Marketing Authorisation Holder should propose appropriate studies to further investigate the nature and frequency of the adverse reactions. A new or updated Risk Management Plan should be proposed accordingly (see Chapter I.3). The studies should comply with the guidance provided in Chapter I.7.

8.3.3 Risk-Benefit Assessment

Whenever possible, both benefits and risks should be considered in absolute terms and in comparison to alternative treatments. The magnitude of risk that may be considered acceptable is dependent on the seriousness of disease being treated and on the efficacy of the medicinal product. For example:

- In the treatment of a disease with high mortality, a high risk of serious adverse reactions may be acceptable providing the benefits associated with treatment have been shown to be greater.
- For medicines used in chronic diseases or in prevention of disabling diseases, some level of risk may be acceptable if there is a substantial improvement in the prognosis or quality of life.
- In situations where the main benefit is symptom relief for minor illnesses in otherwise healthy individuals or where individuals are treated not only for their own benefit but also for the benefit of the community (e.g. vaccination), risk levels must be extremely low.
- In cases where therapeutic benefit is limited, even a few cases of a serious adverse reaction may suffice to render the risk-benefit balance as unfavourable.
- If, for two medicinal products with essentially similar efficacy and types of adverse reactions, one or more serious adverse reactions were shown to differ in frequency, the risk-benefit balance of the product with the higher adverse reaction frequency may no longer be acceptable.

The populations being treated must also be taken into account, as should off-label use.

8.4 Improving the Risk-Benefit Balance

The Marketing Authorisation Holder should aim to optimise the safe use and the risk-benefit balance of an individual product and ensure that the adverse effects of a medicinal product do not exceed the benefits within the population treated. The risk-benefit balance of a medicinal product cannot be considered in isolation but should be compared with those of other treatments for the same disease.

The risk-benefit balance may be improved either by increasing the benefits (e.g. by restricting use to identified responders), or by reducing the risks by risk minimising measures (e.g. by contraindicating the use in patients particularly at risk, reducing dosage, introducing precautions of use and warnings and, if appropriate, pre-treatment tests to identify patients at risk, monitoring during treatment for early diagnosis of adverse reactions (see Table I.3.A for overview on risk minimisation methods). When proposing measures to improve the risk-benefit balance of a product, their feasibility in normal conditions of use should be taken into account. If dose reduction is considered as a method of risk minimisation, the impact of dose reduction on efficacy should be carefully evaluated.

The following types of action may be necessary and may be initiated by the Marketing Authorisation Holder or by the Competent Authorities:

- Variation of marketing authorisation(s) in respect of the indication, dosing recommendations, contraindications, warnings and precautions for use or information about adverse reactions or other sections of the SPC and the Package Leaflet (PL);
- Direct provision of important safety information to Healthcare Professionals and Patients/the public (e.g. through letters and/or bulletins or via electronic media) (see Chapter I.8, Section 6).

If there are important new safety concerns requiring urgent action, the Marketing Authorisation Holder, should initiate an urgent safety restriction (USR) in accordance with Commission Regulations

(EC) No 1084/2003 and (EC) No 1085/2003 followed by a type II variation. These measures should be immediately communicated to the relevant Competent Authorities and in addition to the Agency in case of a centrally authorised product. If no objections are raised within 24 hours after receipt of an application, the USR may be introduced and the corresponding application for the variation should be submitted without delay to the Competent Authorities and, with respect to centrally authorised medicinal products, the Agency. See also Chapter II.1, Section 7, and Chapters II.2.A and II.3.

8.5 Withdrawal of a Product from the Market on Risk-Benefit Grounds

In the event that the overall risk-benefit balance is considered to be unfavourable and proposed risk minimisation measures are considered inadequate to redress the balance, the medicinal product should be withdrawn from the market and Healthcare Professionals and Patients/the public should be informed as appropriate (see Chapter I.8, Section 6). Such action may be taken voluntarily by Marketing Authorisation Holders. It is recommended that any such intended measure be discussed at an early stage with all Competent Authorities concerned. All concerned Competent Authorities and the Agency should be informed immediately of any definite action.

For reporting requirements for Individual Case Safety Reports following withdrawal of a marketing authorisation see Chapter I.5.

8.6 Communication

In the event of a product withdrawal, an urgent safety restriction or an important variation, the content of Public Statements, Direct Healthcare Professional Communication (DHPC) and other communication from the Marketing Authorisation Holder to Healthcare Professionals, Patients and the general public, including the time frame for the distribution of such communication, should be agreed with the relevant Competent Authorities. Marketing Authorisation Holders are reminded of their legal obligations under Article 104(9) of Directive 2001/83/EC not to communicate information relating to pharmacovigilance concerns to the public without notification to the Competent Authorities. For further guidance see Part IV.

PART II: Guidelines for Competent Authorities and the Agency

1. Undertaking of Pharmacovigilance Activities by Competent Authorities in Member States

1.1 Introduction

The basis for undertaking of pharmacovigilance activities is established in EU legislation, as described in Directive 2001/83/EC (mainly Title IX) and Regulation (EC) No 726/2004 (particularly Articles 21-29). The aim of this Chapter is to provide overall guidance for national Competent Authorities on the principles described and in accordance with the Mandate of the Pharmacovigilance Working Party (PhVWP) (see Appendix II.1.A at the end of this Chapter).

For centrally authorised products, the European Commission is the Competent Authority. As the Agency co-ordinates some of the pharmacovigilance activities on behalf of the European Commission, the Agency should be understood as included in the term “Competent Authorities” for the purposes of this guidance.

To meet their legal requirements, Member States should undertake all appropriate activities, including the following:

- To encourage reporting of suspected adverse reactions by Healthcare Professionals;
- To facilitate reporting of adverse reactions by Patients either directly to national Competent Authorities, or via patient organisations, or via Healthcare Professionals, as appropriate in accordance with the national system;
- To maintain awareness of relevant pharmacovigilance publications through regular monitoring of the scientific literature;
- To initiate, as appropriate investigation and assessment of safety concerns;
- To oblige Marketing Authorisation Holders to systematically collect information on risks related to their medicinal products and to transmit this information to the Competent Authorities and the Agency as appropriate in accordance with Part I;
- To ensure that Marketing Authorisation Holders implement appropriate Risk Management Plans to effectively monitor and manage risks associated with the safety of their products;
- To monitor the impact and effectiveness of such Risk Management Plans and regulatory action taken to enhance safe and appropriate use of medicinal products;
- To monitor the compliance of Marketing Authorisation Holders in relation to their pharmacovigilance activities;
- To implement conditions and restrictions with regard to the safe and effective use of centrally authorised products, or products subject to referral procedures, on the basis of Commission Decisions;
- To interact with relevant international organisations, particularly the World Health Organization (WHO), in accordance with agreed guidance and procedures (see Chapter II.6);
- To communicate the outcome of evaluation of safety concerns as appropriate to Healthcare Professionals and as necessary to the public, through timely and appropriate methods of communication and to assess the impact of such communications;
- To make Individual Case Safety Reports (ICSRs) available to the Agency, Competent Authorities of other Member States and to the concerned Marketing Authorisation Holders according to the criteria laid down in legislation, and also described in this Chapter and Chapters II.2.A and II.3 and in Part III on the Electronic Exchange of Pharmacovigilance Information;
- To record electronic data and paper-based ICSRs in a database managed by the national Competent Authority. Data storage should ensure on-line accessibility in line with recommendations specified in Part III.

The requirements and procedures involved in a pharmacovigilance system are described in this Chapter, which relates to medicinal products authorised in the EU (using either centralised, mutual

recognition, decentralised or purely national procedures) and covers collection and evaluation of all information useful in the surveillance of medicinal products. This Chapter should be read in association with other relevant Chapters included in this Volume, in particular Chapter II.2.A on the conduct of pharmacovigilance for centrally authorised products and Chapter II.3 on the conduct of pharmacovigilance for medicinal products authorised through the mutual recognition or decentralised procedure, Part III on electronic reporting, Chapter II.2.B on the Crisis Management Plan for centrally authorised products, Chapter II.4 on the Rapid Alert/Non-Urgent Information System, Chapter I.3 on Risk Management Systems and Part IV on communication to the public.

1.2 Establishment of a Pharmacovigilance System

Each Member State should have in place systems for receipt and evaluation of all pharmacovigilance data and to ensure that appropriate regulatory action may be taken. Such systems, whether involving distribution of activities through regional centres or operated fully by a single national centre, within the Competent Authority, should ensure that pharmacovigilance data are managed in a way that is compatible with the procedures undertaken in other Member States and the Agency in order that pertinent data may be shared between Member States and the Agency.

In accordance with Article 102a of Directive 2001/83/EC, the management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance should be under the permanent control of the Competent Authorities in order to guarantee their independence. According to Article 67(4) of Regulation (EC) No 726/2004, activities relating to pharmacovigilance, operation of communication networks and market surveillance should receive adequate public funding commensurate with the tasks conferred.

Each Member State should ensure appropriate procedures and systems exist between pre-authorisation and post-authorisation functions to ensure the availability of comprehensive and integrated pharmacovigilance systems.

Each Member State should monitor Marketing Authorisation Holder compliance with pharmacovigilance obligations (e.g. timely reporting of expedited adverse reaction reports, timely submission of Periodic Safety Update Reports in accordance with agreed formats and content, appropriate and comprehensive responses to ad hoc queries from Competent Authorities) and should undertake monitoring of compliance and pharmacovigilance inspections in accordance with Chapter I.2 on monitoring of compliance and pharmacovigilance inspections.

The CHMP Pharmacovigilance Working Party (PhVWP) has been given a Mandate, Objectives and Rules of Procedure (see Appendix II.1.A at the end of this Chapter) to provide advice on the safety of medicinal products authorised in the EU and on the investigation of adverse reactions to enable effective identification, assessment, management and communication of risk at any time during the life of a medicinal product and to provide recommendations for regulatory action to the CHMP and the national Competent Authorities. This requires interaction with the CHMP and specialised experts as appropriate, as well as consensus development and coordination of pharmacovigilance issues at EU level. Each Member State should ensure that it actively participates in and cooperates with the PhVWP in order to fulfil its pharmacovigilance obligations at EU level.

All Member States should cooperate with international bodies, in particular the World Health Organization (WHO) and the WHO Collaborating Centre for International Drug Monitoring through their national Competent Authorities, in keeping with the guidance provided in Chapter II.6 on principles of collaborating with WHO.

Competent Authorities and the Agency should also cooperate with regulatory authorities outside the EU on the basis of any formal arrangements in place for exchange of data and other information.

1.3 Management of Spontaneous Reporting Programmes

1.3.1 General Principles

Each Member State should have in place a system for the collection of spontaneous suspected adverse reaction reports from Healthcare Professionals, Marketing Authorisation Holders (see also Chapter I.4) and, where appropriate, from Patients/Consumers (see Chapter 1.4, Section 3.5). Competent Authorities should liaise with Healthcare Professionals in their territory, to increase awareness of the reporting system, stressing its importance and encouraging reporting.

To this end, it is desirable that each Member State should ensure the following:

- That reporting of adverse reactions is straightforward and accessible to Healthcare Professionals and, where appropriate, to Patients/Consumers (by providing a user-friendly reporting system, e.g. free post, telephone and/or web-based systems);
- That all adverse reaction reports are acknowledged where appropriate and further information is forwarded as requested; and
- That regular contact is maintained between the national/regional pharmacovigilance centre(s) and Healthcare Professionals, for example by:
 - Publication of regular pharmacovigilance bulletins;
 - Circulation of Direct Healthcare Professional Communications, where appropriate, (either by the Competent Authority and/or the Marketing Authorisation Holder);
 - Provision of information in response to specific requests from Healthcare Professionals and other stakeholders;
 - Provision of lectures and talks to Healthcare Professionals during scientific meetings and conferences; and
 - Availability of comprehensive websites that facilitate and encourage reporting of suspected adverse reactions.

The following recommendations concern spontaneous reporting system procedures:

- A Healthcare Professional or a Marketing Authorisation Holder reports a suspected adverse reaction, related to one or more medicinal products, to the Competent Authority in the Member State where the reaction occurred. Reports may be made in writing (e.g. using report forms), by telephone, or electronically in the case of Marketing Authorisation Holders.
- Reports are collected and validated by the regional centre or national Competent Authority and are entered into a database. Serious reactions should be handled with the highest priority. The database should be used to identify potential signals and analyse data in order to e.g. clarify risk factors and apparent changes in reporting profiles.
- Case reports should be made accessible to the Agency, to the Competent Authorities of other Member States, and to the concerned Marketing Authorisation Holders according to the criteria laid down in legislation, and described in this Chapter, Chapters II.2.A and II.3, and in Part III on the electronic exchange of pharmacovigilance information.

The following requirements relate to the Competent Authorities of Member States and are independent of the structure of the national pharmacovigilance systems (centralised or regionalised). The requirements are described as follows:

- Receipt and validation of ICSRs;
- Processing of ICSRs;
- Evaluation of ICSRs;
- Reporting of ICSRs;
- Quality management; and
- Confidentiality and security.

1.3.2 Receipt and Validation of Individual Case Safety Reports (ICSRs)

This concerns receipt and validation of primary data, i.e. the data transmitted from the original reporter to the Competent Authority. For validation and management of electronically transmitted reports, the specific requirements should be followed (see Part III).

A single case report concerns one Patient, one or more identifiable reporter(s), one or more suspected adverse reaction(s) and one or more suspected medicinal product(s). Cases that meet the criteria for expedited reporting should be submitted in accordance with the requirements specified in Chapter I.4.

Validation of ICSRs received directly from Healthcare Professionals and Patients/Consumers

National Competent Authorities should attempt to validate all ICSRs submitted to ensure, prior to reporting to the Marketing Authorisation Holders and the Agency, that the minimum information required (see Chapter I.4, Section 1) is included in the ICSR.

This minimum information allows the case to be entered onto a database and become available for signal detection. Every effort should be made to obtain complete case information.

If the original notification of a case is made orally or by telephone to the national Competent Authority, it should be confirmed in writing by a Healthcare Professional. When several suspected adverse reactions to one or more suspected medicinal products occur in one Patient, but are considered to be independent reactions, they should be treated as separate cases. If considered appropriate, especially in the case of serious or unexpected adverse reactions, data in the report concerning the Patient, the medicinal products taken, the adverse reactions experienced, including signs and symptoms and laboratory reports, and the dates should be confirmed by copies of the most important and relevant original documents (e.g. hospital discharge forms, specialist reports, laboratory tests, prescriptions and post mortem reports).

Reports should be followed-up to obtain additional information relevant to the case as necessary, and follow-up information should be reported to the Marketing Authorisation Holder and the Agency. All available clinical information relevant to the evaluation of the reaction should be provided.

For adverse reaction reports relating to biological products, the definite identification of the product with regard to its manufacturing is of particular importance. Therefore, Competent Authorities should give advice to reporters to provide the name of the medicinal product (in accordance with Article 1(20) of Directive 2001/83/EC, see Annex 1.3) and the batch number and should follow-up the reports where this information is missing for completion.

When information is received directly from a Patient/Consumer suggesting that an adverse reaction has occurred, the regional/national pharmacovigilance centre should attempt to obtain consent to contact a Healthcare Professional nominated by the Patient/Consumer for follow-up information. Such cases should be managed in accordance with the guidance described in Chapter I.4 and any relevant national legal requirements and/or guidance.

With regard to interpretation of the term suspected, see Chapter I.4.

1.3.3 Processing Individual Case Safety Reports

Paper-based ICSRs should be stored and treated in the same way as other medical records, with appropriate respect for confidentiality and in accordance with the requirements specified by Directive 95/46/EC on protection of personal data.

Electronic data and paper-based ICSRs should be recorded in a database by the national Competent Authority, taking account of the relevant legal requirements. Data storage should ensure on-line accessibility of data in line with the recommendations specified in **Part III**.

Terminologies

The internationally agreed medical terminology (MedDRA) and other terminologies referred to in **Part III** should be used (see **Annex 3.2**). All coding used in national pharmacovigilance databases should be compatible with or automatically transferable to the format of the ICH-E2B(M) standard (see **Annex 4**).

Reaction terms should be entered as the closest term available in the terminology using the appropriate MedDRA Lowest Level Terms (LLTs), and, if possible, also in the original reporter's words.

Use of terminologies should be monitored and validated, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency verified.

Data Entry

Conformity of stored data with initial and follow-up reports should be ensured by a quality control procedure, which provides for validation against the original data or images thereof.

Storage should ensure traceability (audit trail) of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data.

Case report processing also concerns evaluation of data from ICSRs, as well as identification of individual cases requiring specific handling, signal detection and evaluation and any other processing of aggregate data deemed necessary.

Management of Duplicate Reports

Some ICSRs, especially those which are serious, may be reported to Competent Authorities from more than one source, or from a single source through more than one channel. The Competent Authority should make every effort to ensure that case reports contain sufficient information to identify such duplicates, e.g. from Patient/reporter initials (or names, if appropriate), addresses, date of birth and/or other dates and should liaise with relevant Marketing Authorisation Holders to facilitate identification of possible duplicate cases. Databases should be reviewed regularly to identify duplicates in accordance with national Competent Authority and Agency procedures. After identification, duplicates should be merged into a single new (or merged) ICSR, in accordance with ICH-E2B(M) guidance (see **Part III**).

1.3.4 Reporting of Individual Case Safety Reports

ICSRs that meet the criteria for expedited reporting to other Competent Authorities, the Agency or Marketing Authorisation Holders should be transmitted in accordance with approved formats and timelines, as defined in **Chapter I.4**.

All serious adverse reactions, occurring within a Member State and notified to the national Competent Authority by a Healthcare Professional should be transmitted to the Marketing Authorisation Holder and to the Agency within 15 calendar days of their receipt by the regional/national centre. The clock for expedited reporting starts (day 0) as soon as the minimum information (see **Chapter I.4**) has been brought to the attention of the national or regional pharmacovigilance centre.

The data transmitted should be as complete as possible in order to facilitate assessment, but it is not obligatory for national Competent Authorities to have made a formal evaluation before this transmission (see also Chapter II.4 and Part III).

National Competent Authorities should ensure that ICSRs are transmitted electronically to the Agency, as required (see Part III).

ICSRs associated with use of medicinal products authorised through the mutual recognition or decentralised procedures and for medicinal products which have been the subject of a referral procedure, provided to the RMS or Rapporteur by the Marketing Authorisation Holder should only be transmitted to EudraVigilance by the Competent Authority in the Member State where the case occurred. To avoid duplicate reporting, the Reference Member State/Rapporteur Member State should not re-transmit these ICSRs to EudraVigilance (see Chapter II.3).

In the case of centrally authorised medicinal products, it is the responsibility of the Agency to inform each Member State of serious reports received from other Member States. Information should be transmitted within the timeframe outlined in Chapter II.2.A. ICSRs should also be transmitted to the WHO Collaborating Centre for International Drug Monitoring by the Competent Authority in whose territory the reaction occurred, as described in Chapter II.6.

Data from non-serious, expected or unexpected, adverse reaction reports that are received from all sources should not be reported on an expedited basis, but should be available for transmission to relevant parties (Marketing Authorisation Holder, Member States and the Agency), as necessary (see Chapter II.4 and Part III).

1.3.5 Evaluation of Individual Case Safety Reports

Following validation, evaluation of ICSRs includes assessment of the seriousness and expectedness of the suspected adverse reaction. These terms (seriousness and expectedness) have specific meanings in the context of adverse reaction report evaluation (see Glossary in Annex 1.1). Evaluation of the probability of a causal relationship between the medicinal products and the suspected reaction(s) may be undertaken, when considered appropriate. All methods used to evaluate these parameters should be documented. Evaluators should be trained in the methods used and their training should be verified.

1.3.6 Signal Detection

Database functionality should enable users to search and retrieve data to facilitate cumulative data review, signal detection and trend analysis. Standardised MedDRA Queries (SMQs) may be used for signal detection and the use of SMQs is recommended in order to retrieve and review cases of interest where signals are identified from adverse reaction databases³⁶. When a signal is identified, the possibility of a causal relationship should be considered and in these circumstances, all relevant adverse reaction data should be further analysed. All ICSRs fulfilling the minimum information requirements (see Chapter I.4, Section 1) should be included in the overall analysis. Certain analyses (for example those concerning the role of risk factors) may be confined to cases where sufficient information is available, but it should be made clear that this is a subset of the data.

Competent Authorities and Marketing Authorisation Holders should inform each other of identified signals, which may impact on the known risk-benefit balance of nationally authorised medicinal products and in the case of products authorised through the centralised, mutual recognition or decentralised procedures in accordance with relevant guidance (see Chapters II.2A and II.3). Overall pharmacovigilance evaluation and relevant regulatory action should be initiated by Competent

³⁶ Council for International Organizations of Medical Sciences (CIOMS). Development and rational use of Standardised MedDRA Queries (SMQs). Geneva: CIOMS; 2004. Available on CIOMS website <http://www.cioms.ch/>.

Authorities in accordance with the criteria and guidance described below and in Chapter I.8. The PhVWP Mandate provides a forum for discussion and finalisation of regulatory proposals by the PhVWP at the request of a Member State or the CHMP, following initial review and evaluation of a signal at national level or by the Rapporteur. The Rapid Alert/Non-Urgent Information System should be used by Competent Authorities when applicable and Competent Authorities should communicate with Marketing Authorisation Holders in accordance with the requirements specified (see Chapter II.4).

It is essential that signals/safety concerns are communicated at an early stage, preferably before a national decision is taken.

1.3.7 Provision of Information to the World Health Organization and Other International Bodies

Competent Authorities should ensure that appropriate and timely information is provided to the World Health Organization (WHO), in accordance with the guidance provided in Chapter II.6.

Competent Authorities should also interact regularly and as required with relevant national and international bodies (e.g. national haemovigilance centres, centres for disease control, poison centres), regarding exchange of appropriate and timely information.

1.3.8 Feedback Information to Reporting Healthcare Professionals

National Competent Authorities should ensure that the original reporter(s) of a case is (are) informed of its receipt and are provided with the allocated reference number and, if appropriate, additional information should be requested.

1.3.9 Quality Management

Quality management concerns every step in the processes described above. Quality control and quality assurance should be ensured by national Competent Authorities, who should devise, document and implement appropriate procedures.

1.3.10 Confidentiality and Security

Confidentiality of Patients' records including personal identifiers, if provided, should always be maintained. Identifiable personal details of reporting Healthcare Professionals should be kept in confidence, as appropriate and in keeping with national and EU legislation.

At each stage of storage and processing of pharmacovigilance data, measures should be taken to ensure data security and confidentiality. This involves strict control of access to documents and to databases to authorised personnel sharing the medical and administrative confidentiality of the data. This security extends to the complete data path. Case report information should only be transmitted to stakeholders, or otherwise provided by Competent Authorities in an anonymous form.

In addition, procedures should be implemented to ensure security and non-corruption of data during data transfer.

1.4 Company-Derived Pharmacovigilance Data

The Marketing Authorisation Holder should ensure that a Qualified Person for Pharmacovigilance (QPPV) is permanently and continuously available and that an appropriate system of pharmacovigilance is in place in order to ensure responsibility and liability for marketed products to ensure that appropriate action can be taken, in accordance with the legal requirements described in Article 103 of Directive 2001/83/EC and Article 23 of Regulation (EC) No 726/2004. Guidance for

Marketing Authorisation Holders on the implementation and practical procedures involved in complying with legal requirements is described in [Part I and Part III](#). Competent Authorities should ensure that the information and contact details for QPPVs and back-up services are documented and accessible to facilitate interaction between the Competent Authority and the Marketing Authorisation Holders via QPPVs, as appropriate. Competent Authorities should also ensure that the descriptions of Marketing Authorisation Holders' pharmacovigilance systems are reviewed and assessed, as described in [Chapter I.2](#).

Company-derived pharmacovigilance data includes the following:

- Risk Management Plans;
- Individual Case Safety Reports (ICSRs);
- Periodic Safety Update Reports (PSURs);
- data from company-sponsored post-authorisation safety studies;
- Risk-Benefit Reviews;
- relevant data arising from post-authorisation commitments; and
- other relevant data, e.g. proposed communication texts.

This subchapter deals with the procedures to be undertaken by Competent Authorities in reviewing company-derived pharmacovigilance data.

1.4.1 Risk Management Plans

Applicants and Marketing Authorisation Holders should submit product-specific Risk Management Plans in accordance with the requirements specified in [Chapter I.3](#).

Risk Management Plans should be thoroughly assessed by the Competent Authorities in terms of complexity, content and adequacy. Feedback and comments should be provided to Applicants and Marketing Authorisation Holders, as appropriate. Assessment Reports on Risk Management Plans should be provided to Marketing Authorisation Holders, which may impact on and/or facilitate discussion with other Competent Authorities.

Risk Management Plans serve as a basis for post-authorisation pharmacovigilance activities; therefore they should be stored in a way that allows rapid and complete access to the documentation.

An Assessment Report on a Risk Management Plan should be prepared by the national Competent Authority or Lead Member State for purely nationally authorised products, or by the Reference Member State or the Rapporteur for products authorised via the mutual recognition, decentralised or centralised procedures respectively.

1.4.2 Individual Case Safety Reports

Each Competent Authority should ensure that ICSRs submitted by Marketing Authorisation Holders conform to the requirements described in [Chapter I.4](#), in order to ensure compliance with reporting of suspected adverse reactions by Marketing Authorisation Holders. Furthermore, each national Competent Authority should ensure that suspected, serious adverse reaction reports are followed up by Marketing Authorisation Holders in accordance with the requirements described in [Chapter I.4](#). Competent Authorities should ensure that they have the capability to send and receive ICSRs electronically and should ensure that Marketing Authorisation Holders do so in accordance with agreed legal requirements, procedures and guidance ([see Part III](#)).

1.4.3 Periodic Safety Update Reports

A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a medicinal product to Competent Authorities at defined times post-authorisation ([see](#)

also Chapter I.6). Assessment of PSURs should be undertaken by Competent Authorities in accordance with agreed procedures and taking account of the authorisation process for a medicinal product.

Competent Authorities should liaise with Marketing Authorisation Holders regarding submission of PSURs, particularly to facilitate harmonisation of PSUR periodicity for medicinal products containing the same active substance and to consider circumstances where the PSUR periodicity may be amended.

PSURs for centrally authorised products are evaluated by the Rapporteur and Assessment Reports are circulated to Member States and the Agency according to a timetable agreed by the CHMP (see Chapter II.2.A).

PSURs for products authorised via the mutual recognition or decentralised procedure are evaluated by the Reference Member State. An Assessment Report is circulated by the Reference Member State to all Concerned Member States within 6 weeks of receipt of the PSUR (see Chapter II.3).

It is the responsibility of the national Competent Authorities to evaluate PSURs for purely nationally authorised products in accordance with agreed procedures, as appropriate.

In the case of PSURs requested for immediate submission by Competent Authorities (i.e. outside the regular reporting periodicity), the requesting Competent Authority should liaise with the Marketing Authorisation Holder regarding the timescale for submission and assessment, taking account of the urgency of the issue.

In order to reduce duplication of effort and maximise use of available resources, Competent Authorities are encouraged to participate in the PSUR work-sharing project on assessment of PSURs via a Lead Member State for nationally authorised products and to follow relevant guidance³⁷.

PSUR Assessment Reports should be provided to the Marketing Authorisation Holder.

1.4.4 Data from Company-Sponsored Post-Authorisation Safety Studies

Competent Authorities requesting post-authorisation safety studies (PASS) should liaise with the relevant Marketing Authorisation Holders on preparation and review of study documentation as described in Chapter I.7. In addition, Competent Authorities should ensure that they are notified of PASS undertaken at the initiative of Marketing Authorisation Holders.

For PASS that fall under the provisions of Directive 2001/20/EC on clinical trials, Competent Authorities should follow the relevant provisions accordingly.

Competent Authorities may maintain a register of PASS conducted on their territory, as appropriate.

Serious adverse reactions occurring in non-interventional PASS should be reported on an expedited basis by Marketing Authorisation Holders and processed as such by Competent Authorities.

Competent Authorities should assess, as appropriate, Study Reports from Marketing Authorisation Holders on the progress and completion of PASS (see Chapter I.7, Section 4.3). Any impact of the findings on the Product Information should be evaluated and an Assessment Report prepared and circulated, as appropriate.

Information on medically or scientifically relevant conclusions (e.g. significant change in frequency of a known adverse reaction, new unexpected adverse reaction, new interaction) should be appropriately reflected in the Product Information (SPC, Package Leaflet and Labelling). The timeframe for

³⁷ Available on Heads of Medicines Agencies website <http://heads.medagencies.com>.

incorporation of such changes should be proposed by the Marketing Authorisation Holder with the submission of the study report and agreed by the Competent Authority. If rapid dissemination and discussion of the new information at EU level is deemed necessary by a Competent Authority following assessment of the submitted report (see below), the procedures described in [Chapter II.4](#) should be followed.

In the case of studies conducted for purely nationally authorised medicinal products, the relevant Member State(s) is (are) responsible for evaluation of the Study Reports. Where a PASS is conducted in a number of Member States, a Lead Member State may be appointed by the PhVWP for this evaluation and generation of an Assessment Report.

In the case of medicinal products authorised through mutual recognition or decentralised procedures, evaluation of the Study Reports will normally be carried out by the Reference Member State (see [Chapter II.3](#)).

In the case of medicinal products authorised through the centralised procedure, the Rapporteur will normally assess the final Study Report (see [Chapter II.2.A](#)).

The Assessment Report should be distributed to the Marketing Authorisation Holder, to the CHMP, the Agency and as appropriate, to other Competent Authorities within three months of receipt of the report from the Marketing Authorisation Holder.

In the case of PASS undertaken at the Marketing Authorisation Holder's initiative, progress and final study reports should be included or updated in the corresponding PSUR and/or Risk Management Plan (see also [Chapters I.3 and I.6](#)).

1.4.5 Risk-Benefit Reviews

Risk-Benefit Reviews requested by Competent Authorities should always be thoroughly evaluated by the Competent Authorities and an Assessment Report prepared in accordance with agreed timelines, taking account of the urgency of the issue. As such reviews are prepared and submitted for important reasons, they should be prioritised for assessment. In accordance with the PhVWP Mandate, Risk-Benefit Reviews may be considered by the PhVWP at the request of the CHMP or a Member State. In these circumstances, consideration may be given to review of generic medicinal products containing the same active substance, or other medicinal products belonging to the same therapeutic class. A Lead Member State(s) may be appointed by the PhVWP to carry out evaluation of Risk-Benefit Reviews, taking account of relevant authorisation procedures for the medicinal products concerned. Competent Authorities designated as Lead Member State for the purposes of assessment of such reviews should liaise regarding assignment of products, development of a List of Questions for Marketing Authorisation Holders, the format and content of Assessment Reports and to determine the timeframe for receipt and evaluation of the data.

Assessment Reports should be provided to the Marketing Authorisation Holder and as appropriate, to other Competent Authorities and the Agency.

Changes to the Product Information deemed necessary following evaluation of such Reviews should be notified to other Competent Authorities in accordance with the criteria described in [Chapter II.4](#).

1.4.6 Reports on Post-Authorisation Commitments

Competent Authorities should implement tracking systems to monitor compliance and progress of post-authorisation commitments (see also [Chapter I.2](#)). The system should ensure that any commitment specified at the time of granting of the marketing authorisation is fulfilled. The EMEA maintains the tracking system for post-authorisation commitments related to centrally authorised products.

Reports submitted by the Marketing Authorisation Holder should be assessed and the Assessment Reports provided to the Marketing Authorisation Holder and, as appropriate, to other Competent Authorities and the Agency.

When a product is authorised via the mutual recognition or decentralised procedure, the Concerned Member States should be informed by the Reference Member State.

When a product is centrally authorised, the Agency and all Member States should be informed by the Rapporteur.

1.4.7 Other Data

Competent Authorities should consider all other pharmacovigilance-related data submitted by or requested from Marketing Authorisation Holders to facilitate assessment of signals or emerging safety concerns, such as data on volume of sales and prescription of medicinal products. These data should be evaluated and the outcome reflected in Assessment Reports, as appropriate.

1.5 Pharmacovigilance Data from Other Sources

1.5.1 Intensive Monitoring Schemes

Intensive Monitoring is a system of record collection from designated areas, e.g. hospital units or by specific healthcare professionals in community practice. Competent Authorities may be involved in the preparation of protocols to facilitate data collection or may be informed that such monitoring is taking place. As the national Competent Authority is usually the liaison point for such systems, relevant adverse reaction reports identified should be processed and managed appropriately, with relevant reports notified to the Agency and Marketing Authorisation Holders on an expedited basis.

Furthermore, it may be considered appropriate in the authorisation of certain medicinal products to impose specific requirements in respect of reporting serious or unexpected reactions on the prescribing physician and to make these requirements a condition of use of the product under the terms of the marketing authorisation.

The relevant national Competent Authority should ensure that data and reports are collected at agreed intervals and in an appropriate format (see also Chapters I.4, I.6 and I.7).

1.5.2 Data on Medication Errors, Overdose, Misuse and Abuse

Reports of suspected adverse reactions due to medication errors, overdose, misuse and abuse of medicinal products, which are received by the national Competent Authorities (e.g. directly from Healthcare Professionals or via Marketing Authorisation Holders or poison centres) should be handled in the same way as other Individual Case Safety Reports (see Chapter I.4 and Chapter II.1, Section 3).

Competent Authorities in Member States should ensure cooperation with other national agencies responsible for collation of data associated with medication errors, overdose, misuse and abuse, as appropriate (see also Chapter I.5).

1.5.3 Other Information Sources Relevant to Pharmacovigilance

These information sources may include the following:

- Drug usage data;
- Published adverse reaction reports;
- Data from pharmacoepidemiology studies conducted by organisations other than the Marketing Authorisation Holder;

- Data from pre-clinical studies;
- Significant quality data; and
- Reports on products not currently marketed in Member States.

Such information may be important for determining for example frequency, occurrence of unexpected adverse reactions, new interactions and overall risk-benefit balance. In cases where significant information is received from these sources, these findings may be transmitted to other Member States and the Agency (see Chapter II.1, Section 6 and Chapter II.4).

1.6 Procedures for Data Exchange

This Section describes the procedures that should be implemented in order to facilitate communication of pharmacovigilance information between Competent Authorities in Member States, between Competent Authorities and the Agency and between Competent Authorities and Marketing Authorisation Holders, to optimise use of resources for detection and evaluation of pharmacovigilance signals.

Where a national Competent Authority identifies new information which may influence the overall risk-benefit assessment it is usually appropriate that they communicate this concern to the Marketing Authorisation Holder at the time that such information is shared with other Competent Authorities and the Agency. A comprehensive Assessment Report evaluating the issue and the risks in the context of the benefits should be submitted by the Competent Authority at the earliest opportunity and no later than the agreed date specified in the written communications between the Competent Authority and the Marketing Authorisation Holder. It should be sent to the Marketing Authorisation Holder, all Competent Authorities in Member States where the medicinal product is authorised, and usually in addition to the Agency for discussion at EU level, as appropriate. The Competent Authority should discuss the outcome of the evaluation with the Marketing Authorisation Holder, or in the case of products authorised through EU assessment procedures, with the Rapporteur/Reference Member State. Liaison between Competent Authorities and the Marketing Authorisation Holder on pharmacovigilance related issues should take place via the QPPV.

1.6.1 Technologies for Data Transmission

For data exchange and communication between Competent Authorities in Member States, the Agency and Marketing Authorisation Holders, only appropriate secure communication systems (e.g. EudraNet and EudraVigilance) should be used. EudraLink should only be used when transmission via EudraNet is not possible.

Competent Authorities should ensure that their pharmacovigilance personnel are familiar with the rules and procedures involved in the use of these systems and with the requirements for electronic reporting of adverse reactions (see Part III).

1.7 Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action

The Competent Authority in each Member State, as part of its obligation to undertake ongoing evaluation of the risk-benefit balance of medicinal products, should ensure that all pharmacovigilance data received and evaluated, as outlined above, are taken into account on an ongoing basis.

New data on the benefits and risks of medicinal products will become available during the post-authorisation period and evaluation of this information should be carried out on an on-going basis by Marketing Authorisation Holders and Competent Authorities, taking account of the relevant authorisation procedures and/or any arrangements in place for work-sharing in respect of product specific/class related reviews (see also Chapter I.8). As a consequence of such evaluations, a marketing authorisation may be varied, suspended, revoked, withdrawn or not renewed, as necessary

and according to the appropriate procedure. Criteria for such regulatory action are set out for example in Articles 116 and 117 of Directive 2001/83/EC.

In the case of centrally authorised medicinal products, changes to the marketing authorisation status or Summary of Product Characteristics (SPC) are undertaken according to Commission Regulation (EC) No 1085/2003 and as outlined in [Chapter II.2.A](#).

The procedure to be followed for changes to the marketing authorisation status or the SPC for medicinal products authorised via the mutual recognition or decentralised procedure is described in Commission Regulation (EC) No 1084/2003 and in [Chapter II.3](#). It is the responsibility of the Reference Member State to coordinate the procedure, with changes implemented simultaneously in all Concerned Member States. National decisions should take effect on the day agreed after discussion between the Reference Member State and the Marketing Authorisation Holder in consultation with the Concerned Member States. Every effort should be made to implement these changes as soon as possible.

In the case of purely nationally authorised medicinal products, where updated pharmacovigilance data are considered to impact on the risk-benefit profile of the medicinal product, the Competent Authority in the Member State may request a variation to the marketing authorisation status or the SPC in accordance with national procedures.

As provided for in Commission Regulations (EC) No 1084/2003 and 1085/2003, provisional urgent safety restrictions may be taken in the event of a risk to public health. An urgent safety restriction may be taken by the Marketing Authorisation Holder if the Competent Authority in the Member State or, for centrally authorised products, the Agency does not raise any objection within 24 hours after the Marketing Authorisation Holder's notification. The Competent Authority may also impose an urgent safety restriction. In the case of a centrally authorised product, the Agency will act in accordance with [Chapter II.2.A](#) and notify all Member States, circulating a Rapid Alert ([see Chapter II.4](#)). In case of a non-centrally authorised product, the national Competent Authority will notify any urgent safety restriction to the other Member States and the Agency circulating a Rapid Alert ([see Chapter II.4](#)). Should this concern a product authorised via the mutual recognition or decentralised procedure, the agreed guidance in [Chapter II.3](#) should be followed. An urgent safety restriction should be followed by submission by the Marketing Authorisation Holder of a variation application immediately and in no case later than 15 days after the initiation of the urgent safety restriction.

Under the terms of Articles 31, 36 and 37 of Directive 2001/83/EC, a Member State, the European Commission or the Marketing Authorisation Holder may refer a pharmacovigilance matter relating to a nationally authorised product(s), including those authorised through the mutual recognition and decentralised procedures, to the CHMP whenever the interests of the Community are involved. These matters may be referred by the CHMP to the PhVWP for consideration. The Commission Decision issued on the basis of the CHMP Opinion is binding on all Member States ([see Chapter II.5](#) for reference to further guidance).

Any significant change to the marketing authorisation status or SPC considered or undertaken nationally should be notified to the other Member States, the European Commission and the Agency ([see Chapter II.4](#)).

In the case of centrally authorised products, where urgent action to protect human health or the environment is considered essential, a Member State may suspend the use of a medicinal product on its territory, in accordance with Article 20(4) of Regulation (EC) 726/2004. In such cases, the Member State should inform the European Commission and the Agency immediately and no later than the following working day, providing the reasons for its action. In order to meet this legal requirement and to inform the other Member States, the Member State should circulate a Rapid Alert as described in [Chapter II.4](#). The European Commission should immediately consider the reason given by the

Member State and shall request the Opinion of the CHMP within a specified time limit, determined in accordance with the urgency of the issue (see Chapter II.2.A).

For nationally authorised medicinal products, including those authorised through the mutual recognition, decentralised and ex-concertation procedures, where a Member State considers, following evaluation of pharmacovigilance data, suspension or revocation of a marketing authorisation, or its variation resulting in important changes to the Product Information as described in Chapter II.4, the Rapid Alert System should be used to notify the other Member States and the Agency immediately in accordance with Article 107(1) of Directive 2001/83/EC as well as the European Commission.

Where a Member State suspends the marketing authorisation for a nationally authorised product (this includes products authorised through the mutual recognition and decentralised procedures), in order to urgently protect public health on its territory, the Member State should circulate a Rapid Alert (see Chapter II.4) at the latest one working day after the suspension, informing the other Member States, the Agency and the European Commission of this action in accordance with Article 107(2) of Directive 2001/83/EC.

Where the Agency is informed of a revocation or suspension of a marketing authorisation by a Member State, the CHMP should prepare an Opinion within a timeframe to be determined depending on the urgency of the matter. In the case of a variation resulting in important changes to the Product Information as described in Chapter II.4, the CHMP may be requested by a Member State to prepare such an Opinion. On the basis of the Opinion, the European Commission may request Member States to take temporary measures immediately and final measures may be taken in accordance with Article 121(3) of Directive 2001/83/EC (see Article 107(2) of Directive 2001/83/EC and Chapter II.5).

If suspension, withdrawal or variation resulting in important changes to the Product Information as described in Chapter II.4 seems likely, the Marketing Authorisation Holder should be informed of any intended action at an early stage. In the case of medicinal products authorised through purely national procedures, it is the responsibility of the Competent Authorities in the Member States concerned to inform the Marketing Authorisation Holder. For products authorised through mutual recognition or decentralised procedures, this task is usually undertaken by the Reference Member State. For centrally authorised products, the Agency, in consultation with the Rapporteur should inform and liaise with the Marketing Authorisation Holder.

1.8 Sanctions

In accordance with Directive 2001/83/EC Article 104(9) and Regulation (EC) 726/2004 Article 24(5) and 84, Member States are required to take the necessary measures to ensure that Marketing Authorisation Holders who fail to discharge their obligations are subject to effective, proportionate and dissuasive penalties (see also Chapter I.2).

1.9 Public Communication and Transparency

Competent Authorities should ensure that Healthcare Professionals, Patients/Consumers and the general public are informed, where appropriate, of any significant changes in the Product Information (Summary of Product Characteristics and Package Leaflet) and of any suspected safety concerns requiring vigilance. Competent Authorities should ensure their compliance with requirements for transparency and public communication (see Part IV).

APPENDIX 1.A: MANDATE, OBJECTIVES AND RULES OF PROCEDURE OF THE PhVWP

Available on EMEA website <http://www.emea.europa.eu>, see under EMEA Committees, CHMP;
Doc.Ref. EMEA/CHMP/PhVWP/88786/04.

2.A Conduct of Pharmacovigilance for Centrally Authorised Products

Note: Procedures for the conduct of pharmacovigilance for centrally authorised products are currently under review and an updated version of this Chapter will be subject to public consultation. A Reflection Paper on the Criteria for Requiring One Additional Five-Year Renewal for Centrally Authorised Products (EMA/131973/2006)³⁸ has been made available in 2007.

2.A.1 Introduction

The objective of this Chapter is to describe a framework whereby all centrally authorised products are closely monitored to allow timely evaluation of new information relevant to the risks and benefits of these products, so that appropriate action may be taken, when necessary, to protect public health.

The conduct of pharmacovigilance for centrally authorised products is based on obligations and activities placed, through legislation, on a number of parties, notably the Member States, the European Commission, the Agency and the Marketing Authorisation Holders. In order to ensure that the obligations are met, it is necessary to clarify the respective roles and responsibilities of the various parties.

This Chapter presents:

- Principles relevant to the conduct of pharmacovigilance for centrally authorised products;
- The functions and procedures for conducting pharmacovigilance for these products;
- The specific roles of the Member States, the CHMP, the Pharmacovigilance Working Party (PhVWP), the (Co-)Rapporteur(s), the Agency, the Marketing Authorisation Holders and the European Commission, in carrying out functions and procedures for the conduct of pharmacovigilance for centrally authorised products.

2.A.2 Legal Framework

The legal provisions regarding the conduct of pharmacovigilance for centrally authorised products are set out in Regulation (EC) No 726/2004, notably but not exclusively in Chapter 3 of Title II, as well as Commission Regulation (EC) No 540/95. The examination of variations to the terms of marketing authorisation and urgent safety restrictions is the subject of Commission Regulation (EC) No 1085/2003.

2.A.3 Principles

The responsibilities and functions of the various partners involved in the centralised procedure have been well defined for the coordination and evaluation of centralised marketing authorisation applications and subsequent variation applications. This framework should also be applied to the conduct of pharmacovigilance for centrally authorised products. As a matter of principle, the handling and analysis of pharmacovigilance data should always be done in close cooperation between the (Co-) Rapporteur(s), the Agency and any Member State(s) who has (have) identified a possible issue.

The pre-authorisation Rapporteur should take the lead in pharmacovigilance, acting to evaluate all issues relevant to the centrally authorised product. However, there may be situations where the original Rapporteur is not able to fulfil the functions of such evaluation. In such cases the Co-Rapporteur could take this responsibility. If this is not possible, the CHMP would need to appoint another Rapporteur who could take on these responsibilities. In the particular case that one would be confronted with a class-related effect and different Rapporteurs were involved in the pre-authorisation assessment of the various centrally authorised products, the CHMP would need to appoint a “leading” Rapporteur.

³⁸ Available on EMA website <http://www.emea.europa.eu>.

In view of the large number of issues to be handled in the post-authorisation period for centrally authorised products, the Rapporteur will have the responsibility for evaluating and reaching conclusions on these issues in accordance with an agreed timetable, and for determining the issues which need to be considered by PhVWP and CHMP, in close cooperation with the Agency.

Information relevant to the risks and benefits of centrally authorised products need to be continuously collected in all Member States. Therefore, each Member State plays an important role in collecting information on adverse reactions and in identifying and evaluating possible safety concerns for centrally authorised products. The scientific expertise of the Member States will be utilised by the Rapporteurs in carrying out pharmacovigilance evaluations. The Rapporteur will generally use the expertise of the Member State from which he originates. However, if considered more appropriate, the Rapporteur may work with another Member State, e.g. the Member State that identified the issue under investigation.

In accordance with current legislation the Agency should collect all information about serious suspected adverse reactions and distribute this information to the Member States. The role of the Agency, therefore, is one of continuous coordination of the pharmacovigilance system for centrally authorised products. The Agency will ensure that Marketing Authorisation Holders for centrally authorised products adhere to the requirements for safety reporting in accordance with current legislation. Meetings for Marketing Authorisation Holders will be organised at the Agency at regular intervals in order to provide guidance on adverse reaction reporting to the Agency. The PhVWP will be informed of such meetings in advance and will be given the opportunity to participate.

The Agency, in close cooperation with the Rapporteur, will inform the CHMP/PhVWP of any safety concern wherever there is a need for discussion and subsequent action to be taken. It will, in agreement with the Rapporteur, participate in the identification of signals of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions.

The PhVWP evaluates potential signals, investigates adverse reactions and provides advice on the safety of medicinal products, enabling effective risk identification, assessment and management in the pre-and post-authorisation phase (see Appendix II.1.A). Following a CHMP request, their recommendations on centrally authorised products are transmitted to the CHMP for consideration. A Drug Monitor, including centrally authorised products, is in place to track safety issues and is reviewed at each meeting of the PhVWP. In addition specific issues relating to Periodic Safety Update Reports, specific obligations, follow-up measures or the need for safety variations may be discussed by the PhVWP at the request of the Rapporteur.

The primary responsibility of the Marketing Authorisation Holders is to assure the safety of their product. The Marketing Authorisation Holder is obliged to adhere to the legal provisions as to the spontaneous reporting of adverse reactions as well as to the submission of PSURs and other information. Furthermore, issues requiring clarification, further information or specific actions by the Marketing Authorisation Holder need to be clearly presented to the Marketing Authorisation Holder in writing. Such requirements of the Marketing Authorisation Holder should be prepared in collaboration between the Rapporteur, the Agency and any Member State requesting further information, and endorsed where necessary by the CHMP. Meetings with the Marketing Authorisation Holder should involve the Rapporteur, the Agency and others as considered necessary. Minutes of such meetings should be taken and distributed to attendees.

A summary of the role and responsibilities of each of the parties involved in the pharmacovigilance system for centrally authorised products is provided in the Table II.2.A.A at the end of this Chapter.

2.A.4 Functions and Procedures

2.A.4.1 Reporting of Adverse Reactions and Other Safety-Related Information

2.A.4.1.a) Pre-Authorisation Phase

Once an application for a marketing authorisation is submitted to the Agency, in the pre-authorisation phase, information relevant to the risk-benefit evaluation may become available from the Applicant, or Member States where the product is already in use on a compassionate basis, or from third countries where the product is already marketed. Since it is essential for this information to be included in the assessment carried out by the (Co-)Rapporteur(s) assessment teams, the Applicant is responsible for informing immediately the Agency and the (Co-)Rapporteur(s).

In the period between the CHMP reaching a final Opinion and the Commission Decision there need to be procedures in place to deal with information relevant to the risk-benefit balance of centrally authorised products, which were not known at the time of the Opinion. It is essential for this information to be sent to the Agency and (Co-)Rapporteur(s) so that it can be rapidly evaluated to an agreed timetable and considered by the CHMP to assess what impact, if any, it may have on the Opinion. The Opinion may need to be amended as a consequence.

2.A.4.1.b) Post-Authorisation Phase

Suspected adverse reactions related to centrally authorised products are reported directly by Healthcare Professionals, to each Member State. Marketing Authorisation Holders report serious suspected adverse reactions to the Member State in which the reactions occurred, within 15 calendar days of receipt. Each Member State is responsible for following up the Individual Case Safety Reports it receives to obtain further information as necessary.

The Member States should forward to the Agency serious suspected adverse reactions occurring within their territories.

The Agency and all Member States should receive directly from the Marketing Authorisation Holders suspected serious and unexpected adverse reactions that occur in a country outside of the EU.

The Agency should ensure that all relevant information about suspected serious unexpected adverse reactions from outside the EU are entered into the EudraVigilance database, and Member States should ensure that data on suspected serious adverse reactions occurring in their territory are uploaded into the EudraVigilance database. For details see Chapter I.4 and Part III.

2.A.4.2 Monitoring of the Safety Profile

2.A.4.2.a) Signal Identification

It is likely that many potential signals will emerge in the early stages of marketing and it will be important for these to be effectively evaluated.

A signal of possible unexpected hazards or changes in severity, characteristics or frequency of expected adverse effects may be identified by:

- the Marketing Authorisation Holders;
- the Rapporteur;
- the Member States;
- the Agency in agreement with the Rapporteur.

It is the responsibility of each Member State to identify signals from information arising in their territory. However, it will be important for the Rapporteur and the Agency to have the totality of information on serious adverse reactions occurring inside and outside the EU in order to have an overall view of the experience gathered with the concerned centrally authorised product.

As a matter of routine, the Rapporteur should continually evaluate the adverse reactions included in the EudraVigilance system and all other information relevant to risk-benefit balance in the context of information already available on the product, to determine the emerging adverse reactions profile. Additional information should be requested from the Marketing Authorisation Holder and Member States as necessary, in liaison with the Agency.

When a Member State other than the Rapporteur wishes to request information from the Marketing Authorisation Holder (apart from routine follow-up of cases occurring on their own territory) for the purposes of signal identification, the request should be made in agreement with the Rapporteur and the Agency.

Member States will inform the Rapporteur(s) and the Agency when performing class-reviews of safety issues which include centrally authorised products.

The PhVWP should regularly review emerging safety issues which will be tracked through the Drug Monitor.

2.A.4.2.b) Signal Evaluation

As signals of possible unexpected adverse reactions or changes in the severity, characteristics or frequency of expected adverse reactions may emerge from many different sources of data (see above), the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal.

Irrespective of who identified the signal, a signal evaluation should be carried out by:

- the Rapporteur; or
- the Member State where a signal originated.

The Rapporteur should work closely with the identifier of the signal to evaluate the issue. Agreement needs to be reached in each case on the responsibility for the Assessment Report on the risk-benefit balance, by the Rapporteur or the Member State where the signal originated from, or jointly.

A Member State other than that of the Rapporteur should not start a full evaluation prior to having contacted the Agency and the Rapporteur, in order to prevent any unnecessary duplication of effort.

At request of the CHMP, the PhVWP evaluates signals arising from any source and keeps any potential safety issues under close monitoring.

2.A.4.2.c) Evaluation of Periodic Safety Update Reports

The Marketing Authorisation Holder is required to provide Periodic Safety Update Reports (PSURs) to all the Member States and the Agency, as detailed in [Chapter I.6](#). It is the responsibility of the Agency to ensure that the Marketing Authorisation Holder meets the deadlines.

The Marketing Authorisation Holder should submit any consequential variations simultaneously with the PSUR at the time of its submission, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CHMP.

It is the responsibility of the Rapporteur to evaluate and provide a report in accordance with the agreed timetable and to determine what issues if any need to be referred to the PhVWP and CHMP.

Actions required following the evaluation of a PSUR will be determined by the Rapporteur and the Marketing Authorisation Holder will be informed by the Agency, after agreement by the CHMP.

Where changes to the marketing authorisation are required, the CHMP will adopt an Opinion which will be forwarded to the European Commission for preparation of a Decision.

2.A.4.2.d) Evaluation of Post-Authorisation Studies, Worldwide Literature and Other Information

Final and interim reports of Marketing Authorisation Holder sponsored post-authorisation studies and any other studies, and other relevant information, may emerge from the Marketing Authorisation Holder, the Member States or other countries at times in between PSURs.

The Rapporteur should receive and assess any relevant information and provide an Assessment Report where necessary.

As above, the Rapporteur should determine what issues if any need to be referred to the PhVWP and CHMP.

The actions required following an evaluation will be determined by the Rapporteur and the Marketing Authorisation Holder will be informed by the Agency, after agreement by the CHMP.

Where changes to the marketing authorisation are required, the CHMP will adopt an Opinion which will be forwarded to the European Commission for preparation of a Decision.

The Marketing Authorisation Holder should submit any consequential variations simultaneously with the data, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CHMP.

2.A.4.2.e) Evaluation of Post-Authorisation Commitments

It is the responsibility of the Agency to ensure that the Marketing Authorisation Holder meets the deadlines for the fulfilment of specific obligations and follow-up measures, and that the information provided is available to the Rapporteur and the CHMP.

The Marketing Authorisation Holder should submit any consequential variations simultaneously with the requested information for the fulfilment of specific obligations/follow-up measures, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CHMP.

For marketing authorisations granted under exceptional circumstances, specific obligations will be set out in Annex II.C of the CHMP Opinion. Specific obligations should be reviewed by the Rapporteur, at the interval indicated in the Marketing Authorisation and at the longest annually, and should be subsequently agreed by the CHMP. As above, the Rapporteur should determine what issues if any need to be referred to the PhVWP and CHMP.

For marketing authorisations granted under exceptional circumstances, the annual review will include a re-assessment of the risk-benefit balance. The annual review will in all cases lead to the adoption of an Opinion which will be forwarded to the European Commission for preparation of a Decision.

For all marketing authorisations (whether or not the authorisation is granted under exceptional circumstances) follow-up measures may be established, which are annexed to the CHMP Assessment

Report. These will be reviewed by the Rapporteur, and will be considered by PhVWP and CHMP at the Rapporteur's request.

Where changes to the marketing authorisation are required, the CHMP will adopt an Opinion which will be forwarded to the European Commission for preparation of a Decision.

In the case of non-fulfilment of specific obligations or follow-up measures, the CHMP will have to consider the possibility of recommending a variation, suspension, or withdrawal of the marketing authorisation.

2.A.4.3 Handling of Safety Concerns

2.A.4.3.a) Safety Concerns in the Pre-Authorisation Phase

Following the receipt of Individual Case Safety Reports or other information relevant to the risk-benefit balance of a product by the Agency and the (Co-)Rapporteur(s), the latter should assess these pharmacovigilance data. The outcome of the evaluation should be discussed at the CHMP for consideration in the Opinion.

If pharmacovigilance findings emerge following an Opinion but prior to the Decision, a revised Opinion, if appropriate, should be immediately forwarded to the European Commission to be taken into account before preparation of a Decision.

2.A.4.3.b) Safety Concerns in the Post-Authorisation Phase

A Drug Monitor, including centrally authorised products, is in place as a tracking system for safety concerns and is reviewed on a regular basis by the PhVWP at its meetings. This summary document also records relevant actions that have emerged from PSURs, specific obligations, follow-up measures and safety variations.

Following the identification of a signal the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal:

a) Non-urgent safety concerns

Potential concerns that do not fulfil the criteria for a Rapid Alert should be brought to the attention of the Rapporteur and the Agency only in the first instance.

Further information may be requested from:

- other Member States by the originator of the concern, issuing a Non-Urgent Information (see Chapter II.4);
- the Marketing Authorisation Holder by the Agency, in agreement with the originator of the concern and the Rapporteur.

The Rapporteur should work closely with the originator of the concern to evaluate it.

Following evaluation, the need for further discussion at the PhVWP and CHMP will be determined by the Rapporteur, and any necessary actions will be agreed by CHMP.

The Agency is responsible for transmitting the outcome of the evaluation to the Marketing Authorisation Holder.

However, if deemed necessary, the CHMP should formulate an Opinion on the pharmacovigilance data and forward it to the European Commission accordingly in order to take a Decision.

These issues will be included in the Drug Monitor by the Agency if a Non-Urgent Information has been issued.

b) Urgent safety concerns

A Rapid Alert (see Chapter II.4) should be issued by the Rapporteur, the Member States or the Agency when a signal is identified which leads to concern about the risk-benefit balance of a centrally authorised product and which could lead to major changes for the status of the authorisation. If it is the Marketing Authorisation Holder who first identifies a potentially urgent and serious issue, he needs to inform the Agency without delay.

The Rapid Alert should be transmitted to the contact points of the Member States, the Agency and the European Commission, and to the Rapporteur of the centrally authorised product which is the subject of the Rapid Alert.

The Agency, in agreement with the Rapporteur, should promptly start an inquiry and information exchange with the Marketing Authorisation Holder(s).

The Agency will coordinate the process.

The Rapporteur should work closely with the originator of the concern to evaluate the issue. Agreement needs to be reached in each case on the responsibility for the Assessment Report on the risk-benefit balance, by the Rapporteur, the Member State where the signal originated from, or jointly.

Following risk evaluation a discussion should be held at the PhVWP and subsequently at the CHMP within a defined timeframe.

Any resulting CHMP Opinion on the measures to ensure the safe and effective use of the centrally authorised product will be transmitted by the Agency to the European Commission, in order to take a Decision.

In some cases immediate action is essential to protect public health. In such cases the basic steps outlined above need to be followed, but within a much shorter time frame, with the involvement of PhVWP and CHMP at a much earlier stage, and with particular mechanisms in place to provide a CHMP Opinion and Commission Decision rapidly. Rapid actions will need to be coordinated across all Member States, however in some situations one or a number of Member States may consider it necessary to take immediate suspensive action before such coordinated action occurs.

Crisis Management:

- Following detection of an urgent safety concern, which could have a serious impact on public health, immediate action needs to be taken to evaluate and consider the options and timescale for action. An urgent safety restriction to be completed within 24 hours may be initiated by the Marketing Authorisation Holder or the European Commission if necessary. A Crisis Management Plan, agreed with the CHMP, has been implemented by the Agency in close consultation with the European Commission (see Chapter II.2.B).

Action taken by a Member State:

- Upon detection of a safety concern where urgent action is deemed essential to protect human health, a Member State may suspend the use of a medicinal product on its territory.
- The Member State must inform the Agency, the European Commission and other Member States no later than the following working day of the reasons for its action. A Rapid Alert should be issued for this purpose (see Chapter II.4).

- The European Commission will request the Opinion of the Agency within a time frame which it shall determine depending on the urgency of the matter. In that respect two possible procedures can be envisaged for implementation by the Agency depending on the time frame:
 - the first procedure is described in the Crisis Management Plan (see Chapter II.2.B);
 - the second is the convening of an extraordinary CHMP by the Executive Director of the Agency, after consultation with the CHMP Chairperson, in order to provide the European Commission with a recommendation on the measures.

2.A.4.4 Information to Healthcare Professionals and the Public

Healthcare Professionals and, if considered appropriate, the public need to be informed about safety issues relevant to centrally authorised products, in addition to the information provided in Product Information. It is important that consistent information is provided in all Member States. If there is such a requirement the Rapporteur or the Marketing Authorisation Holder in cooperation with the Rapporteur should propose the content of information for consideration by the PhVWP and subsequent discussion and adoption by the CHMP. The agreed information may be distributed in Member States, for example, by Direct Healthcare Professional Communication from the Marketing Authorisation Holder, or by Competent Authorities in Member States or through Member States' drug bulletins. In some cases coordinated press releases, in addition to the CHMP Public Statements, may be necessary. The text and timing for release of such information should be agreed by all parties prior to their despatch. The Marketing Authorisation Holder should notify, at his own initiative, the Agency at an early stage of any information he intends to make public, in order to facilitate consideration by the PhVWP and adoption by the CHMP as well as agreement about timing for release, in accordance with the degree of urgency. Marketing Authorisation Holders are reminded of their legal obligations under Article 24(5) of Regulation (EC) No 726/2004 to not communicate information relating to pharmacovigilance concerns to the public without notification to the Competent Authorities/Agency (see Part IV).

2.A.4.5 Advertising

Title VIII of Directive 2001/83/EC lays down the legal base for the control of advertising medicinal products. Because company marketing strategies for centrally authorised products may be similar across the EU, consideration should be given to what interactions should take place between Member States in the event of an important advertising concern with potential public health implications occurring with a centrally authorised product. The Agency and the Rapporteur should be informed by the Member States of such concerns. The PhVWP may be an appropriate forum to discuss such issues in order to ensure that when it is considered that a company is making misleading claims with safety implications in several Member States, consistent action is taken whenever possible. The CHMP should be informed subsequently.

TABLE II.2.A.A: ROLES AND THE RESPONSIBILITIES OF PARTNERS INVOLVED IN THE CONDUCT OF PHARMACOVIGILANCE FOR CENTRALLY AUTHORISED PRODUCTS

Marketing Authorisation Holder	• Establish and maintain a system, accessible at a single point in the EU, to collect, collate, and evaluate pharmacovigilance data • Meet legal obligations for reporting of suspected adverse reactions • Meet legal obligations regarding the preparation and the submission of Periodic Safety Update Reports • Respond fully to requests from authorities for additional information necessary for the evaluation of the benefits and risks of a medicinal product • Ensure the marketing authorisation is maintained and reflects the latest information
Member States	• Have in place national pharmacovigilance systems • Inform the European Commission, the CHMP, the Agency, the Member States and the Marketing Authorisation Holders of any relevant actions • Collect and collate data on the risk-benefit balance • Provide serious adverse reaction cases which have occurred in its territory to the Agency and the relevant Marketing Authorisation Holder within 15 calendar days of receipt • Identify and evaluate safety concerns and conduct benefit-risk evaluations • Provide representation on CHMP, PhVWP and Rapporteurs/Co-Rapporteurs • Implement Commission Decisions • In case of urgent action to protect public health, suspend the use of the product in the Member State's territory and inform, in accordance with the legislation, the Agency and the European Commission of the basis for action
Agency	• Coordination of the pharmacovigilance system for centrally authorised products • Monitor the legal obligations of the Marketing Authorisation Holders • Receipt of serious adverse reaction reports and provision to the Member States and the Rapporteur • In agreement with the Rapporteur, identify signals of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions • In agreement with the Rapporteur, inform all involved parties of any safety concern • Coordination of the evaluation of data by the Rapporteurs and consideration by the CHMP to reach Opinions • Communication of Opinions to the European Commission • Communication with the Marketing Authorisation Holder on all relevant issues in consultation with the Rapporteur • Maintenance of the crisis management system for centrally

	authorised products
Rapporteur	• Responsible for evaluating all safety concerns and risk-benefit issues for centrally authorised products • Regularly evaluate adverse reactions and other risk-benefit data on receipt, Periodic Safety Update Reports, company reports and variation applications to agreed timetables, obtaining additional information from the Marketing Authorisation Holder and Member States as necessary • Provide Assessment Reports to agreed timetables for consideration by the PhVWP and CHMP as necessary, with proposals on appropriate action
CHMP Pharmacovigilance Working Party	• Evaluation of potential signals arising from spontaneous reporting, including those identified from EudraVigilance, and all other sources • Investigation of adverse reactions • Regularly review Drug Monitor of safety concerns • Discussion of emerging safety concerns at the request of the Rapporteur • Discussion of PSURs at the request of the Rapporteur • Providing advice to the CHMP on safety, enabling effective risk identification, assessment and management in the pre- and post-authorisation phase • Recommendations to the CHMP on risk-benefit evaluations and actions necessary to minimise risk and maximise benefit
CHMP	• Discussion of the risk-benefit balance on the basis of the Rapporteur's Assessment Report • Formulation of Opinions
European Commission	• Competent Authority for centrally authorised products • Formulation of Decisions • Enforcement of legal requirements and enforcement of the implementation of Decisions by Member States and Marketing Authorisation Holders

2.B Crisis Management Plan regarding Centrally Authorised Products

Note: Procedures for crisis management for centrally authorised products are currently under review and an updated version of this Chapter will be subject to public consultation.

2.B.1 Introduction

This Chapter outlines the principles underlying a Crisis Management Plan which allows rapid and efficient handling of crisis situations involving a centrally authorised product. In order to achieve this objective, it is necessary to plan and agree in advance with all the involved parties, how the crisis will be managed.

The Crisis Management Plan outlines the procedures to be followed in order to deal with the crisis and also highlights the management structures and systems to be set up. These procedures will be followed in response to new information in the context of pharmacovigilance while the procedures on how to deal with new quality-related information with potential adverse effects are included in the *Compilation of Community Procedures on Inspections and Exchange of Information*³⁹, on behalf of the European Commission.

2.B.2 Principles of the Crisis Management Plan

The objective of the Crisis Management Plan is to define and implement a strategy for the rapid and efficient handling of crisis situations by the Agency in liaison with the CHMP, the Rapporteur, the Competent Authorities of the Member States, the European Commission and the Marketing Authorisation Holder(s).

A crisis is defined in the present document as an event which occurs when new information, which could have a serious impact on public health, is received for a centrally authorised product, and which requires immediate action.

In some cases the new information can be related to both quality and safety concerns (for instance problems of viral contamination with biological products).

Crises may be subdivided into those where, at the time the crisis is identified, the information has not become public, and those where it has. In the latter case, the handling of communications becomes crucial especially when public confidence is at risk.

Sometimes a crisis may be triggered when there is no new information but media exposure leads to serious public concerns about a product. In this case implementation of the Crisis Management Plan may be appropriate.

There are two possible outcomes to a crisis:

- Urgent regulatory action is needed; in this case, a recommendation on the action to be taken and, if needed, on the public communication has to be provided;
- Urgent regulatory action is not required; in this case, a recommendation on the follow-up and, if needed, public communication has to be provided.

In both cases the basis of the conclusion should be documented.

As a matter of principle, the handling of crises should always involve a close cooperation between all parties concerned, i.e. the Competent Authorities of the Member States, the European Commission, the Agency, the CHMP, the Rapporteur and the Marketing Authorisation Holder(s). In accordance

³⁹ Doc.Ref. EMEA/INS/GMP/3351/03 latest version, available on EMEA website <http://www.emea.europa.eu>.

with the principles laid down in [Chapter II.2.A](#) on the conduct of pharmacovigilance for centrally authorised products, the Rapporteur should have a key role when there is a safety issue, in close cooperation with the Agency.

The timeframe, during which a crisis should be dealt with, will depend upon the urgency of the matter. The proposed procedure should, however, be flexible enough to allow for immediate action to be taken (e.g. an urgent product recall), if considered necessary by the European Commission and/or the Member States. However, in the case of urgent action required to protect public health, Member States may need to take pre-emptive action in accordance with the legislation.

2.B.3 Crisis Management Structures

Three different management structures are foreseen, i.e.:

- A European Crisis Group;
- An Agency Crisis Team;
- An advisory network at the level of the Member States.

2.B.3.1. European Crisis Group

In order to deal successfully with a crisis, a European Crisis Group needs to be created. For logistical reasons and rapid and efficient issue management, the core members of the European Crisis Group should be kept to a minimum. Due to logistical and time constraints, some meetings may need to take place without all members being present. Of course additional members and expertise may be co-opted into the European Crisis Group as need arises.

The core European Crisis Group comprises:

- The Chairperson of the CHMP;
- The Chairperson of the CHMP Pharmacovigilance Working Party (PhVWP);
- The Rapporteur of the product concerned, supported by his/her scientific assessment team;
- If appropriate, a representative of the Member State where the signal originated;
- The Executive Director of the Agency, as well as the other members of the Agency Crisis Team (for further details, [see Chapter II.2.B, Section 3.2](#)).

The primary role of the European Crisis Group is to deal with containing and controlling the situation. This will be achieved by:

- Confirming the crisis;
- Managing the crisis situation by:
 - Defining a strategy to handle the crisis;
 - Convening an extraordinary CHMP meeting, if necessary, or referring the matter to the next regular CHMP meeting, in order to define what possible action should be taken considering the seriousness of the crisis;
 - Ensuring that all Competent Authorities and relevant Marketing Authorisation Holders are rapidly and fully informed;
 - Developing the appropriate communication strategy towards the public, including Patients and Healthcare Professionals.

The decision to convene the European Crisis Group will be taken by the Executive Director, in consultation with the CHMP Chairperson.

2.B.3.2 Agency Crisis Team

The availability of an internal Agency crisis management structure involves the creation of an Agency Crisis Team, which should become operational within the shortest possible timeframe. It should be set

up in such a way that it is also able to deal with crises arising during weekends or public holidays. The Agency Crisis Team should consist of an identified group of individuals.

The Agency Crisis Team is normally chaired by the Executive Director, or, in his absence, a designated deputy.

It has a core membership with optional/additional participants. The core members, in addition to the Executive Director, are:

- The Head of Unit Post-authorisation Evaluation of Medicines for Human Use;
- The Head of Sector Pharmacovigilance and Post-authorisation Safety & Efficacy of Medicines;
- The Product Team Leader concerned;
- The Agency's Press Officer.

Optional/additional participants may be co-opted as necessary; for example a legal administrator, other Product Team Members or Product Team Leaders, as well as support personnel (technical, secretarial and linguistic support) will be needed.

The role of the Agency Crisis Team consists of:

- co-ordinating all activities;
- acting at all stages in cooperation with the other participants of the European Crisis Group.

The following Members have the following specific tasks:

The Executive Director (or, in his absence, a designated deputy):

- deciding, together with the CHMP Chairperson, to convene a European Crisis Group;
- chairing the Agency Crisis Team;
- deciding upon the Communication Plan;
- liaising with the European Commission.

The Head of Unit Post-authorisation Evaluation of Medicines for Human Use:

- liaising with the Executive Director, the Chairperson of the CHMP and the Agency's Press Officer;
- providing all necessary scientific resources.

The Head of Sector Pharmacovigilance and Post-authorisation Safety & Efficacy Medicines:

- acting as overall coordinator, responsible for:
 - organising and coordinating the actions of the Agency Crisis Team Members;
 - centralising all updated information related to the crisis;
 - preparing all documents for public communication;
 - informing the Executive Director and the Head of Unit Post-authorisation Evaluation of Medicines for Human Use of all developments.

The Product Team Leader:

- collecting internal and external information on an ongoing basis;
- writing file notes on meetings and ensure that key action points and recommendations are documented and filed.

A list of all crisis contact points within the Agency is available.

2.B.3.3 Advisory Network at the Level of the Member States

A prerequisite in this respect is the availability of designated contact points within the Member States. This network should also foresee the involvement of the national pharmacovigilance systems in case of safety concerns.

A consolidated list of all contact points at the level of the Member States has been prepared. This list is continuously updated. It is the responsibility of the Member States to inform the Agency of any changes to be implemented.

2.B.4 Key Points of the Procedure

In addition to the management structures, management systems are put in place at the level of the Agency and the Competent Authorities of the Member States. They aim to meet the following objectives:

- To activate all available networks and to coordinate the different activities between the interested parties;
- To arrive at a common conclusion and, where regulatory action is considered necessary, an Opinion, and to implement the regulatory action at the same moment in the whole EU; this implies the availability of efficient immediate links with the Heads of Medicines Agencies;
- To convey a unified message to the public, including Patients and Healthcare Professionals; this requires efficient contacts with the European Commission and with the press officers available in Member States.

In order to achieve these objectives, a close cooperation between all the different parties involved and the following steps should be ensured:

1. Confirmation of the crisis;
2. Initiation, if considered necessary, of the crisis procedure;
3. Rapid scientific re-appraisal of the risk-benefit balance of the product concerned;
4. Definition of strategy;
5. Recommendation on action or no action with documentation of the reasons for the recommendation;
6. In case of regulatory action, monitoring of the implementation in all Member States;
7. Development of an action plan to monitor the sequelae.

2.B.5 Public Relations

In all cases it is essential that public relations are handled sensitively and in a timely fashion. Failure to do so may mean that, however well the crisis is managed from a safety and regulatory perspective, public confidence will be lost and the image of the Competent Authorities will be damaged.

For this reason, the responsibility for press briefing and the preparation of Public Statements is at the highest levels. A Communication Plan will be decided by the Agency's Executive Director on the basis of the communication strategy proposed by the European Crisis Group, with the Head of Sector Pharmacovigilance and Post-authorisation Safety & Efficacy of Human Medicines being responsible for drafting the communication documents, and the Agency's Press Officer acting as the public spokesperson. The ideal is that press releases should be coordinated between the Member States, the Agency and the Marketing Authorisation Holder(s). However in some situations, this ideal may not be met. In such cases, close cooperation between the Agency and the Member States should ensure that the messages coming from them are consistent.

3. Conduct of Pharmacovigilance for Medicinal Products Authorised through the Mutual Recognition or Decentralised Procedure

3.1 Introduction

The objective of this guidance is to develop a framework whereby all medicinal products for human use which fall under the mutual recognition procedure (MRP) or the decentralised procedure (DCP) are closely monitored to allow timely evaluation of new information relevant to the risks and benefits of these products, so that appropriate action may be taken, when necessary, to protect public health. Products covered by these procedures include those authorised through MRP, DCP or ex-concertation procedure and those previously referred under Articles 30 and 31 of Directive 2001/83/EC.

Article 31(2) of Directive 2001/83/EC provides the Agency with the option to limit the procedure to certain parts of the authorisation if the referral to the CHMP concerns a range of products or a therapeutic class. In that case, following completion of such a referral procedure, all subsequent variations, renewals and other maintenance activities of the relevant Marketing Authorisations granted through national procedures remain to be handled at national level. That means that after the referral, products authorised through MRP or DCP will follow the MRP and DCP, and purely nationally authorised products will be handled through purely national procedures again.

The responsibility for the conduct of pharmacovigilance of any MRP or DCP product rests with the Competent Authorities of all individual Member States who have granted the authorisation.

The smooth running of MRP and DCP is facilitated by the Coordination Group for the Mutual Recognition and Decentralised Procedures (CMD(h)) in accordance with Article 27 of Directive 2001/83/EC. The CMD(h) acts to support the development of consensus where differences of view arise so as to minimise the need for arbitration at the level of the Committee for Medicinal Products for Human Use (CHMP). The Member States have agreed that for pharmacovigilance issues arising with MRP and DCP products, the CHMP Pharmacovigilance Working Party (PhVWP) is the forum for exchange of information, evaluation and views and that the PhVWP advises the CMD(h) on actions to be taken (see PhVWP Mandate in Appendix II.1.A).

Because of the need to coordinate the process of pharmacovigilance and any consequential regulatory action across all relevant Member States, best practice guidance has been made available on the cooperation between the CMD(h) and the PhVWP (see MRFG Best Practice Guide on the Cooperation between Mutual Recognition Facilitation Group and Pharmacovigilance Working Party⁴⁰). This will facilitate harmonised actions in the Member States.

This Chapter presents:

- Principles relevant to the conduct of pharmacovigilance for MRP and DCP products; and
- The specific roles of the different parties involved in carrying out these functions.

Directive 2001/83/EC outlines the basis for the authorisation of medicinal products through the MRP and DCP and for pharmacovigilance procedures and obligations of Marketing Authorisation Holders, Competent Authorities and the Agency thereafter. Commission Regulation (EC) No 1084/2003 provides the legislative basis for variation of MRP and DCP marketing authorisations including urgent safety restrictions.

3.2 Principles

The responsibilities and functions of the various parties involved in the handling of marketing authorisation and subsequent variation applications in the MRP and DCP are defined in the legislation.

⁴⁰ Available on Heads of Medicines Agencies website <http://heads.medagencies.com>.

Member States have accordingly agreed principles that should be applied for the conduct of pharmacovigilance for MRP and DCP products, with the Reference Member State (RMS) taking the lead on pharmacovigilance in close co-operation with the Concerned Member States (CMS). Any reference to Member States below should be taken to mean both the RMS and CMS. The roles of the relevant parties are presented below.

3.3 Roles and Responsibilities

3.3.1 Reference Member State

Article 104(5) of Directive 2001/83/EC stipulates that the Marketing Authorisation Holder should ensure that all serious adverse reactions occurring in the EU are reported in such a way as to be accessible to the RMS and that the RMS shall assume the responsibility of analysing and monitoring such serious adverse reactions. For practical reasons, Member States have agreed that the RMS should be assigned responsibility for evaluating all safety concerns relevant to MRP or DCP products, for providing Assessment Reports to the CMS according to an agreed timetable and presenting the safety concerns which need to be considered by the PhVWP. The RMS will be responsible for liaising with the Marketing Authorisation Holder on all such matters. In cases where the RMS is unable to carry out these functions, another Member State may be agreed between the national Competent Authorities to undertake this task. In situations where a class-related effect is identified for products with different RMSs, a Lead-RMS may be appointed by agreement between the relevant RMSs to take forward evaluation of the class-related effect.

3.3.2 Concerned Member States

The Competent Authorities of all CMS have a responsibility to continuously collect information on adverse reactions and play an important role in identifying and evaluating possible safety concerns for MRP and DCP products. The CMS will work closely with the RMS on such concerns, and will respond to proposals from the RMS within the agreed timetable.

All Competent Authorities are responsible for ensuring implementation of regulatory action in their Member State.

3.3.3 CHMP Pharmacovigilance Working Party (PhVWP)

The PhVWP facilitates coordination of pharmacovigilance of MRP and DCP products across Member States and the development of consensus on conclusions and proposed actions where differences arise between Member States.

The PhVWP is the forum for discussing all safety concerns relevant to MRP and DCP products. Items for discussion may be raised by the RMS or CMS. The Mandate of the PhVWP (see Appendix II.1.A) encompasses consideration of items at the request of the CHMP or a Member State.

3.3.4 Coordination Group for Mutual Recognition and Decentralised Procedures

The Coordination Group for Mutual Recognition and Decentralised Procedures (CMD(h)) will be kept closely informed on issues relevant to it, e.g. variations for safety reasons, by provision of the agendas and minutes of the PhVWP or otherwise as appropriate (see PhVWP Mandate, Appendix II.1.A) and MRFG Best Practice Guide on the Cooperation between Mutual Recognition Facilitation Group and Pharmacovigilance Working Party⁴¹).

⁴¹ Available on Heads of Medicines Agencies website <http://heads.medagencies.com>.

3.3.5 Agency and the Committee for Medicinal Products for Human Use

The Agency will be kept informed about safety data and (proposed) regulatory actions by the Member States according to Directive 2001/83/EC, Articles 105 and 107.

The CHMP will become involved in the discussion on safety concerns relevant to MRP or DCP products whenever there is a procedure according to Directive 2001/83/EC, Articles 29(4), 31 or 36(1). The Agency will coordinate all activities in the event of referral to the CHMP, see Chapter II.5 and Chapter 3, Volume 2A (Notice to Applicants) of The Rules Governing Medicinal Products in the European Union⁴².

For CHMP Opinions according to Article 107(2) of Directive 2001/83/EC, see Chapters II.1 and II.5.

3.3.6 European Commission

The European Commission takes the final decision relating to medicinal products on any CHMP Opinion adopted as a result of referrals according to the procedures laid down in Articles 32, 33 and 34 of Directive 2001/83/EC and of CHMP Opinions according to Article 107(2) of Directive 2001/83/EC, see also Chapters II.1 and II.5.

3.3.7 Marketing Authorisation Holders

According to Article 104(5), the Marketing Authorisation Holder should report all serious adverse reactions with MRP and DCP products occurring in the EU in such a way as to be accessible to the RMS. The Marketing Authorisation Holder is further obliged to adhere to the other legal requirements for pharmacovigilance (e.g. reporting of adverse reactions occurring outside the EU, submission of Periodic Safety Update Reports and other information including post-authorisation safety studies) for MRP and DCP products, as for any other nationally authorised products. This information should be provided to all Member States at the same time. Member States have agreed that the RMS will normally act as the primary liaison with the Marketing Authorisation Holder, specifying issues requiring clarification, further information or specific actions by the Marketing Authorisation Holder. This will be clearly presented in writing to the Marketing Authorisation Holder by the RMS working closely with CMS. Meetings with the Marketing Authorisation Holder should involve the RMS, and any other CMS by request. The conclusions of such meetings should be distributed to the PhVWP and the CMD(h). The RMS may also ask the Marketing Authorisation Holder to present further clarification to the plenary meeting of the PhVWP. In the case of bilateral contact between a CMS and the Marketing Authorisation Holder, the relevant CMS should keep the RMS informed.

3.4 Functions and Procedures for the Conduct of Pharmacovigilance

3.4.1 Pre-Authorisation Phase

In the period between an application for a marketing authorisation through the DCP or MRP and granting of the marketing authorisation, information relevant to the safety of the product may become available to the Applicant/Marketing Authorisation Holder. Since it is essential for this information to be included in the assessment of the risk-benefit balance, the Applicant/Marketing Authorisation Holder is responsible for the immediate submission of any information that may impact on this assessment to the RMS and the other CMS (see also Chapter 1, Section 5.1.1, Volume 2A (Notice to Applicants) of The Rules Governing Medicinal Products in the European Union⁴³). The RMS should take the new information into account when drafting the preliminary or final Assessment Report as applicable. If the Assessment Report has already been distributed, the RMS should prepare and

⁴² Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

⁴³ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

distribute either an amended or a supplementary Assessment Report. For reporting requirements [see Chapter I.5, Section 2](#).

3.4.1.a) Risk Management Plans

If the Applicant/Marketing Authorisation Holder has submitted a Risk Management Plan as part of the application dossier, the RMS will include an assessment of it in the Assessment Report. The role and responsibilities of the RMS, the options for the CMS to contribute and the options for the Applicant/Marketing Authorisation Holder to respond to questions and to liaise with the Competent Authorities are described in [Chapter 2, Volume 2A \(Notice to Applicants\) of The Rules Governing Medicinal Products in the European Union](#)⁴⁴ (see also relevant CMD(h) Standard Operating Procedures⁴⁵). The Assessment Report will be discussed at a PhVWP meeting at the request of the RMS or a CMS. When the Marketing Authorisation(s) are granted the Marketing Authorisation Holder should appropriately execute the final agreed Risk Management Plan.

3.4.1.b) Concerns during the ongoing Mutual Recognition or Decentralised Procedure

If, in the course of a MRP or DCP and following the assessment of all information relevant to the safety of a product, the RMS considers that a significant risk has emerged to change the risk-benefit balance, the outcome of the evaluation should be discussed at the PhVWP. The PhVWP will report the outcome of the discussion to the CMD(h).

3.4.2 Post-Authorisation Phase

3.4.2.a) Expedited Reporting of Individual Case Safety Reports

Directive 2001/83/EC lays down specific obligations for national Competent Authorities and Marketing Authorisation Holders on the expedited reporting of serious adverse reactions. Member States are responsible for collecting, collating and evaluating reports occurring in their respective territories. Member States are further obliged to forward reports of serious adverse reactions received to the respective Marketing Authorisation Holders, see also Chapter II.1. In accordance with Article 104(5) of Directive 2001/83/EC, for products which have been the subject of a MRP or DCP, the Marketing Authorisation Holder should additionally transmit these reports to the RMS ([see also Chapter II.3, Section 3.1 and Chapter I.4](#)). To avoid duplicate reporting the RMS should not retransmit these reports to EudraVigilance.

The responsibility to collate and evaluate these reports has been assigned to the RMS by the Member States.

3.4.2.b) Periodic Safety Update Reports and Other Relevant Post-Authorisation Information

The Marketing Authorisation Holder is required to provide all Competent Authorities with Periodic Safety Update Reports (PSURs) and relevant safety information from post-authorisation commitments, post-authorisation studies, worldwide literature, or other sources as outlined in the Directive 2001/83/EC and guidance documents for Marketing Authorisation Holders. Any consequential variation should be submitted by the Marketing Authorisation Holders to the RMS and all CMS at the same time. The RMS will evaluate the information and circulate a preliminary Assessment Report to the CMS and Marketing Authorisation Holder within 6 weeks of receipt of the information. The CMS should respond within 3 weeks of receipt of the RMS Assessment Report. The RMS will distribute the final Assessment Report after a further 3 weeks. This Assessment Report will,

⁴⁴ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

⁴⁵ Available on Heads of Medicines Agencies website <http://heads.medagencies.com>.

if requested by the RMS or a CMS, be discussed at a PhVWP meeting. The PSUR submission schedule to be followed in the CMS is the one in place in the RMS, unless otherwise agreed during the MRP or DCP. This should be decided on a case-by-case basis, [see also Chapter I.6, Section 2.4](#).

For the assessment of PSURs within the scope of the PSUR Work Sharing initiative the following timetable has been agreed: The preliminary Assessment Report will be distributed by the P-RMS (Member State responsible for the assessment of the PSUR) to the CMS and the Marketing Authorisation Holder(s) within 60 days. The CMS may comment within 30 days after receipt of the Assessment Report. The P-RMS will distribute the final Assessment Report after a further 30 days.

3.4.2.c) Risk Management Plans

If the Marketing Authorisation Holder has submitted a new or updated Risk Management Plan in the post-authorisation phase, the RMS will distribute an Assessment Report and collect comments from the CMS. Thereafter the RMS will distribute the final Assessment Report, which will also be sent to the Marketing Authorisation Holder. The Marketing Authorisation Holder may be requested to revise the Risk Management Plan. The Risk Management Plan and the Assessment Report will, if requested by the RMS or CMS, be discussed at a PhVWP meeting. Results of post-authorisation studies performed in the frame of the Pharmacovigilance Plan should be processed in a similar way by the RMS ([see Chapter I.3](#)).

3.4.2.d) Signal Detection

It is possible that potential signals will emerge in the early stages of the marketing of a MRP or DCP product especially for a new active substance. It will be important for these signals to be evaluated effectively. A signal of a possible unexpected adverse reaction or a change in severity, characteristics or frequency of an expected adverse reaction may be identified from many different sources of information held by the Marketing Authorisation Holders, the RMS, or any CMS or the Agency.

It is the responsibility of each Member State to transmit reports of serious adverse reactions to the EudraVigilance database in an expedited way and to identify signals from information arising in its territory. It is important for the RMS to have the totality of information in order to have an overall view of the experience gathered in relation to the concerned MRP or DCP product. Additional information requested from the Marketing Authorisation Holder should be provided to the RMS and all CMS simultaneously. The EudraVigilance database services are a very important source of information, since all reports of serious adverse reactions are included in the database in accordance with the Community legislation ([see also Part III](#)).

As a matter of routine, the RMS should continually evaluate all newly submitted information in the context of information already available on the product, to determine the emerging adverse reaction profile. Signals of a possible safety concern will, if requested by the RMS or a CMS, be discussed at a meeting of the PhVWP.

3.4.2.e) Signal Evaluation

As signals of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions emerge, the relevant information needs to be analysed for effective evaluation over a timescale appropriate to the importance and likely impact of the signal.

Any risk evaluation prompted by a signal should normally be carried out by the RMS unless other arrangements are agreed with another Member State, this could be for example the CMS where the original signal was identified. The RMS should in any case work closely with the originator of the alert. Agreement needs to be reached in each case on the responsibility for the risk-benefit Assessment Report, by the RMS or the originating Member State, or jointly. The RMS should liaise with the Marketing Authorisation Holder as appropriate for the provision of additional relevant information, if

available, to ensure that all relevant data is taken into account in the Assessment Report. The Assessment Report should be distributed to all Member States through the EudraNet Pharmacovigilance mailbox and may be discussed at a PhVWP meeting at request of the RMS or CMS. According to Article 23 fifth subparagraph of Directive 2001/83/EC the Marketing Authorisation Holder may be asked to provide data demonstrating that the risk-benefit balance remains favourable. All data to be provided by the Marketing Authorisation Holder to the RMS should simultaneously be distributed to all CMS.

A Member State other than the RMS should not start a full evaluation prior to having contacted the RMS, in order to prevent any unnecessary duplication of effort.

3.4.2.f) Proceedings in Case of Safety Concerns

Non-Urgent Safety Concerns

Safety concerns that do not fulfil the criteria for a Rapid Alert (see Chapter II.4) should be brought to the attention of the RMS. The RMS should work closely with the Member State who identified the issue to evaluate the matter. Agreement needs to be reached in each case on the responsibility for the risk-benefit Assessment Report, by the RMS or the originator Member State, or jointly. The RMS should liaise with the Marketing Authorisation Holder as appropriate for the provision of additional relevant information, if available, to ensure that all relevant data is taken into account in the Assessment Report. The Assessment Report should be distributed to all Member States through the EudraNet Pharmacovigilance mailbox. The RMS should consider sending a Non-Urgent Information request (see Chapter II.4). Following evaluation, the need for further discussion at the PhVWP will be at the request of the RMS or CMS. The CMD(h) should be informed by the RMS.

Urgent Safety Concerns

The Rapid Alert System should be used to communicate information on safety concerns with MRP and DCP products which meet the criteria described in Chapter II.4. The RMS should preferably take the lead, but in case the concern was raised in a CMS, agreement needs to be reached who will transmit the Rapid Alert. The Rapid Alert should be transmitted to the contact points of the RMS, the CMS, the European Commission and the Agency (see Chapter II.4). The Marketing Authorisation Holder should also be informed by the RMS at the same time. The RMS should work closely with the CMS where the concern was raised (if not the RMS) and responsibilities for management and assessment of the safety concern should be agreed between them. They should also decide what additional information should be requested from the Marketing Authorisation Holder and CMS. Following risk evaluation, a discussion should be held at the PhVWP with the aim of finalising an agreed position between the RMS and all CMS. In cases of particular urgency a special meeting of the PhVWP may need to be set up. The RMS should keep the CMD(h) informed. Any Member State may initiate immediate suspension of the marketing and use of the medicinal product concerned if considered necessary (see below under b) for actions by Competent Authorities).

Actions Consequential to Safety Concerns

Safety concerns may emerge from the many sources of information considered above which warrant amendment to the conditions of the marketing authorisation, through a short type II variation procedure, or urgent safety restriction procedure. In the case of serious risk, which is considered to outweigh the benefit of a product, there may be a need to withdraw the product from the market or revoke the marketing authorisation. Such actions may be taken either by Marketing Authorisation Holder or by Competent Authorities as described below.

a) Actions by the Marketing Authorisation Holder

Variations of the marketing authorisation submitted by the Marketing Authorisation Holder because of safety concerns should be handled through the 30 day-type II variation procedures for MRP and DCP

products with the RMS evaluating the variation and circulating an Assessment Report to the CMS within the standardised timetable. For urgent safety concerns, the Marketing Authorisation Holder may submit an urgent safety restriction.

In the case of a Marketing Authorisation Holder wishing to withdraw its product from the market for safety reasons, action needs to be coordinated across the CMS. It is recommended that the Marketing Authorisation Holder notifies the intention for a withdrawal to all Competent Authorities concerned at the same time and at an early stage. The RMS should normally take the lead and coordinate the actions. The RMS and CMS should use the Rapid Alert system to communicate with each other. The RMS and Marketing Authorisation Holder should wherever possible agree on the timetable to be used for the different steps and actions to be taken. The timetable will depend on the urgency of the situation (see Chapter I.8, Section 5). It is important that the same action is followed in all Member States including communication to Healthcare Professionals (see Part IV).

b) Actions by the Competent Authorities

If following risk evaluation by the RMS, it is considered that action is necessary to vary the terms of, or to suspend, revoke or withdraw, the marketing authorisation of a medicinal product, the RMS should inform the CMS, the Agency and the Marketing Authorisation Holder. The RMS should also keep the CMD(h) informed.

Where possible, in order to ensure a coordinated approach, efforts should be made to reach a consensus on the proposed action to be taken, through discussion within the PhVWP.

Where appropriate, the RMS should communicate with the Marketing Authorisation Holder on the reasons for the conclusions reached by the Member State and the action that should be taken by the Marketing Authorisation Holder. If the Marketing Authorisation Holder does not voluntarily vary, withdraw or suspend the marketing authorisation, an urgent safety restriction procedure should be started by the RMS, or a referral according to Directive 2001/83/EC Article 36 to the CHMP should be initiated (see Chapter II.5). The resulting CHMP Opinion will be followed by a single Decision of the European Commission binding on all Member States and the Marketing Authorisation Holder.

In urgent cases, any Member State may initiate immediate suspension of the marketing and use of a medicinal product on its territory, informing all Member States, the European Commission and the Agency within 24 hours. Such action should preferably be taken in all Member States in a coordinated manner facilitated by a proposal from the PhVWP to the Competent Authorities of Member States.

For CHMP Opinions according to Article 107(2) of Directive 2001/83/EC, see Chapter II.5.

3.4.2.g) Communication to Healthcare Professionals and the Public

When a marketing authorisation is issued, according to Article 21(4) of Directive 2001/83/EC, the Competent Authorities should make publicly accessible without delay the Assessment Report, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. Thus the RMS is obliged to prepare a Public Assessment Report (PAR). The preliminary PAR should be provided to the Marketing Authorisation Holder in particular for consideration of any commercially sensitive data or information. See also CMD(h) Best Practice Guide for the Public Assessment Report in the Decentralised and Mutual Recognition Procedures⁴⁶.

Such a PAR needs updating, without delay, once regulatory action in response to a safety concern has been taken.

In case of a referral to the CHMP, the CHMP Opinion should be made publicly accessible.

⁴⁶ Available on Heads of Medicines Agencies website <http://heads.medagencies.com>.

In addition it may be appropriate to inform Healthcare Professionals and the public about safety concerns related to MRP and DCP products in other ways (e.g. Direct Healthcare Professional Communication (DHPC), Public Statements). It is important that consistent information is provided in all Member States.

In such cases, the RMS should propose the content of the information to be provided, and whenever possible, this should be agreed by the CMS and, if necessary considered by the PhVWP. There should be agreement whenever possible, on the method and timing of distribution of the information e.g. by letters from Marketing Authorisation Holder or Member States' Competent Authorities, or through Competent Authorities' bulletins. Agreement should also be reached on the need for and timing of Public Statements and the reaction to press enquiries.

For guidance on pharmacovigilance communication, [see Part IV](#).

4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance

4.1 Introduction

During the marketing period of a medicinal product, urgent measures to safeguard public health may be necessary. Within the EU pharmacovigilance system it is essential that information regarding safety concerns, particularly those which may result in major changes to the marketing authorisation status or revocation or withdrawal of a product, is exchanged between the Member States, the Agency and the European Commission with the appropriate degree of urgency.

In general, any safety concern identified by a Member State after evaluation of the data available in that Member State or the receipt of any other relevant important information should be shared with other Member States, the Agency and the European Commission. This should also include any action initiated by the Marketing Authorisation Holder(s).

Early exchange of information will enable the Competent Authorities of Member States to initiate data research and seek specialist expertise, so that appropriate action may be taken in a co-ordinated manner as soon as possible.

To support rapid notification of safety concerns and exchange of information required to take appropriate action, the Competent Authorities of Member States, the Agency and the European Commission operate a Rapid Alert and Non-Urgent Information System in accordance with the procedures laid down in this Chapter. In order to avoid multiplication of effort and to ensure more efficient resource utilisation of national systems, information during the phase of signal detection may also be exchanged in order to support informal communication between Member States (pre-signal information exchange). The Marketing Authorisation Holder should be informed of suspected signals deemed to require further analysis, as appropriate.

The purpose of a Rapid Alert (RA) is to alert, with an appropriate degree of urgency, the Competent Authorities, the Agency and the European Commission about pharmacovigilance data related to medicinal products, which indicate that action may be needed urgently to protect public health. It is essential that communication of such problems occurs at an early stage, normally before a decision is taken in a Member State.

A RA should also be used by Member States for informing the Competent Authorities of other Member States, the European Commission and the Agency in accordance with Articles 107(1) and (2) and 36(2) of Directive 2001/83/EC and Article 20(4) of Regulation (EC) 726/2004.

It should be noted that Article 107(1) also requires that the Member State concerned informs the Marketing Authorisation Holder.

RAs should not be circulated for the exchange of less urgent information. For this purpose, a Non-Urgent Information (NUI) should be used.

A NUI supports collection and exchange of pharmacovigilance information between the Competent Authorities and the Agency, which does not fulfil the criteria for an RA.

A RA or NUI may also be initiated by the Agency.

Following an RA or NUI, the safety concern may then be reviewed as follows:

- at the PhVWP on the basis of the Drug Monitor and an Assessment Report if applicable; or
- at the CHMP; or
- within procedures laid down in Articles 31, 36 and 37 or Article 107(2) of Directive 2001/83/EC or Article 20 of Regulation (EC) No 726/2004.

An RA/NUI should primarily be used to highlight concerns relating to the risk-benefit balance of a medicinal product authorised according to Directive 2001/83/EC or Regulation (EC) No 726/2004.

In case of safety concerns for products not authorised as medicinal products, e.g. chemical products, the system may also be used if the information could be relevant to medicinal products.

Occasionally, an NUI may be circulated to solicit information on national policies or views on draft guidance documents or certain organisational matters, in order to prepare for discussions on such matters at the level of the PhVWP.

An RA/NUI may be also used for sharing information on major findings from pharmacovigilance inspections.

Rapid Alerts regarding quality problems of a medicinal product or specific batches of a medicinal product are not considered in this Chapter, but guidance for this is available in the **Compilation of Community Procedures on Inspections and Exchange of Information**⁴⁷. However, in cases of an adverse reaction, lack of efficacy, or suspicion thereof, which are associated with quality issues, liaison with Inspectorate colleagues should be initiated to assess the safety implications of the quality problem.

4.2 Criteria

4.2.1 Rapid Alert

An RA should be used when a Member State or the Agency has a safety concern which potentially has a major impact on the known risk-benefit balance of a medicinal product and which could warrant prompt regulatory action and communication to Healthcare Professionals/the general public, such as:

- Urgent safety restriction, suspension, revocation or withdrawal of the marketing authorisation and/or recall of the medicinal product from the market;
- Suspension of marketing and/or use of a medicinal product;
- Action for human blood- and plasma-derived medicinal products following occurrence of vCJD in a blood donor (with specification of batches on the market as well as expired batches);
- Important changes in the Summary of Product Characteristics (SPC), e.g.:
 - Introduction of new contraindications;
 - Introduction of new warnings;
 - Reduction in the recommended dose;
 - Restriction of the indications;
 - Restriction in the availability of a medicinal product;
- Need to inform Healthcare Professionals or Patients about an identified risk without delay.

Where as a result of the evaluation of pharmacovigilance data related to a medicinal product authorised through national procedures, a Member State considers suspension or revocation of the marketing authorisation or its variation resulting in important changes to the SPC such as listed above, an RA should be used to inform the other Member States and the Agency immediately in accordance with Article 107(1) of Directive 2001/83/EC as well as the European Commission.

Where a Member State suspends the marketing authorisation for a nationally authorised product in order to urgently protect public health on its territory, the Member State should circulate a RA at the latest one working day after the suspension, informing the other Member States, the Agency and the European Commission of this action in accordance with Article 107(2) of Directive 2001/83/EC.

⁴⁷ Doc.Ref. EMEA/INS/GMP/3351/03 latest version, available on EMEA website <http://www.emea.europa.eu>.

Where a Member State suspends the marketing and use of a medicinal product authorised through the mutual recognition or decentralised procedure on their territory for urgent protection of public health, a RA should be used at the latest one working day after the suspension providing the reasons for the action, thereby informing the other Member States and the European Commission in accordance with the legal requirements of both Articles 107 and 36(2) of Directive 2001/83/EC as well as informing the Agency.

In the case of centrally authorised products, where urgent action to protect human health or the environment is considered essential, a Member State may suspend the use of a medicinal product on its territory, in accordance with Article 20(4) of Regulation (EC) 726/2004. In such cases, the Member State should inform the European Commission and the Agency immediately and no later than the following working day, providing the reasons for its action. In such cases and in order to fulfil the legal requirements, Member States should circulate a RA, thereby informing the European Commission, the Agency and the other Member States.

Where a RA is used with regard to medicinal products derived from human blood or plasma to notify the occurrence of variant Creutzfeldt-Jakob disease (vCJD) in a blood donor, the RA system in pharmacovigilance should be used in addition to the Official Medicines Control Laboratories (OMCL) Alert and, if a batch recall is necessary, the Inspection Rapid Alert (see *Compilation of Community Procedures on Inspections and Exchange of Information*⁴⁸).

In addition to the above criteria, a RA may also be used when there are concerns about a change in the risk-benefit balance of a medicinal product or an active ingredient, following:

- a series of reports (or rarely a single well documented case) of an unexpected and serious adverse reaction;
- reports of an expected adverse reaction which suggest greater severity or long-term sequelae than previously known, or which identify new risk factors;
- a significant increase in the reporting rate of an expected serious adverse reaction;
- evidence from studies (clinical trials or non-interventional studies) indicative of an unexpected risk, or a change in frequency or severity of a known risk;
- knowledge that the efficacy of a medicinal product is not established as assumed to date; or
- evidence that the risks of a particular product are greater than alternatives with similar efficacy.

4.2.2 Non-Urgent Information

An NUI should be used for information exchange in relation to safety concerns not fulfilling the criteria for an RA as defined above. For example, an NUI should be used to communicate pharmacovigilance data which do not require immediate or urgent action and/or where additional information is required from other Member States to support the evaluation of the concern.

In each case the reason for sending an NUI should be provided:

- Provision of emerging pharmacovigilance information at an early stage;
- Information on a potential new safety signal;
- Information on status of implementation of regulatory action;
- Information which may be of interest to other Member States, but does not require a response (e.g. the withdrawal of a product for reasons other than safety, the outcome of discussions from national safety committees, when to expect an Assessment Report on certain items, Public Statements (press releases), Direct Healthcare Professional Communication, current media activity);
- Request for information;

⁴⁸ Doc.Ref. EMEA/INS/GMP/3351/03 latest version, available on EMEA website <http://www.emea.europa.eu>.

- Organisational matters;
- Facilitation of data collection for interaction with external parties.

4.3 Procedures

4.3.1 Sending a Rapid Alert or a Non-Urgent Information

In accordance with Article 26 of Regulation (EC) No 726/2004 and Article 105 of Directive 2001/83/EC, the Agency, in consultation with Member States and the European Commission, has set up a data-processing network for the rapid transmission of data between the Competent Authorities in the event of an alert relating to faulty manufacture resulting in adverse reactions, serious adverse reactions and other pharmacovigilance data regarding medicinal products marketed in the EU. RAs and NUIs fall under other pharmacovigilance data and use EudraNet as the data-processing network.

To send a RA or NUI, the established EudraNet RA mailbox (address list "All Human RA") should be used, which refers to the contact points of the Competent Authorities of Member States, the Agency and the European Commission. The latest adopted EudraNet E-mail policy applies accordingly.

Following successful implementation between the Agency, the Member States and the European Commission, electronic submission has replaced the telefax system used in the past to exchange this kind of information. However, for emergencies, e.g. EudraNet access is not available or there is a network failure, the former telefax system needs to be maintained and should be used as an alternative. Changes related to the fax numbers should be notified immediately to the Agency, the European Commission and the contact points in Member States. The Agency and all Competent Authorities should dedicate a fax machine to the Rapid Alert and Non-Urgent Information System which allows storage of the fax numbers and process group dialling.

Electronic communication with partners that are not connected via EudraNet, i.e. Marketing Authorisation Holders and the World Health Organization (WHO), should be performed in a way that guarantees security and confidentiality of the data exchanged, e.g. via EudraLink⁴⁹.

Templates for RAs and NUIs are annexed (see Annexes 5.3.1 and 5.3.2). These templates are also available on the EudraNet website (<http://www.eudra.org/eudraportal/>) and may be accessed via the established pharmacovigilance domain.

When preparing a RA or NUI, the following rules apply:

- The Template (see Annexes 5.3.1 and 5.3.2) chosen should comply with the criteria either for a RA or for an NUI.
- Clear and concise information on the safety concern and reasons for sending the RA or NUI should be provided so that there is no need for clarification in the first instance.

a) The product(s) concerned should be identified by the International Non-Proprietary Name (INN) and when available and relevant, its strength, formulation and the name of the Marketing Authorisation Holder.

b) The authorisation status of the product should be specified, i.e. if the product is centrally authorised, purely nationally authorised, subject to mutual recognition or decentralised or referral procedure, or the nature of the product if not authorised.

c) The Competent Authority generating the RA/NUI should transmit at least the minimum information listed in Table II.4.A at the end of this Chapter and use the Templates (see Annexes 5.3.1 and 5.3.2).

⁴⁹ See EudraLink website <https://eudralink.emea.eu.int>.

d) Any information required from recipients should be clearly specified, together with the timeframe for response.

e) Annexes to the RA/NUI, where necessary, should also be transmitted electronically, if available. The format to be used for the electronic transmission of the annexes is the one specified in the latest adopted EudraNet E-mail policy. If the annexes are not available electronically, the RA/NUI Template should be completed including a reference that the referred annexes will be submitted separately via telefax, and should be sent via the defined address list to the dedicated mailboxes. A hardcopy of this completed form should be attached to the faxed annexes.

f) The RA/NUI should be transmitted to the nominated contact points of the Member States, the Agency, the CHMP Chairperson and the European Commission. In case of a centrally authorised product, the RA/NUI also needs to be sent to the Rapporteur. In cases where telefax transmission is used, the fax should be transmitted to the established contact points as indicated above.

g) The title line in the e-mail message which contains the completed Template should:

- identify the product(s) concerned by INN, name of the product class or another appropriate name;
- provide a key word identifying the safety concern or other reason for sending the RA or NUI, using commonly understandable abbreviations (e.g. “GI tox” for gastrointestinal toxicity);
- identify if the message is a RA or NUI;
- provide the deadline for response if requested.

Title lines would therefore look for example like “INN-GI tox-RA” or “INN-Eye disorder-NUI - by ddmmyy”.

h) In case of urgency, when the Concerned Member State has suspended the marketing authorisation of a medicinal product or has withdrawn the medicinal product from the market in order to protect public health, the Agency, the European Commission and all Competent Authorities in the Member States should be informed on the following working day at the latest.

i) When a Rapid Alert is circulated

- in relation to a nationally authorised product, the initiating Member State should inform the Marketing Authorisation Holder(s) concerned in their country adequately and promptly with view to start an inquiry and information exchange. Receiving Member States are responsible for informing Marketing Authorisation Holder(s) in their own country. In case of products authorised through the mutual recognition or decentralised procedure, the Reference Member State should inform the Marketing Authorisation Holder adequately and promptly.
- in relation to a centrally authorised product, the Agency in agreement with the Rapporteur will promptly start an inquiry and information exchange with the Marketing Authorisation Holder(s).
- the initiator should consider if the Rapid Alert meets the criteria for notification to the World Health Organization (WHO) in accordance with **Chapter II.6**.

j) An RA may be used for the preparation and conduct of an urgent safety restriction in line with the relevant guidance on post-authorisation procedures (for centrally authorised products this is the **CHMP Post-Authorisation Guidance Human Medicinal Products**⁵⁰ and for products authorised through the mutual recognition or decentralised procedures this is the **Urgent Safety Restriction Member State Standard Operating Procedure**⁵¹).

⁵⁰ Doc.Ref. EMEA/19984/03 latest version, available on EMEA website <http://www.emea.europa.eu>.

⁵¹ Available on Heads of Agencies website <http://heads.medagencies.com>.

4.3.2 Responses to a Rapid Alert or Non-Urgent Information

Responses to an RA should be sent to all Member States, the Agency and the European Commission no later than one week after the receipt of the RA, unless otherwise specified. The initiator of an RA requesting information should compile the RA Responses and circulate the compilation to all Member States, the European Commission and the Agency as quickly as possible.

In case of an NUI, requested NUI Responses should be provided to the initiating Competent Authority and the Agency only and within the time frame indicated by the initiator, unless otherwise specified. A document compiling all NUI Responses should be circulated by the initiator of the NUI to all Member States, the European Commission and the Agency.

A compilation of RA/NUI Responses should at least include the original RA/NUI and all Responses from Member States.

The title line in the e-mail message which contains the completed response should identify if the message is a RA or NUI Response (e.g. “INN-GI tox-RA Response; analogous to Chapter II.4, Section 3.1.g). The RA or NUI Response should refer to the original message (name of sender, date of original message, alert reference).

The information requested by the initiator of the RA/NUI should be provided.

The Agency will summarise the issues raised in the RAs and NUIs in the Drug Monitor, which will be discussed and updated at each meeting of the PhVWP.

4.3.3 Assessment of a Rapid Alert

After transmission of the initial RA, an interim Assessment Report should be prepared for the next meeting of the PhVWP:

- For a purely nationally authorised medicinal product, the initiating Member State, taking into account all information, including that received and collated from other Member States, prepares the Assessment Report on the risk-benefit balance.
- For a product authorised through the mutual recognition or decentralised procedure, any risk evaluation should normally be carried out by the Reference Member State unless other arrangements are agreed between Member States. In each case agreement needs to be reached on the responsibility for the management of the RA and the Assessment Report on the risk-benefit balance by the Reference Member State, or initiating Concerned Member State, or jointly.
- For a centrally authorised product, the Rapporteur should work closely with the initiator of the RA to provide an assessment in relation to the safety concern. Agreement needs to be reached in each case on the responsibility for the Assessment Report on the risk-benefit balance, by the Rapporteur or the initiating Member State, or jointly.

When the collated information provides evidence of a serious safety concern, a full Assessment Report on the risk-benefit balance should be prepared, for consideration by the PhVWP.

The Assessment Report should be sent to all Competent Authorities in Member States, the Agency and the European Commission and the Marketing Authorisation Holder and should be discussed at the next meeting of the PhVWP.

The Assessment Report should be distributed electronically using the established EudraNet Pharmacovigilance mailbox (address list “All Human Pharmacovigilance”) as indicated in the latest adopted EudraNet E-mail policy.

Consideration will need to be given to whether the matter is of Community interest and should be referred under Article 31, 36 or 37 of Directive 2001/83/EC (see Chapter II.5 for reference to further guidance).

4.3.4 Assessment of Non-Urgent Information

On the basis of the Drug Monitor the PhVWP will discuss all topics on which information was exchanged as a NUI and will agree on a case-by-case basis how to process the safety concern. In the event that preparation of an Assessment Report is considered necessary, the same assessment procedure applies as indicated for a RA (see Chapter II.4, Section 3.3).

TABLE II.4.A: MINIMUM INFORMATION FOR TRANSMISSION OF A RAPID ALERT OR NON-URGENT INFORMATION ALWAYS TO BE PROVIDED

1. Identification
- Type of message - Document reference - Initiator - Recipients - Date of message
2. Medicinal Product
- Active substance(s) by INN (and name of class if applicable) - Invented name(s) - Marketing authorisation procedure of the medicinal product: ☐ Centrally Authorised Product ☐ Mutual Recognition ☐ Decentralised Product ☐ Purely Nationally Authorised Product ☐ Product which has been subject to a referral process - Pharmaceutical form and dosage if appropriate - Marketing Authorisation Holder(s) - Manufacturer if essential
3. Reason for the Rapid Alert/Non-Urgent Information
4. Action(s)
- Action(s) proposed - Action(s) taken (steps taken to collect more information at national level and temporary measure taken to protect public health)
5. Information Exchange
- Information requested

5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product by a Member State

Guidance on Community Referrals is provided in Chapter 3, Volume 2A (Notice to Applicants) of The Rules Governing Medicinal Products in the EU⁵².

Guidance on Opinions issued by the Committee for Medicinal Products for Human Use (CHMP) in accordance with Article 107(2) of Directive 2001/83/EC following notification of consideration of suspension, revocation or variation of the marketing authorisation for a medicinal product by a Member State and on subsequent Commission Decisions is anticipated for public consultation. With regard to the procedure to be followed by the Competent Authorities in Member States for informing the Agency, the Commission and the other Member State in accordance with Article 107(1) and (2) of Directive 2001/83/EC, in case a Competent Authority considers suspension, revocation or variation of a marketing authorisation as a result of pharmacovigilance data evaluation or has suspended the marketing authorisation of a medicinal product in order to urgently protect public health, see Chapter II.4. With regard to the Member State's obligation to inform the Marketing Authorisation Holder according to Article 107(1), see Chapter II.1.

⁵² Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

6. Principles of Collaboration with the World Health Organization in Matters of International Pharmacovigilance

6.1 Introduction

As laid down in Article 27 of Regulation (EC) No 726/2004, the Agency shall collaborate with the World Health Organization (WHO) in matters of international pharmacovigilance and shall submit promptly to WHO appropriate and adequate information regarding the measures taken in the EU which may have a bearing on public health protection in countries outside the EU.

In addition, it should be noted that the Agency, in accordance with Article 58 of Regulation (EC) No 726/2004, may give a scientific opinion, in the context of cooperation with WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the EU. A guideline on the related procedural aspects (Guideline on Procedural Aspects regarding a CHMP Scientific Opinion in the Context of Cooperation with the World Health Organization (WHO) for the Evaluation of Medicinal Products Intended Exclusively for Markets Outside the Community⁵³) also addresses the conduct of pharmacovigilance for such products.

This Chapter describes the principles for providing WHO with pharmacovigilance information on measures taken for medicinal products in the EU and other collaboration with WHO in the field of pharmacovigilance⁵⁴. The Competent Authorities of the EU Member States are members of the WHO Programme for International Drug Monitoring and should fulfil their membership obligations accordingly (see also Chapter II.1). The principles below have been agreed between the Competent Authorities and the Agency at the level of the PhVWP, reflecting their respective roles and responsibilities as part of the EU pharmacovigilance system for the medicinal products authorised in the EU.

6.2 Provision of Individual Case Safety Reports

Cases of adverse reactions occurring in the EU should be reported to the WHO Collaborating Centre by the Competent Authority of the Member State in whose territory the reaction occurred, in accordance with the agreements between the WHO Collaborating Centre and countries participating in the WHO Programme for International Drug Monitoring. This applies to adverse reaction case reports for centrally and non-centrally authorised medicinal products submitted to the Competent Authorities either by Healthcare Professionals or by the Marketing Authorisation Holders⁵⁵.

6.3 Review of Signals Raised by the WHO Collaborating Centre

Competent Authorities in Member States and, for centrally authorised products, the Agency, should consider the summary document on signals provided by the WHO Collaborating Centre as feedback information from their case report database Vigibase. This database may be consulted by all countries participating in the WHO Programme for International Drug Monitoring.

⁵³ Doc.Ref. EMEA/CHMP/5579/04 latest version, available on EMEA website <http://www.emea.europa.eu>.

⁵⁴ Unless otherwise specified below, any information is provided to the WHO Headquarters in Geneva and the WHO Collaborating Centre for International Drug Monitoring in Uppsala, thereafter referred to as WHO Collaborating Centre.

⁵⁵ Adverse reactions occurring in Luxembourg will be transmitted to the WHO Collaborating Centre by the French Competent Authority.

6.4 Provision of Information on Safety-Related Regulatory Action in the EU

a) Centrally authorised products

The Agency transmits to WHO EMEA Public Statements on safety-related regulatory action for centrally authorised products prior to the embargo date. The Agency will also transmit any other EMEA Public Statements concerning centrally authorised products prior to the embargo date.

The Agency should provide responses to Vigimed⁵⁶ queries in relation to centrally authorised products as appropriate.

b) Nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure

Information on safety-related regulatory action for purely nationally authorised products will be transmitted to WHO by the Competent Authority of the Member State if measures related to such marketing authorisations (restrictive measures, variations, suspension, revocation, withdrawal) are implemented or a Public Statement or a Direct Healthcare Professional Communication is issued by, or in agreement, with the Competent Authority.

For products authorised through mutual recognition or the decentralised procedure, the Reference Member State is responsible for provision of such information on behalf of the Concerned Member States.

Member States or the Reference Member State respectively should provide responses to Vigimed queries as appropriate.

In addition, Member States should provide any additional information to WHO for nationally authorised products according to requirements specified by national legislation and agreements.

Occasionally, the Agency issues EMEA Public Statements on safety-related matters for nationally authorised products which have been discussed at the level of the CHMP in the context of legal proceedings as per Community legislation. Such information will also be sent to WHO by the Agency prior to embargo date.

6.5 Participation in the Annual Meetings of the WHO Programme for International Drug Monitoring

Member States and the Agency should attend regularly the Annual Meetings of the WHO Programme for International Drug Monitoring, participating, as appropriate, in the exchange of information and data on topics of common concern and of interest to international pharmacovigilance.

6.6 Other Collaboration

Other collaboration with WHO and their Collaborating Centres will be considered, as need arises, by the Agency or the Competent Authorities of Member States.

⁵⁶ Vigimed is an e-mail-based system for information exchange between the countries participating in the WHO Programme for International Drug Monitoring maintained by the WHO Collaborating Centre.

PART III:
Guidelines for Marketing Authorisation Holders,
Competent Authorities and the Agency on
Electronic Exchange of Pharmacovigilance Information in the EU

1. Introduction

Part III reflects the requirements for mandatory electronic reporting of adverse reactions, save in exceptional circumstances, as defined in Regulation (EC) No. 726/2004 and Directive 2001/83/EC.

During the revision of the previous Volume 9, Part III has been updated to incorporate:

- All applicable ICH Guidelines and Standards for electronic reporting of Individual Case Safety Reports (i.e. ICH-E2A, ICH-E2B(M), ICH-E2C(R), ICH-E2D, ICH-M1, ICH-M2; [see Annex 4](#)).
- The ‘Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area (EEA)’ (EMEA/115735/2004, adopted at EU level in September 2004, [see Annex 3.1.1](#)).
- The EMEA Guidance ‘Technical Documentation – EudraVigilance Human Version 7.0 Processing of Safety Messages and ICSRs’ (EMEA/H/20665/04, adopted at EU level in July 2004, [see Annex 3.1.2](#)).
- ‘Detailed Guidance on the European database of Suspected Unexpected Serious Adverse Reactions’ (EudraVigilance – Clinical Trial Module), (ENTR/CT4, Revision 1, adopted at EU level in April 2004, Volume 10 of The Rules Governing Medicinal Products in the EU, Chapter II⁵⁷).
- The recommendations of the EudraVigilance Ad Hoc Group and EMEA proposal as endorsed by the Heads of Human Medicines Agencies in February 2005 and the EMEA Management Board in March 2005.

This updated Part III replaces the following previous Guidelines:

- Note for Guidance on Electronic Exchange of Pharmacovigilance Information for Human and Veterinary Medicinal Products in the European Union (CXMP/PhVWP/2056/99).
- Note for Guidance on Regulatory Electronic Transmission of Individual Case Safety Reports (ICSRs) in Pharmacovigilance (EMEA/H/31387/01).

The mandatory electronic reporting of adverse reactions, save in exceptional circumstances, is defined in Regulation (EC) No. 726/2004 and Directive 2001/83/EC and applies to all medicinal products authorised in the European Union (EU), independent of the authorisation procedure. For further details reference should be made to [Chapter I.2](#).

Part III of Volume 9A refers to the electronic exchange of pharmacovigilance information and provides a reference to the preparation and electronic transmission of Individual Case Safety Reports (ICSRs). It applies to national Competent Authorities, the European Medicines Agency (hereafter referred to as the Agency) and Marketing Authorisation Holders in the EU.

The standards to support the electronic transmission of ICSRs on an expedited and periodic basis are defined in the frame of the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (referred to as ICH).

Taking into account the international dimension of adverse reaction reporting and the need to achieve uniformity and high quality with regard to content and format of ICSRs between all involved parties it is of utmost importance that all parties follow the applicable ICH and EU guidelines. This applies in particular to electronic reporting, which requires strict adherence to uniform standards.

⁵⁷ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

The requirements for the electronic reporting obligations of ICSRs on an expedited and periodic basis are defined in EU legislation Regulation (EC) No. 726/2004, Article 24(2) and Directive 2001/83/EC, recital 56 and Article 104(1).

Electronic reporting of ICSRs should be conducted by the following electronic data interchange (EDI) partners: Competent Authorities in Member States as well as Iceland, Liechtenstein and Norway, Marketing Authorisation Holders and the Agency.

To support the fulfilment of these electronic reporting obligations, the European Commission, in collaboration with the Agency established EudraVigilance, the European pharmacovigilance database and data-processing network as defined in Regulation (EC) No. 726/2004, Article 26 and Article 57(d) and Directive 2001/83/EC Article 105, with the following main objectives:

- Assist the rapid and secure transmission of ICSRs between all EDI partners;
- Fully comply with the respective ICH and EU guidelines and standards as outlined in **Chapter III.2**;
- Facilitate the electronic reporting by providing the necessary technical tools to the EDI partners;
- Assist the administration and management of ICSRs;
- Provide signal detection functionalities and support scientific evaluation of ICSRs;
- Establish a central repository of highest quality data on electronically reported adverse reactions occurring within and outside the EU.

2. Applicable Electronic Reporting Guidelines

The electronic transmission and management of ICSRs should be carried out by all EDI parties according to the following Guidelines and specifications:

- The ICH-E2A Guideline ‘Clinical Data Management: Definitions and the Standards for Expedited Reporting’, which presents the standard definitions and terminology for key aspects of clinical safety reporting and provides guidance on the appropriate mechanism for handling expedited reporting in the investigational phase (see Annex 4).
- The ICH-E2B(M) Guideline ‘Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of Individual Case Safety Reports’ (recommended for adoption at Step 4 of the ICH Process on 17 July 1997 and amended for maintenance on 10 November 2000 by the ICH Steering Committee (including the Post-Step 4 corrections agreed by the Steering Committee on 5 February 2001), CPMP/ICH/287/95 modification corr.), which extends the above Guideline to standardise the data elements for the transmission of all types of ICSRs, regardless of their source and destination (see Annex 4).
- The ICH-E2B(M) ‘Implementation Working Group Questions & Answers, Version 1.1’ (3 March 2005) (see Annex 4).
- The ICH-E2C Guideline ‘Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs’ (CPMP/ICH/288/95) and its Addendum (CPMP/ICH/4679/02), which provides guidance on the format and content of safety updates, which need to be provided to regulatory authorities, at defined intervals, after the medicinal products have been authorised (see Annex 4).
- The ICH-E2D Guideline ‘Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting’ (November 2003, CPMP/ICH/3945/03), which provides further guidance on definitions and standards for post approval expedited reporting, as well as good case management practices (see Annex 4).
- The ICH-M1 Standard ‘Medical Dictionary for Regulatory Activities (MedDRA)’ in the latest version and related guidelines and Points-to-Consider Documents. The MedDRA terminology

is designed to support the classification, retrieval, presentation and communication of medical information throughout the medicinal product regulatory life cycle (see Annex 4).

- The ICH-M2 Standard ‘Electronic Transmission of Individual Case Safety Reports Message Specification (ICH ICSR DTD Version 2.1)’ (CPMP/ICH/285/95 modification), which provides the standards for the safety messages, which can contain one or more ICSRs (see Annex 4).
- The ICH-M2 Recommendations (see Annex 4):
 - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer for the Regulatory Information (ESTRI) General Recommendation – Procedure (10NOV2005)
 - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) General Recommendation – ESTRI Gateway (10NOV2005)
 - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) Physical Media Recommendation – Floppy Disks (10NOV2005)
 - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) Physical Media Recommendation – CD-R 10NOV2005
 - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) Physical Media Recommendation – DVD-RAM 10NOV2005
 - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) File Format Recommendation – PDF 10NOV2005
 - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) File Format Recommendation – XML 10NOV2005
 - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) Information Transfer Recommendation – EDIINT AS1 10NOV2005.
- The ICH-M5 ‘Routes of Administration Controlled Vocabulary’ (CHMP/ICH/175860/2005), which provides standard terms for routes of administration (see Annex 4).
- The ICH-M5 ‘Units and Measurement Controlled Vocabulary’, (EMEA/CHMP/ICH/175818/2005), which provides standard terms for units and measurements (see Annex 4).
- The Standard Terms on Pharmaceutical Dosage Forms as published by the Council of Europe as ‘Standard Terms on Pharmaceutical Dosage Forms, Routes of Administration and Containers’ in the latest version.
- The ‘Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area (EEA)’ (EMEA/115735/2004, adopted at EU level in September 2004, see Annex 3.1.1).
- The EMEA Guidance ‘Technical Documentation – EudraVigilance Human Version 7.0 Processing of Safety Messages and ICSRs’ (EMEA/H/20665/04, adopted at EU level in July 2004, see Annex 3.1.2).

- ‘Detailed Guidance on the European database of Suspected Unexpected Serious Adverse Reactions’ (EudraVigilance – Clinical Trial Module), (ENTR/CT4, adopted at EU level in April 2004, Volume 10 of The Rules Governing Medicinal Products in the EU, Chapter II⁵⁸).

As technical standards are evolving over time, the above reference documents may require revision and maintenance. In this context, the latest version of these documents should always be taken into account.

For general terms and definitions reference should be made to the relevant chapters of the documents listed above.

3. Message Format and Message Processing

Safety Messages including one or several ICSRs need to follow the specifications as outlined in the EMEA Guidance ‘Technical Documentation – EudraVigilance Human Version 7.0 Processing of Safety Messages and ICSRs’ (EMEA/H/20665/04, adopted at EU level in July 2004, see Annex 3.1.2).

Medicinal Product Messages including one or several medicinal product reports need to follow the specifications as outlined in the

- EudraVigilance Medicinal Product Dictionary (EVMPD) Version 2.0 Technical Specifications (9 November 2004, EMEA/140190/2004); and the
- EudraVigilance Medicinal Product Dictionary (EVMPD) Version 2.0 Message and Acknowledgement Specifications (8 December 2004, EMEA/178966/2004).

For details refer also to Chapter III.11, Section 6.

With regard to the Safety and Medicinal Product Report Message processing, the specifications as outlined in the ‘Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area (EEA)’ (EMEA/115735/2004, adopted at EU level in September 2004, see Annex 3.1.1) should be followed.

4. Electronic Reporting of Individual Case Safety Reports and Definition of ‘Exceptional Circumstances’

Since 20 November 2005, electronic reporting, save in exceptional circumstances, is mandatory for all authorised medicinal products in the EU. Non-adherence to this requirement constitutes non-compliance with EU legislation as referred to in Chapter III.1.

With regard to the provisions set out in Regulation (EC) No. 726/2004, Article 24(2) and Directive 2001/83/EC, Article 104(1), ‘exceptional circumstances’ are defined as mechanical, programme, electronic or communication failures that prevent electronic reporting as described in Chapter IV of the ‘Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area (EEA)’ (EMEA/115735/2004, adopted at EU level in September 2004, see Annex 3.1.1).

Technical tools (EVWEB) have been made available by the Agency to interested EDI partners, specifically Small and Medium-Sized Enterprises (SMEs), to facilitate compliance with the electronic reporting requirements as defined in EU legislation. In addition, local reporting arrangements should be discussed with the national Competent Authorities. However, with regard to the electronic

⁵⁸ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

reporting obligations of adverse reactions towards the Agency, these need to be maintained independent of any local arrangements.

In accordance with EU legislation as outlined in [Chapter III.1](#), the national Competent Authorities in the EU are responsible for electronic reporting of adverse reactions occurring within their respective territory to the Agency (EudraVigilance).

5. Preparation of Individual Case Safety Reports and Data Privacy Laws

5.1 How to Prepare Individual Case Safety Reports

Medical and administrative data related to individual cases, which qualify for expedited and periodic reporting, should be provided in line with ICH-E2A, ICH-E2B(M), ICH-E2D, ICH-M1, ICH-M2 and EU guidelines and standards as referred to in [Chapter III.2](#). These data should be reported electronically in a fully structured format using all applicable and relevant E2B(M) data elements and standard terminologies. Any supporting information related to the individual case should be sufficiently described within an individual case safety report (ICSR) with reference to the documents that are held by the sender (ICH A.1.8.2: ‘List of documents held by sender’), which may need to be provided on request.

It is recognised that it is often difficult to obtain all details on a specific case. However, complete information for an individual case, that is available to the sender, should be reported in each ICSR. This applies to all types of ICSRs, i.e. reports with initial information on the case, follow-up information and cases highlighted for nullification (ICH-E2B(M) A.1.13: ‘Report nullification’ set to ‘yes’ and ICH-E2B(M) A.1.13.1: ‘Reason for nullification’ completed see also [Chapter III.6](#) on nullification of individual cases).

In accordance with the international guideline on pharmacovigilance (ICH-E2D), a case narrative, i.e. a complete medical description of the case (ICH-E2B(M) B.5.1: ‘Case narrative including clinical course, therapeutic measures, outcome and additional relevant information’) should be provided at least for all serious cases. This case narrative should be a medical report containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, adverse reactions including the outcome, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes an adverse reaction. The narrative should serve as a comprehensive, stand-alone “medical report”. The information should be presented in a logical time sequence; ideally this should be presented in the chronology of the patient’s experience. Furthermore, the available information should be entered in structured format in the applicable ICH-E2B(M) fields, which should be repeated as necessary.

In follow-up reports, new information should be clearly identifiable in the case narrative section and provided in structured format in the applicable ICH-E2B(M) fields.

Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units.

Key information from supplementary records should be included in the report, and their availability should be mentioned in the narrative as well as in section ICH A.1.8.2: ‘List of documents held by sender’. Any relevant autopsy or post-mortem findings should also be summarised in the narrative and related documents should be provided according to national regulation and if allowed by the national data privacy laws.

An example of a standard narrative template is provided in CIOMS V⁵⁹.

In situations where it is unclear or evident that the sender has not transmitted the complete information available on the case in an ICSR in line with the instructions provided in this chapter, the receiver may request the sender to re-transmit the ICSR with the complete case information in electronic ICH-E2B(M) format as described in **Chapter III.2** within 24 hours.

This should be seen in the light of qualitative signal detection and evaluation, where it is important for the receiver to have all available information on a case to perform the medical assessment.

The use of EU languages in adverse reaction reporting is described in **Chapter III.11, Section 5** and **Chapter I.4**.

The suspect, interacting and/or concomitant active substance(s)/invented name of the reported medicinal product(s) should be reported in accordance with the ICH-E2B(M) and as outlined in this Section. For combination medicinal products, which contain more than one active substance, each active substance needs to be reflected individually in section B.4.k.2.2 'Active substance name(s)' of ICH-E2B(M), which needs to be repeated for each active substance contained in the combination product.

Where medicinal products cannot be described on the basis of the active substance(s) or the invented name, e.g. in case only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should be reflected in section B.5.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information'.

5.2 How to Prepare Individual Case Safety Reports Related to Parent-Child/Foetus Cases

With regard to parent-child/foetus cases, the following principles should be adhered to:

- In cases where a foetus or nursing infant is exposed to one or several medicinal products through the parent and experiences one or more adverse reactions/events, information on both the parent and the child/foetus should be provided in the same report. Reports of these cases are referred to as parent-child/foetus reports.
- If there has been no reaction/event affecting the child/foetus, the parent-child/foetus report does not apply; i.e. the ICH-E2B(M) B.1 fields 'Patients characteristics' apply only to the parent (mother or father) who experienced the adverse reaction/event.
- For those cases describing miscarriage or foetal demise or early spontaneous abortion, only a parent report is applicable, i.e. ICH-E2B(M) B.1 fields 'Patients characteristics' apply to the mother. However, if suspect medicinal product(s) were taken by the father this information should be indicated in the section B.4.k.13 'Time intervals between drug administration and start of reaction/event'.
- If both the parent and the child/foetus sustain adverse reactions, two separate reports, i.e. one for the parent (mother or father) and one for the child/foetus, should be provided but they should be linked by using the ICH-E2B(M) field A.1.12 'Identification number of the report which is linked to this report' in each report.
- If only the child/foetus has an adverse reaction/event (other than early spontaneous abortion/foetal demise) the information provided in this section applies only to the child/foetus, and characteristics concerning the parent (mother or father), who was the source

⁵⁹ Council for International Organizations of Medical Sciences (CIOMS). Current Challenges in Pharmacovigilance: Pragmatic Approaches (CIOMS V). Geneva: CIOMS; 2001. Available on CIOMS website <http://www.cioms.ch/>.

of exposure to the suspect medicinal product should be provided in ICH-E2B(M) B.1.10 section 'For a parent-child/fetus report, information concerning the parent'.

- If both parents are the source of the suspect drug(s) then the case should reflect the mother's information in ICH-E2B(M) B.1.10 section 'For a parent-child/fetus report, information concerning the parent' and the case narrative (section B.5.1) should describe the entire case, including the father's information.

5.3 How to Report Follow-up Information

ICSRs are sent at different times to multiple receivers. Therefore the initial/follow up status is dependent upon the receiver. For this reason an item to capture follow-up status is not included in the ICH-E2B(M) data elements. However, the field 'date of receipt of the most recent information for this report' ICH-E2B(M) (A.1.7) taken together with the field 'sender identifier' ICH-E2B(M) (A.3.1.2) and the field 'sender's (case) report unique identifier' ICH-E2B(M) (A.1.0.1) provide a mechanism for each receiver to identify whether the report being transmitted is an initial or follow-up report. For this reason these items are considered critical for each transmission. A precise date should be used (i.e. day, month, year).

This date should be changed each time follow up information is received by the sender.

New information should be clearly identifiable in the case narrative section and provided in structured format in the applicable ICH-E2B(M) fields.

The sender should report follow-up information on an expedited basis, if significant new medical information has been received. Significant new information relates e.g. to new adverse reaction(s), a change in the causality assessment and any new or updated information on the case that impacts on the medical interpretation of the case. Therefore, the identification of significant new information requiring expedited reporting always requires medical judgement.

Situations where the seriousness criteria and/or the causality assessment related to an individual case are downgraded (e.g. follow up information leads to a change of the seriousness criteria from serious to non-serious; causality assessment is changed from related to non-related) should be also considered as significant change and thus reported on an expedited basis.

In addition, the sender should also report follow-up information on an expedited basis, where new administrative information is available, that could impact on the case management e.g. new case identifiers have become known to the sender, which may have been used in previous transmissions (ICH-E2B(M) field A.1.11 'Other case identifiers in previous transmissions'); this information may be specifically relevant for the receiver to manage potential duplicates. Another example refers to ICH-E2B(M) field A.1.8 'Additional available documents held by sender', whereby new documents that have become available to the sender may be relevant for the medical assessment of the case.

In contrast, non-significant information, which does not impact on the medical evaluation of the case, does not require expedited reporting. This may refer for example to minor changes of dates (e.g. the day of the birth date) or corrections of typos in the previous case version. Naturally, medical judgment should be applied, as a change to the birth date may constitute a significant change (e.g. with implications on the age information of the patient).

In these situations where the case is amended without requiring expedited reporting, the date of receipt of the most recent information reported in the field ICH-E2B(M) A.1.7 'Date of receipt of the most recent information for this report' should not be changed.

Similarly, a change of the status of a MedDRA code/term from current to non-current *due to a version change* of MedDRA can be considered as a non-significant change as long as this change has no impact on the medical content of a case. However, a change in the MedDRA coding due to a change in

the interpretation of a previously reported adverse reaction may constitute a significant change and therefore should be reported on an expedited basis.

5.4 What to Take into Account for Data Privacy Laws

To comply with EU legislation on the protection of individuals with regard to the processing of personal data as referred to in **Chapter I.7, Section 7**, electronic transmission of ICSRs should operate on the principles of anonymised information, whereby the ICH guidelines should be adhered to as follows:

- ICH-E2B(M) field B.1.1 ‘Patient name or initials’:
The information should be provided when it is in conformance with the confidentiality requirements. This also applies to medical record number(s) ICH-E2B(M) field (B.1.1.1). If the initials are known to the sender but cannot be transmitted due to data privacy requirements, this field should be populated with “PRIVACY”.
If the initials of the patient are unknown to the sender, this field should be populated with “UNKNOWN”.
- ICH-E2B(M) field B.1.2.1 ‘Patient birth date’, ICH-E2B(M) field B.1.2.2 ‘Patient age at the time of the onset of reaction/event’ or ICH-E2B(M) field B.1.2.3 ‘Patient age group’:
Only one of the elements describing age should be used. The choice should be based upon the most precise information available and in conformance with the national confidentiality requirements.
- Narratives in ICH-E2B(M)
When information on individuals is reflected in narratives (e.g. ICH-E2B(M) section B.1.7 ‘Relevant medical history and concurrent conditions’ ICH-E2B(M) section B.1.10.7 ‘Relevant medical history and concurrent conditions of parent’ ICH-E2B(M) section B.5 ‘Narrative case summary and further information’), it should be provided in such a way that it can support the case evaluation and assessment by the receiver, but does not allow for the identification of the individual concerned. Taking the example of age, no date of birth should be provided but the age or age group in accordance with national confidentiality requirements.

6. Nullification of Individual Cases

In line with the ICH-E2B(M) guideline, the nullification of individual cases should be used to indicate that a previously transmitted report should be considered completely void (nullified), for example when the whole case was found to be erroneous or in case of duplicate reports. It is essential to use the same case report number (ICH-E2B(M) field A.1.0.1 ‘Sender’s (case) safety report unique identifier’ and ICH-E2B(M) field A.1.10 ‘Worldwide unique case identification number’) previously submitted. A nullified case is one that should no longer be considered for scientific evaluation.

When nullifying a case the following principles need to be taken into account:

- The flag ICH-E2B(M) field A.1.13 ‘Report nullification’ should be set to ‘Yes’ and the nullification reason should be provided in the field ICH-E2B(M) field A.1.13.1 ‘Reason for nullification’. The nullification reason should be clear and concise to explain why this report is no longer considered to be a valid report. For example a nullification reason stating, ‘the report no longer meets the reporting criteria’ or ‘report sent previously in error’ are not detailed enough explanations.
- An individual case can only be nullified by the sending organisation.
- Once an individual case has been nullified, the case cannot be reactivated.
- If it becomes necessary to resubmit the case that has been previously nullified, a new ICH-E2B(M) A.1.0.1 ‘Sender’s (case) safety report unique identifier’ and ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ should be assigned.

- Individual versions of ICSRs cannot be nullified, only the individual case to which they refer.
- Individual cases that have been nullified should not be used for scientific evaluation, however they should remain in the database for auditing purposes.

In addition, in case of duplicate reports where one report needs to be nullified, the update of the remaining case should be performed in the form of a follow-up report. The duplicate number fields in this report ICH-E2B(M) field A.1.11.1 ‘Source(s) of the case identifier (e.g. name of the company, name of regulatory agency)’ and ICH-E2B(M) field A.1.11.2 ‘Case identifier(s)’ should be updated with the case identification numbers of the nullified case.

The Table below gives examples for different scenarios for which nullifications should and should not be carried out. It will also provide information on what to do in specific situations.

TABLE III.6.A: EXAMPLES OF DIFFERENT SCENARIOS FOR WHICH CASE NULLIFICATIONS SHOULD AND SHOULD NOT BE CARRIED OUT

1. Scenarios for which individual cases should be nullified:		
Ex.	Scenario	Action
1	An individual case has been identified as a duplicate of another individual case previously submitted.	One of the individual cases should be nullified. The remaining valid case should be updated with any additional information as relevant to the nullified case. The update of the remaining case should be performed in form of a follow-up report. The duplicate number fields in this report ICH-E2B(M) A.1.11.1 ‘Source(s) of the case identifier (e.g. name of the company, name of regulatory agency)’ and ICH-E2B(M) A.1.11.2 ‘Case identifier(s)’ should be updated with the case identification numbers of the nullified case.
2	A wrong ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ was accidentally used. This wrong ICH-E2B(M) A.1.10 Worldwide unique case identification number did not refer to any existing case.	The report with the wrong ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ should be nullified. A new case should be created based on an ICSR with the correct ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’.
3	On receipt of further information it is confirmed that the adverse reaction occurred before the suspect drug(s) was taken.	The case should be nullified.
4	On receipt of further information on an individual case, it is confirmed that the patient did not receive the suspect drug and the minimum reporting criteria for an ICSR as outlined in the ICH-E2B(M) guideline are no longer met.	The case should be nullified.
5	On receipt of further information it is confirmed that the reported adverse reaction(s) did not occur to the patient.	The case should be nullified.

6	On receipt of further information it is confirmed that there was no valid patient for the individual case minimum reporting criteria for an ICSR as outlined in the ICH-E2B(M) guideline are no longer met.	If it is not possible to obtain confirmation of the patient's existence, then the case should be nullified.
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2. Scenarios, for which individual cases should NOT be nullified		
Ex.	Scenario	Action
7	A wrong ICH-E2B(M) A.1.10 'Worldwide unique case identification number' was accidentally used. This wrong ICH-E2B(M) A.1.10 'Worldwide unique case identification number' referred to an existing case.	The report with the wrong ICH-E2B(M) A.1.10 'Worldwide unique case identification number' should <u>not</u> be nullified. A follow-up report should be created to correct the information previously submitted. A new ICSR should be created and submitted with the correct ICH-E2B(M) A.1.10 'Worldwide unique case identification number'.
8	On receipt of further information on an individual case, it is confirmed that the patient did not receive the MAH's suspect drug. However, the patient received other suspect drugs and the minimum reporting criteria for an ICSR as outlined in the ICH-E2B(M) guideline are still met.	The case should not be nullified.
9	On receipt of further information it is confirmed that the individual case was not medically confirmed.	The case should not be nullified. A follow-up report should be submitted within the appropriate timeframe with the primary source information updated: The field ICH-E2B(M) A.2.1.4 'Qualification' should be set to 'Consumer or other non health professional' or 'Lawyer' as applicable; the field ICH-E2B(M) A.1.14 'Was the case medically confirmed, if not initially from a health professional?' should be set to 'No'.
10	On receipt of further information the reporter has confirmed that the reported adverse reaction is no longer considered to be related to the suspect drug(s).	The case should not be nullified. A follow-up report should be submitted within the appropriate timeframe with the updated information on the case.
11	Change of the individual case from serious to non-serious (downgrading).	The case should not be nullified. A follow-up report should be submitted with the seriousness flags ICH-E2B(M) field A.1.5.1 'Seriousness' set to 'No' without selection of a value for the ICH-E2B(M) field A.1.5.2 'Seriousness criteria'. The flag ICH-E2B(M) field A.1.9 'Does this case fulfil the local criteria for an expedited report?' should also be set to 'No'.

12	The reported adverse reaction was considered to be a post-study event (it occurred outside of the study period, including follow-up period).	The case should not be nullified. If the adverse reaction is no longer reportable under the terms of an investigational clinical trial, a new case should be created and submitted with the appropriate report type selected for the field ICH-E2B(M) A.1.4 ‘Type of report’.
13	The primary source country has changed, which has an impact on the ICH-E2B(M) convention regarding the creation of the ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’.	The case should not be nullified. The ICH-E2B(M) A.1.0.1 ‘Sender’s (case) safety report unique identifier’ can be updated on the basis of the new primary source country code. However, the ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ should remain unchanged. If, for some technical reason, the sender’s local system is not fully ICH-E2B(M) compliant and cannot follow this policy, then the sender should nullify the original case. A new case should be created with a new ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ reflecting the changed primary source country code. The ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ of the case that was nullified should be reflected in fields ICH-E2B(M) A.1.11.1 ‘Source(s) of the case identifier (e.g. name of the company name of regulatory agency)’ and ICH-E2B(M) A.1.11.2 ‘Case identifier(s)’.
14	The drug taken belongs to another MAH (e.g. a product with the same active substance but marketed under a different invented name).	The case should not be nullified. It is recommended that the initial sender informs the other MAH about this case (including the ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ used). The original organisation should also submit a follow-up report to provide this new information. The other concerned MAH should create a new case and specify in the fields ICH-E2B(M) A.1.11.1 ‘Source(s) of the case identifier (e.g. name of the company name of regulatory agency)’ and ICH-E2B(M) A.1.11.2 ‘Case identifier(s)’ the reference case number and the name of the initial sending MAH.
15	The suspect drug taken does not belong to the MAH (same active substance, the invented name is unknown and the report originates from a country, where the MAH has no marketing authorisation for the medicinal product in question).	The case should not be nullified. The MAH should submit a follow-up report with this information (see Chapter I.4)

16	The case is mistakenly reported by MAH A although MAH B as co-marketer is responsible for reporting the case.	The case should not be nullified. An explanation should be sent by the MAH A to the co-marketer MAH B that the case has already been reported. The MAH B should provide any additional information on the case as a follow-up report with the same ICH-E2B(M) A.1.10 'Worldwide unique case identification number'.
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7. Handling of Adverse Reaction Reports Published in the Worldwide Literature

General requirements in relation to adverse reaction reports published in the worldwide literature are described in [Chapter I.4, Section 3.2](#).

When reports from the world-wide literature are submitted as ICSRs, the literature references should be provided in the Vancouver Convention (known as "Vancouver style") as developed by the International Committee of Medical Journal Editors in the field ICH-E2B(M) A.2.2 'Literature reference(s)'. The standard format as well as those for special situations can be found in the following reference, which is in the Vancouver style⁶⁰.

For initial reporting of a case described in the literature in the form of an ICSR, a summary of the case in English (English abstract of the literature article) is regarded as sufficient to meet the expedited reporting criteria. This case summary should be provided in the field ICH-E2B(M) B.5.1 'Case narrative including clinical course, therapeutic measures'.

If considered necessary, a national Competent Authority may request a full translation of the copy of the literature article from the sender.

In addition to the ICSR, a copy of the literature article should be provided. Until standards for the electronic transmission of attachments (e.g. copies of literature articles) are developed in the frame of ICH, the sender should follow the rules outlined below:

- Mailing address and format of literature articles:
 - Literature articles reportable to the Agency should be provided in PDF format and sent via e-mail to the following e-mail address: EVLIT@emea.europa.eu.
 - Literature articles reportable to the national Competent Authorities should be provided in PDF format and sent according to the local requirements.

With regard to potential copyright issues in relation to copies of articles from the worldwide published literature, senders may wish to follow the non-binding recommendations from the Pharma Documentation Ring (P-D-R). These recommendations apply only to the transmission and handling of electronic copies of literature articles in the frame of regulatory activities.
- File name of literature articles sent in electronic format to the Agency:

The file name of a literature article sent in PDF format should match exactly the 'World-Wide Unique Case Identification Number' (ICH-E2B(M) A.1.10.1 or A.1.10.2 as applicable) assigned to the individual case, which is described in the article and which is reported in the E2B(M) ICSR format.

⁶⁰ International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med. 1997;336:309-15. The Vancouver recommendations are also available on the International Committee of Medical Journal Editors website <http://www.icmje.org>.

If there is a follow-up article to the individual case published in the literature, the file name with the World-Wide Unique Case Identification Number must be maintained but should include a sequence number separated with a dash.

Example:

ICSR: FR-ORGABC-23232321 (ICH-E2B(M) field A.1.10.1 World-Wide Unique Case Identification Number);

File name: FR-ORGABC-23232321.pdf.

Follow-up information published in the literature in a separate article:

ICSR: FR-ORGABC-23232321 (ICH-E2B(M) field A.1.10.1 World-Wide Unique Case Identification Number remains unchanged);

File name: FR-ORGABC-23232321-1.pdf.

- Reporting of cases reported in the worldwide literature referring to more than one patient:
When the worldwide literature article refers to the description of more than one patient, the copy of the literature article should be sent only once.
The file name of a literature article sent in PDF format should match exactly the 'World-Wide Unique Case Identification Number' (ICH-E2B(M) field A.1.10.1 or A.1.10.2 as applicable) assigned to the first reportable individual case described in the article.
In addition, all ICSRs which relate to the same literature article should be cross referenced in the section ICH-E2B(M) field A.1.12 'Identification number of the report which is linked to this report' and the section should be repeated as necessary to cross refer all related cases.
See Table below for an example for the reporting of cases reported in the worldwide literature referring to more than one patient.

TABLE III.7.A: EXAMPLE FOR THE REPORTING OF CASES ORIGINALLY REPORTED IN THE WORLDWIDE LITERATURE REFERRING TO MORE THAN ONE PATIENT

Example	Action
A literature article describes serious adverse reactions that have been experienced by 3 patients. For this scenario 3 ICSRs should be submitted, reporting for each individual patient the adverse reactions and all other available information on the case.	For Case 1 described in the literature article: • ICH-E2B(M) A.1.10.1 ‘World-Wide Unique Case Identification Number’: UK-ORGABC-0001 • ICH-E2B(M) A.1.12 Linked Report: UK-ORGABC-0002 • ICH-E2B(M) A.1.12 Linked Report: UK-ORGABC-0003 • ICH-E2B(M) A.2.2 ‘Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15. • File name for the copy of literature article to be sent via e-mail to EVLIT@emea.europa.eu: UK-ORGABC-0001.pdf For Case 2 described in the literature article: • ICH-E2B(M) A.1.10.1 ‘World-Wide Unique Case Identification Number’: UK-ORGABC-0002 • ICH-E2B(M) A.1.12 Linked Report: UK-ORGABC-0001 • ICH-E2B(M) A.1.12 Linked Report: UK-ORGABC-0003 • ICH-E2B(M) A.2.2 ‘Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15. • No copy of the literature article required since the copy was already submitted for case 1. For Case 3 described in the literature article: • ICH-E2B(M) A.1.10.1 ‘World-Wide Unique Case Identification Number’: UK-ORGABC-0003 • ICH-E2B(M) A.1.12 Linked Report: UK-ORGABC-0001 • ICH-E2B(M) A.1.12 Linked Report: UK-ORGABC-0002 • ICH-E2B(M) A.2.2 ‘Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15. • No copy of the literature article required since the copy was already submitted for case 1.

8. Compliance with Required Reporting Timeframes

Marketing Authorisation Holders and Competent Authorities in Member States as well as Iceland, Liechtenstein and Norway should ensure that the timeframes regarding the expedited reporting requirements as defined in EU legislation and in **Chapter I.4, Section 2** are adhered to.

Fall-back procedures in case of system failure for electronic case reporting are described in the ‘Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area (EEA)’ (EMEA/115735/2004, adopted at EU level in September 2004, **see Annex 3.1.1**).

9. Electronic Re-transmission of Cases between Multiple Senders and Receivers

The electronic re-transmission of cases refers to the electronic transmission of ICSRs between multiple senders and receivers, e.g. where a case was first reported by a Marketing Authorisation Holder to the Competent Authorities in Member States as well as Iceland, Liechtenstein and Norway and from there to the Agency.

Based on the reporting obligations in pharmacovigilance, ICSRs are re-transmitted between different senders and receivers. During this re-transmission process, information on the case should not be omitted or changed if no new information on the case is available to the re-transmitting sender.

Exceptions are the following:

- ‘Sender’s (case) safety report unique identifier’ (ICH-E2B(M) A.1.0.1);
- ‘Date of this transmission’ (ICH-E2B(M) A.1.3);
- ‘Date report was first received from source’ (ICH-E2B(M) A.1.6) for initial reports;
- ‘Date of receipt of the most recent information for this report’ (ICH-E2B(M) A.1.7);
- Sender and receiver details (ICH-E2B(M) A.3: ‘Information on sender and receiver of case safety report’);
- Relatedness of drug to reaction(s)/event(s) (ICH-E2B(M) section B.4.k.18: repeat B.4.k.18.1 through B.4.k.18.4 as necessary);
- Sender's diagnosis/syndrome and/or reclassification of reaction/event (ICH-E2B(M) field B.5.3);
- Sender’s comments (ICH-E2B(M) field B.5.4: ‘Sender's comments’);
- English translation of the free text fields in the ICSRs.

In addition, any EDI partner should adhere to the ICH-E2B(M) rules regarding the provision of follow-up information, i.e. the ‘Worldwide unique case identification number’ (ICH-E2B(M) A.1.10) should be maintained in accordance with the ICH-E2B(M) guideline. Non-adherence to these administrative requirements endangers the electronic case management, leads to unnecessary duplication of reports at the receiver’s database and should therefore be avoided.

10. Electronic Reporting through Company’s Headquarters

The Marketing Authorisation Holder’s QPPV should ensure that all ICSRs are submitted electronically to the relevant Competent Authorities in Member States as well as Iceland, Liechtenstein and Norway and the Agency in line with the reporting rules defined in EU legislation. If a pharmaceutical company decides to centralise the electronic reporting of the ICSRs (e.g. reporting through the company’s headquarters), it is the Marketing Authorisation Holder’s (e.g. the local affiliate) responsibility to ensure that ICSRs are submitted electronically to the Competent Authority as applicable.

The following should be taken into account:

- The arrangement should be clearly specified in the Marketing Authorisation Holder's internal Standard Operating Procedures (SOPs).
- The Agency and the Competent Authorities in the EU should be notified in writing about the arrangement (a template is available at the EudraVigilance website).
- The Marketing Authorisation Holder should be registered with EudraVigilance.
- Whoever is the physical sender of the electronic ICSRs, the Marketing Authorisation Holder (i.e. local affiliate) will remain the contact point for all pharmacovigilance-related matters and responsible for the compliance with the pharmacovigilance obligations as defined in EU legislation.

For the reporting from the Competent Authorities in the EU to the Marketing Authorisation Holder, the same principles apply, i.e. Competent Authorities in Member States as well as Iceland, Liechtenstein and Norway report electronically to the address of the headquarters instead of that of the local affiliate.

11. Specific Provisions for the Electronic Reporting to EudraVigilance

11.1 EudraVigilance Database Modules

On the basis of the requirements defined in EU legislation to set up a data-processing network and a pharmacovigilance database as described in [Chapter III.1](#), two EudraVigilance modules for medicinal products for human use were established to address the collection of the different types of adverse reactions reportable in the frame of the EU pharmacovigilance activities.

These modules are as follows:

- EudraVigilance Post-Authorisation Module (EVPm) (in line with the requirements as defined in Regulation (EC) No. 726/2004, Directive 2001/83/EC and EU guidelines);
- EudraVigilance Clinical Trial Module (EVCTM) (in line with the requirements defined in Directive 2001/20/EC and implementing texts).

11.1.1 Adverse Reaction Data Collected in EudraVigilance Post-Authorisation Module

Different types of adverse reaction reports related to all medicinal products authorised in the EU (see [Chapter I.2](#), Legal Framework for Pharmacovigilance) are currently collected in the EudraVigilance Post-Authorisation Module based on the reporting obligations of national Competent Authorities and Marketing Authorisation Holders in the EU.

The reporting obligations of Marketing Authorisation Holders with regard to the Agency/EVPM are described in [Chapters I.4 and I.5](#). The reporting obligations of national Competent Authorities with regard to the Agency via EVPM are described in [Chapter II.1, Section 6.1](#).

The adverse reaction reports collected in EVPM refer to spontaneous reports and reports from non-interventional studies. Reports that need to be prepared in relation to the reporting in special situations (as described in [Chapter I.5](#)) should be also submitted to EVPM. Depending on their nature, these reports should be classified according to ICH-E2B(M) as one of the following categories:

Category I: ICH-E2B(M) field A.1.4 'Type of report:

- Spontaneous report
- Other
- Not available to sender (unknown)

Or

Category II: ICH-E2BM) field A.1.4 ‘Type of report:

- Report from study and
- ICH-E2B(M) field A.2.3.3 ‘Study type in which the reaction(s)/event(s) where observed’ relates to
 - Individual patient use; (e.g. ”compassionate use” or named-patient basis),
 - Other studies (e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring, PMS, etc.).

11.1.2 Adverse Reaction Data Collected in EudraVigilance Clinical Trial Module

All suspected unexpected serious adverse reactions (SUSARs) related to Investigational Medicinal Products (IMPs) studied in interventional clinical trials, are collected in the EudraVigilance Clinical Trial Module (EVCTM). These reports should be classified according to ICH-E2B(M) as the following category:

Category: ICH-E2BM) field A.1.4 ‘Type of report:

- Report from study and
- ICH-E2B(M) field A.2.3.3 ‘Study type in which the reaction(s)/event(s) where observed’ relates to Clinical Trials.

The reporting obligations of sponsors of clinical trials concerned with the monitoring of adverse reactions occurring in clinical trials with IMPs are outlined in Directive 2001/20/EC and the related implementing texts and do not fall within the scope of pharmacovigilance activities as described in these Guidelines (see Chapter I.2).

To avoid duplicate reports in EVCTM, only the sponsor of the clinical trial in the EU should report all SUSARs electronically to EVCTM in line with the ‘Detailed Guidance on the European Database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module)’ (ENTR/CT4, Volume 10 of The Rules Governing Medicinal Products in the EU, Chapter II⁶¹), adopted at EU level in April 2004. This includes electronic reporting of 3rd country (non-EU) SUSARs.

11.2 Data Quality of Individual Case Safety Reports Transmitted Electronically

EudraVigilance should contain all reports of adverse reactions reportable according to EU legislation to support pharmacovigilance activities and the European Risk Management Strategy. This applies to all medicinal products, i.e. IMPs or authorised medicinal products regardless of the authorisation procedure.

In addition, EudraVigilance should be based on the highest internationally recognised data quality standards. To achieve these objectives, all Competent Authorities in Member States as well as Iceland, Liechtenstein and Norway and Marketing Authorisation Holders should fully adhere to:

- The electronic reporting requirements as defined in EU legislation;
- The concepts of data structuring, coding and reporting in line with the guidelines and standards referred to in Chapter III.2 and the principles outlined in Chapters III.3 to Chapter III.11.

This is a pre-requisite to establish a properly functioning European pharmacovigilance system (EudraVigilance) intended to support the European Risk Management Strategy.

⁶¹ Available on EC website <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>.

11.3 Reporting of all Serious Cases from outside the European Union

According to Directive 2001/83/EC and Regulation (EC) No 726/2004, the Marketing Authorisation Holder is required to report all suspected serious unexpected adverse reactions that occur in third countries on an expedited basis to the Agency and to all national Competent Authorities in the EU and where the medicinal product is authorised.

However, for non-centrally authorised medicinal products, Marketing Authorisation Holders experience problems to determine the expectedness for serious cases from outside the EU and to decide if the case is reportable to the Agency. This is due to the fact that for non-centrally authorised medicinal products the SPCs vary in the different Member States.

To facilitate the overall reporting process to the Agency, Marketing Authorisation Holders are encouraged to

- report electronically to EudraVigilance all suspected serious adverse reactions that occur in a third country, for all medicinal products authorised in the EU, regardless of the authorisation procedure (national, centralised, decentralised or mutual recognition procedures).

11.4 Retrospective Electronic Population of EudraVigilance Post-Authorisation Module

The retrospective population of EudraVigilance has to be seen in the light of the best collaborative effort between all involved stakeholders to support the European Risk Management Strategy, agreed by the Heads of Human Medicines Agencies (“Implementation of the Action Plan to Further Progress the European Risk Management Strategy: Rolling Two-Year Work Programme (Mid 2005 – Mid 2007)”⁶²), and the protection of public health. It is an effort to retrospectively populate the system electronically with the ICSRs that were reportable to the Agency during the post-authorisation phase in line with EU legislation since 1 January 1995⁶³ (the date when the Agency was established). Furthermore, the retrospective population of EVPM is considered vital in the context of Article 28 of Regulation (EC) No 726/2004.

A phased approach should be followed in the retrospective population of EudraVigilance Post-Authorisation Module (EVPM) based on the following principles:

- All spontaneous reports of serious cases and non-interventional studies from within or outside the EU (without the need to reassess expectedness according to the current Summary of Product Characteristics) should be submitted based on the responsibilities outlined below;
- To start with ICSRs that occurred since 1 January 1995, which have not been submitted yet electronically in the ICH-E2B(M) format involving suspected serious adverse reactions related to centrally authorised medicinal products and mutually recognised medicinal products; as a next step ICSRs related to suspected serious adverse reactions for other nationally authorised medicinal products should be provided;
- Only the most recent version of the case report should be transmitted electronically;
- For cases published in the worldwide literature, it is not required to provide a copy of the original literature article;
- It is not required to transmit cases involving nationally authorised products that are no longer authorised in the EU;

⁶² Doc.Ref.: EMEA/372687/2005, available on EMEA website <http://www.emea.europa.eu>.

⁶³ Regulation (EC) No 726/2004 and Directive 2001/83/EC.

- Unless otherwise specified in contractual agreements between partners, all the cases involving divested marketed medicinal products should be transmitted by the current Marketing Authorisation Holder.

From a practical point of view, the retrospective population of EudraVigilance should be achieved as follows:

- National Competent Authorities in the EU should provide all spontaneous reports of serious cases and non-interventional trials that occurred in their territory. Where no electronic reports or only limited data are available in structured format by national Competent Authorities, those national Competent Authorities should see to it that the data are entered in EudraVigilance.
- Marketing Authorisation Holders should provide all spontaneous reports of serious cases and non-interventional studies that occurred outside the EU.
- With regard to the Member States that joined the EU in May 2004, Marketing Authorisation Holders should provide all spontaneous reports of serious cases and non-interventional studies for the period 1 January 1995 to 1 May 2004.
- The handling of EU languages should follow the recommendations outlined in [Chapter III.11, Section 5](#). In order to maintain homogeneity in the database and to facilitate signal detection, ICSRs should preferably be transmitted in English.
- ICSRs already reported electronically to EudraVigilance should not be included as part of the retrospective data transmission.
- All Marketing Authorisation Holders and national Competent Authorities in the EU are requested to take the necessary steps to ensure that the complete retrospective population of EudraVigilance is completed no later than 1 February 2008.

In this context it needs to be recognised that the retrospectively transmitted data may vary from the original information submitted on expedited basis in accordance with EU legislation at the time the case was initially reported, for example due to the conversion of the legacy data to the ICH-E2B(M) and M1 standards. As a result, the data submitted retrospectively to populate EudraVigilance should not be used for retrospective pharmacovigilance inspections and checking of previous reporting compliance.

The retrospective electronic population of the EudraVigilance Post-Authorisation Module should follow the applicable ICH standards and guidelines referred to in [Chapter III. 2](#). As a general principle, the information available on the case to the sender should be provided in the ICSR format based on the ICH-E2B(M) data elements.

The technical specifications regarding the retrospective transmission rules are described in [Chapter III.11, Section 4.1](#).

11.4.1 Retrospective Electronic Population of EudraVigilance Post-Authorisation Module: Transmission Rules

The ICSRs to be transmitted in the frame of the retrospective population of EudraVigilance (see [Chapter III.11, Section 4](#)) should follow the ICH and EU guidelines and standards as described in [Chapter III.2](#) including the medical information coded in MedDRA.

The retrospectively transmitted ICSRs need to be clearly flagged in EudraVigilance to exclude these reports from expedited reporting compliance checks.

To achieve a consistent flagging of these ICSRs, the ICH-E2B(M) message header field M.1.1 ('Message Type') should include the specification '**backlog**' instead of 'ichicr'. The field value is case-sensitive and should be reported in lower case.

All 'backlog' messages should be addressed to the message receiver identifier 'EVHUMAN'.

The following rules will be applied to the ICSR transmissions flagged according to this rule:

- The 15-day (expedited) reporting compliance, as set out in EU legislation, will not be applied.
- The business rules will be applied in line with the EMEA Guidance 'Technical Documentation – EudraVigilance Human Version 7.0 Processing of Safety Messages and ICSRs' (EMEA/H/20665/04, adopted at EU level in July 2004, [see Annex 3.1.2](#)).
- ICH-E2B(M) fields requiring MedDRA coding will accept MedDRA LLTs with a MedDRA version 4.0 or higher.
- The information provided in the ICSRs related to the retrospective population of the EudraVigilance system, should follow the specifications outlined in [Chapters III.2 to III.11](#).
- 'Backlog messages' should not contain more than 100 retrospective ICSRs.
- The sender of retrospectively transmitted ICSRs – as described in [Chapter III.11, Section 4](#) – should perform some initial testing with the Agency, using the EudraVigilance test system (EVTEST) before transmitting the retrospective ICSRs to the EudraVigilance production environment.
- The retrospective ICSRs should be transmitted through the EudraVigilance Gateway or for non-gateway users by means of EVWEB.
- Alternatively, retrospective ICSRs can be transmitted via physical media in line with the applicable ESTR1 recommendations (floppy disks, CD-R, DVD).
- The Agency will return acknowledgement messages to the sender of the retrospective ICSRs always via the EudraVigilance Gateway, independent of the media used for the ICSR transmission. The Agency gives priority in the processing of messages to expedited ICSRs. As a result, the generation and return of acknowledgement messages for retrospectively transmitted ICSRs may take longer than two business days. The acknowledgement message for the message type 'backlog' follows the ICH-E2B(M)/M2 standards reflecting as message type 'backlog'. The sender is requested by the Agency to retransmit safety messages and ICSRs in case of a transmission ACK code 02 or 03 following the receipt of the acknowledgement message. In practice this should be handled as follows:
 - ICH-E2B(M) field A.1.6 ACK code 02:
ICSR Error, not all reports loaded into the database; refer to the acknowledgement code for the reports (ICH-E2B(M) B.1.8 01= Report Loaded Successfully; 02=Report Not Loaded) in the safety messages; only those ICSRs with the acknowledgement code 02, which caused the error at message acknowledgement level, need to be corrected and re-transmitted.
 - ICH-E2B(M) field A.1.6 ACK code 03:
XML parsing error, no data extracted: all the ICSRs need to be transmitted again via a corrected safety message.

11.5 Handling of Languages

The E2B(M) concept is based on the fact that structured and coded information in the ICSRs is used for data outputs of pharmacovigilance systems (e.g. listings) and for signal detection. However, for scientific case assessment and signal evaluation, the medical summary provided in the case narrative fields, specifically in section ICH-E2B(M) B.5: 'Narrative case summary and further information' is normally required.

Taking into account the international dimension of pharmacovigilance, English translations of ICSRs are performed by the Marketing Authorisation Holders. Marketing Authorisation Holders should therefore report ICSRs to EudraVigilance and national Competent Authorities in English. In addition to the English summary, the original verbatim text in the local language may be maintained in the ICH-E2B(M) B.5.1 ‘Case narrative including clinical course, therapeutic measures, outcome and additional relevant information’.

The summary should focus on the most relevant medical information applicable to the case and required for the case assessment.

Competent Authorities in Member States as well as Iceland, Liechtenstein and Norway can report case narratives to EudraVigilance and to the Marketing Authorisation Holders in the national language. For these reports, Competent Authorities should provide case translations in the English language when requested by the EMEA or other national Competent Authorities for the evaluation of potential signals. Such translation must be provided within 24 hours or the next working day.

Additional documents held by the sender, which may be only available in a local language, should be listed in ICH-E2B(M) A.1.8.2: ‘List of documents held by sender’. These documents should only be translated if requested by the receiver.

11.6 Population of the EudraVigilance Medicinal Product Dictionary

The population of the EudraVigilance Medicinal Product Dictionary (EVMPD) is necessary to permit the correct identification of medicinal products, related to adverse reactions reported in line with the reporting obligations set out in EU legislation, as well as data analysis and signal detection. The best way of achieving the correct identification of medicinal products in ICSRs is to ask all Marketing Authorisation Holders to enter each medicinal product for which they hold a marketing authorisation within the EU, in the EudraVigilance Medicinal Product Dictionary (EVMPD).

From a practical point of view, Marketing Authorisation Holders are therefore requested by national Competent Authorities and the Agency to enter information on the medicinal products, for which they hold a license in the EU, in the EVMPD in line with the following guidelines and specifications:

- EudraVigilance Medicinal Product Dictionary (EVMPD) Version 2.0 Technical Specifications, 9 November 2004 (EMEA/140190/2004).
- EudraVigilance Medicinal Product Dictionary (EVMPD) Version 2.0 Message and Acknowledgement Specifications, 8 December 2004 (EMEA/178966/2004).
- EudraVigilance (EV) Access Simple Database Version 2.0 8 November 2004 (EMEA/140327/2004).
- EudraVigilance (EV) Access Simple Database Version 2.0 Forms Documentation, 31 January 2005, (EMEA/35416/2005).
- EudraVigilance (EV) Access Simple Database Version 2.0 Step by Step Guide, 8 December 2004, (EMEA/191986/2004).

As technical standards are evolving, the above reference documents may require revision and maintenance. In this context, the latest version of these documents should always be taken into account.

With regard to the timeframes for the population of the EVMPD, a timetable can be discussed by the MAH with the Agency. As a general principle, priority should be given to centrally authorised medicinal products, medicinal products authorised through the mutual recognition or decentralised procedures and other nationally authorised medicinal products, for which ICSRs are reportable.

In addition, the MAH should attempt, where possible, to provide the EVMPD medicinal product data to the Agency before the retrospective electronic transmission of ICSRs in line with [Chapter III.11, Section 4](#).

The EVMPD is also a fundamental component of the EudraVigilance system for signal detection and data analysis. Therefore medicinal product data should be submitted concomitantly to the submission of a Risk Management Plan.

11.7 Periodic Transmission of Individual Case Safety Reports not Transmitted on an Expedited Basis in Electronic Format

In line with Regulation (EC) No. 726/2004, Article 24 (3), Periodic Safety Update Reports (PSURs), should be transmitted for centrally authorised medicinal products at defined intervals to the Agency and national Competent Authorities in the EU. The requirements for the preparation of PSURs are described in [Chapter I.6](#).

The objective of the periodic transmission of ICSRs is to obtain a complete set of adverse reactions as described in the PSUR line listings. These data, which are used to facilitate the data review and analysis, are submitted complementary to the PSUR, which is assessed independently.

To facilitate the scientific evaluation of the safety data as referred to in PSURs for centrally authorised medicinal products, it is important to collect this information in one common repository and one common format. Therefore, Marketing Authorisation Holders are encouraged to conduct a periodic electronic transmission of these suspected adverse reaction data for centrally authorised medicinal products to EudraVigilance in the format of ICSRs (hereafter referred to as periodic ICSRs) as applicable.

From a practical point of view, the following principles should be taken into account for the transmission of periodic ICSRs in electronic format:

- Periodic ICSRs should be transmitted for Centrally Authorised Products.
- Periodic ICSRs (initial and follow-up) should be transmitted at regular intervals by the Marketing Authorisation Holder but at the latest at the time of submission of the PSUR in line with the time frames defined in the EU legislation.
- Transmissions of periodic ICSRs should include all suspected adverse reactions reportable in a PSUR, which are/were not transmitted on expedited basis in electronic format to EVPM or EVCTM. Taking into account that the MAH is requested to annex also medically unconfirmed spontaneous reports that originate with Consumers or other non-health care professionals, these should be included systematically in the transmission of periodic ICSRs.
- Transmissions of periodic ICSRs should exclude:
 - all suspected adverse reactions reportable in a PSUR, that were reported on expedited basis by the Marketing Authorisation Holder to EVPM or EVCTM ([see Chapter III.11, Sections 1.1 and 1.2](#));
 - all suspected serious adverse reactions that occur in the EU (they are reportable by the national Competent Authorities to the Agency in line with EU legislation); and
 - all SUSARs and suspected serious adverse reactions (SARs) that relate to interventional clinical trials and which have been reported electronically in the frame of Directive 2001/20/EC and the implementing texts to EVCTM.
- In case of the submission of several PSURs for the same medicinal product (e.g. for different indications, for the combinations of several active substances, for product authorised to more than one MAH), the MAHs should ensure that the periodic ICSRs are transmitted only once in electronic format to EudraVigilance ([see Chapter I.6, Sections 2.2 and 2.3](#) for the Requirements for Periodic Safety Update Reports).

- Periodic ICSRs should be reported to EVPM if they qualify as:
 - ‘Spontaneous reports’, ‘Others’ or ‘Not available to the sender’ (see ICH-E2B(M) A.1.4);
 - ‘Report from study’ (see ICH-E2B(M) A.1.4) and the ‘Study type in which the reaction(s)/event(s) were observed’ (ICH-E2B(M) A.2.3.3) is ‘Individual patient use’ (e.g. compassionate or named-patient basis) or ‘Other studies’ (e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring, PMS, etc.);
- Periodic ICSRs should be reported to EVCTM if they qualify as:
 - ‘Report from study’ (see ICH-E2B(M) A.1.4) and the ‘Study type in which the reaction(s)/event(s) were observed’ (ICH-E2B(M) A.2.3.3) is ‘Clinical trials’.

11.7.1 Periodic Transmission of Individual Case Safety Reports in Electronic Format

With regard to the transmission rules of periodic ICSRs as outlined above in this Chapter, the following principles should be adhered to:

- Periodic ICSRs should refer to an active substance or a combination of active substances as reportable in the relevant PSUR (ICH-E2B(M) field B.4.k.2.2 ‘Active substance name(s)’).
- The case information available to the sender should be submitted in fully structured format as ICSRs using the ICH-E2B(M) data elements and other applicable standards as outlined in [Chapter III.2](#).
- Periodic ICSRs should follow the message specifications as outlined in [Chapter III.3](#). The field Message Type (ICH-M2: M.1.1) should display the value:
 - “psur” for ICSRs related to spontaneous reports and reports from non-interventional studies;
 - “ctasr” for ICSRs related to interventional clinical trials.
- All “psur” messages should be addressed to the message receiver identifier ‘EVHUMAN’.
- All “ctasr” messages should be addressed to the message receiver identifier ‘EVCTMPROD’.
- The business rules are applied as specified in the The EMEA Guidance ‘Technical Documentation – EudraVigilance Human Version 7.0 Processing of Safety Messages and ICSRs’ (EMEA/H/20665/04, adopted at EU level in July 2004, [see Annex 3.1.2](#)).
- ICH-E2B(M) fields requiring MedDRA coding accept MedDRA LLTs with MedDRA version 4.0 or higher. Senders are encouraged to use the latest version of MedDRA.
- Periodic ICSRs should be transmitted through the EudraVigilance Gateway or for non-gateway users by means of EVWEB.
- Alternatively, periodic ICSRs can be transmitted via physical media in line with the applicable ESTRi recommendations (Floppy Disks, CD-R, DVD).
- The sender of periodic ICSRs – as described above in this Chapter – should perform some initial testing with the Agency, using the EudraVigilance test system EVTEST regarding periodic ICSRs to be transmitted to EVPM and the EudraVigilance test system EVCTMTEST regarding periodic ICSRs to be transmitted to EVCTM.
- “psur” and “ctasr” messages should not contain more than 100 periodic ICSRs.

EudraVigilance will return an acknowledgment message for each “psur” or “ctasr” message. The Agency will always return acknowledgement messages to the sender of the periodic ICSRs via the EudraVigilance Gateway, independent of the media used for the ICSR transmission. The Agency gives priority in the processing of safety messages related to expedited ICSRs. As a result, the generation and return of acknowledgement messages for periodic transmitted ICSRs may take longer than two business days. The acknowledgement message for the message type “psur” or “ctasr” follows

the ICH-E2B(M)/M2 standards reflecting as message type “psur” or “ctasr” as applicable. The sender is requested by the Agency to retransmit safety messages and ICSRs in case of a transmission ACK code 02 or 03 following the receipt of the acknowledgement message. In practise this should be handled as follows:

- ICH-E2B(M) field A.1.6 ACK code 02:
ICSR Error, not all reports loaded into the database; refer to the acknowledgement code for the reports (ICH-E2B(M) B.1.8 01= Report Loaded Successfully; 02=Report Not Loaded) in the safety messages; only those ICSRs with the acknowledgement code 02, which caused the error at message acknowledgement level, need to be corrected and re-transmitted.
- ICH-E2B(M) field A.1.6 ACK code 03:
XML parsing error, no data extracted: all the ICSRs need to be transmitted again via a corrected safety message.

PART IV:
**Guidelines for Marketing Authorisation Holders
and Competent Authorities on Pharmacovigilance Communication**

1. Introduction

In addition to the guideline “Direct Healthcare Professional Communications” it is anticipated that further guidance for marketing authorisation holders and competent authorities on pharmacovigilance communication will be developed. Any new guideline will be subject to public consultation.

2. Direct Healthcare Professional Communications

2.1 Introduction

The aim of this guidance is to establish principles for the content and format of Direct Healthcare Professional Communications (DHPCs) (commonly called “Dear Doctor-letters” (DDL)), as well as describing situations where dissemination of DHPCs should be considered. The guidance also aims to describe the main requirements and procedures for such communications on the safe and effective use of medicinal products for human use. DHPCs relating to quality defects with medicinal products are outside the scope of this guidance.

Directive 2001/83/EC and Regulation (EC) No 726/2004 impose requirements on Competent Authorities in Member States and the European Medicines Agency (“the Agency”) for communication to the public on matters relating to pharmacovigilance and the safe use of medicinal products.

In addition, such communication is considered as part of the risk management process (see Chapter I.3).

2.2 Definition of Direct Healthcare Professional Communication

A Direct Healthcare Professional Communication (DHPC) is defined as information aimed at ensuring safe and effective use of medicinal products which is delivered directly to individual Healthcare Professionals by a Marketing Authorisation Holder, or by a Competent Authority (this excludes direct personal replies to requests from individual Healthcare Professionals). Such DHPCs should not include any material or statement which might constitute advertising within the scope of Title VIII of Directive 2001/83/EC, or which is considered to be promotional or commercial by the Competent Authority.

2.3 Key Principles for Public Communication on Medicinal Products

The following key principles should be considered for public communication on medicinal products in general and by means of DHPCs in particular:

- Provision of information about the safe and effective use of medicinal products supports appropriate use and should be considered as a public health responsibility.
- Communication of such information needs to be considered throughout the risk management process (see Chapter I.3).
- It is essential that such information is communicated to Healthcare Professionals and relevant partners including Patient and Healthcare Professional organisations, learned societies and pharmaceutical wholesalers.
- In principle, significant new or emerging information should be brought to the attention of Healthcare Professionals before the general public, in order to enable them to take action and respond to Patients adequately and promptly. The important function of Healthcare Professionals in disseminating such information to Patients and the general public is recognised and should be supported.
- The overriding principle should be to ensure that the right message is delivered to the right persons at the right time.
- Effective communication on safe and effective use of medicinal products authorised in the European Union (EU) entails:
 - co-operation of all partners;
 - co-ordination between relevant partners, within and, if possible, outside the EU; and

- a strategy which meets the requirements resulting from the urgency to communicate and the expected public health impact of the information.
- A DHPC should not usually be distributed before the corresponding regulatory procedure has been completed, however, exceptionally (e.g. in the case of an urgent safety restriction) there may be a need to disseminate a DHPC prior to completion of a procedure. For centrally authorised products, the appropriate point in time for dissemination of a DHPC is usually once the CHMP Opinion has been adopted.
- In general, an agreement between the Marketing Authorisation Holder and the national Competent Authority(ies)/the Agency (and other partners as appropriate) is needed on the format and content of the information, recipients and the timetable. The agreed timetable for release of the information should be fully respected by all partners.

2.4 Situations Where a Direct Healthcare Professional Communication Should Be Considered

Dissemination of a DHPC is usually required in the following situations:

- Suspension, withdrawal or revocation of a marketing authorisation with recall of the medicinal product from the market for safety reasons; or
- Important changes to the Summary of Product Characteristics (SPC), for instance those introduced by means of an urgent safety restriction (e.g. introduction of new contraindications, warnings, reduction in the recommended dose, restriction of the indications, restriction in the availability of the medicinal product); or
- Completion of a referral procedure triggered for safety concerns which results in a significant change to the product information; or
- In other situations relevant to the safe and effective use of the medicinal product at the request of a national Competent Authority or, in the case of centrally authorised product, at the request of the Agency or European Commission.

Other situations where dissemination of a DHPC may be appropriate include:

- A change in the outcome of the evaluation of the risk-benefit balance due to:
 - new data, in particular from a study or spontaneous reports that identify a previously unknown risk or a change in the frequency or severity of a known risk; or
 - new data on risk factors and/or on how adverse reactions may be prevented; or
 - substantiated knowledge that the medicinal product is not as effective as previously considered ; or
 - evidence that the risks of a particular product are greater than those of alternatives with similar efficacy;

or

- Availability of new recommendations for treating adverse reactions; or
- Ongoing assessment of a possible significant risk, but insufficient data at a particular point in time to take any regulatory action (in this case, the DHCP should encourage close monitoring of the safety concern in clinical practice and encourage reporting, or provide information about means to minimise the potential risk); or
- A need for communication of other important information, in particular where the issue has been/is the subject of significant media coverage.
- In cases where a regulatory agency outside the EU independently requests dissemination of a DHPC in their territory for a product also authorised in the EU, the Marketing Authorisation

Holder should notify the appropriate Competent Authority/the Agency in the EU. The need for any subsequent action in the EU should be considered and agreed on a case-by-case basis.

A DHPC should not be used to provide safety information which does not require urgent communication or is otherwise important to be communicated to Healthcare Professionals at individual level, such as changes to the SPC which do not impact on the conditions of appropriate use of the medicinal product.

2.5 Key Principles for Preparation of Texts for Direct Healthcare Professional Communications

When drafting a DHPC, the Template (see Annex 5.4) and the guidance provided there should be followed as appropriate, together with the principles described below:

- The message of the DHPC should be clear and concise with regard to the safety concern. It should not exceed two pages.
- The reason for dissemination of a DHPC at a particular point in time should be explained.
- Recommendations to Healthcare Professionals on how to minimise the risk should be provided if known.
- The safety concern should be placed in the context of the overall benefit of the treatment and not be presented as stand-alone information.
- The Marketing Authorisation Holder should ensure that pharmacovigilance information to the general public (this includes Healthcare Professionals) is presented objectively and is not misleading. This requirement is legally binding in accordance with Article 24(5) of Regulation (EC) No 726/2004 for centrally authorised products and for nationally authorised products, including those authorised through the mutual recognition or decentralised procedures, in accordance with Article 104(9) of Directive 2001/83/EC.
- In general, the texts of DHPCs should be reviewed by, or if the timetable allows, tested among representatives of the target groups of Healthcare Professionals in order to assess clarity and understanding of the risk and expected adherence to the recommendations provided in the DHPC. Alternatively, standard phrases may be tested and subsequently used, as appropriate, particularly in urgent situations.
- In order to allow Healthcare Professionals to prepare responses to questions from Patients, the DHPC should also include the content of any information communicated directly to the general public. In case of suspension, withdrawal or revocation of a marketing authorisation, the DHPC should detail the type and procedure of recall of the medicinal product(s) from the market (e.g. pharmacy or patient level, date of recall).
- Public communication of the safety information issued to any target population by other Competent Authorities and other public bodies, ideally within and outside the EU, should be taken into account.
- The DHPC should include a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.
- The estimated timeschedule for follow-up action, if any, by the national Competent Authority(ies)/the Agency or the Marketing Authorisation Holder should be provided.
- A list of contact points for further information, including website address(es), telephone numbers and a postal address to write to, should be provided at the end of the DHPC.
- A list of literature references should be annexed, when relevant.
- The DHPC may include a statement indicating that the DHPC has been agreed with the national Competent Authority/the Agency.

2.6 The Processing of Direct Healthcare Professional Communications

2.6.1 The Roles and Responsibilities of Marketing Authorisation Holders, the Competent Authorities and the Agency

The Competent Authorities are those who have issued a marketing authorisation for the medicinal product concerned.

For centrally authorised products, the Competent Authority is the European Commission, however the Agency (the Committee for Medicinal Products for Human Use (CHMP)) normally deals with DHPCs on behalf of the Commission.

For products authorised through the mutual recognition or decentralised procedures, the Competent Authorities are those of the Reference Member State (RMS) and the Concerned Member State(s) (CMS(s)); for practical reasons, the RMS usually takes over co-ordination of consistent and synchronised DHPCs in the RMS and all CMSs (see Chapter IV.2, Section 6.3 for translations).

For purely nationally authorised products, the Competent Authorities are those of the Member States where the product is authorised, but it is suggested that one Member State may take the lead in co-ordinating the process with the Marketing Authorisation Holder and apply synchronised timetables across the relevant Member States.

Consequently, the contact points for the Marketing Authorisation Holders with regard to DHPCs are as follows:

- for centrally authorised products: the Agency together with the Rapporteur (with parallel submission of documentation to all Member States);
- for products authorised through the mutual recognition or decentralised procedures: the RMS or, in case of several products authorised through the mutual recognition or decentralised procedures with the same active substance and different RMSs, the Lead Member State agreed between the RMSs and CMS(s) (with parallel submission of documentation to all RMS(s) and CMS(s));
- for purely nationally authorised products: the Member States where the product is authorised or, if agreed between these Member States, the designated Lead Member State for the safety concern (with parallel submission of documentation to all Member States where the product is authorised); and
- for products subject to referral procedures: the Agency in relation to CHMP Opinions and Commission Decisions and otherwise the RMS or the Agency, as appropriate (see below in this Section for further details).

Where the Marketing Authorisation Holder proposes or is requested by the national Competent Authority/the Agency to disseminate a DHPC, the relevant national Competent Authority(ies)/the Agency should be provided with:

- the proposed Communication Plan; including
- the proposed communication text of the DHPC; and
- the proposed texts of any related communication documents (see Chapter IV.2, Section 6.2.(2)).

The timing of the submission should allow national Competent Authority(ies)/the Agency (CHMP) reasonable time (a minimum of two working days) to comment on the Communication Plan and the proposed communication texts prior to their finalisation. Exceptionally, less than two working days may be acceptable in the case of some urgent safety restrictions. The Marketing Authorisation Holder should take into account comments from the national Competent Authority(ies)/the Agency and

discuss any outstanding issues when finalising these proposals. Ideally, the Marketing Authorisation Holder should closely co-operate with the Rapporteur/RMS/Member State(s) to finalise the text of the DHPC. The final Communication Plan and communication texts should be submitted to the national Competent Authorities/the Agency.

Member States and the Agency should use the Rapid Alert-Non-Urgent Information System (see Chapter II.4) in order to keep each other and the European Commission informed during all the phases of the communication process.

The national Competent Authorities and the Agency should keep their Press Officers informed about any DHPC.

Marketing Authorisation Holders are reminded of the legal obligations described in Article 24(5) of Regulation (EC) No 726/2004 and Article 104(9) of Directive 2001/83/EC. With the exception of the requirement to notify the Agency for centrally authorised products and the Competent Authority for nationally authorised products, the requirements in both legal texts are identical and are reproduced here for ease of reference:

“The holder of a marketing authorisation may not communicate information relating to pharmacovigilance concerns to the general public in relation to its authorised medicinal product without giving prior or simultaneous notification to the competent authority [Directive 2001/83/EC]/Agency [Regulation (EC) No 726/2004].

In any case, the marketing authorisation holder shall ensure that such information is presented objectively and is not misleading.

Member States shall take the necessary measures to ensure that a marketing authorisation holder who fails to discharge these obligations is subject to effective, proportionate and dissuasive penalties.”

In addition, the following should be considered:

- For centrally authorised products:
 - In order to enable the Agency and the Competent Authorities in Member States to fulfil their roles in public health protection, Marketing Authorisation Holders should give prior notification, allowing a minimum of two working days for comments by the Agency (CHMP) on the Communication Plan and the proposed communication texts. Exceptionally, less than two working days may be acceptable in case of some urgent safety restrictions.
 - When a Member State considers it necessary that a DHPC concerning a centrally authorised product should be disseminated in its own territory, the Agency (CHMP) should be informed at least two days prior to the proposed dissemination day and consider whether EU-wide dissemination of such a DHPC is necessary or dissemination in only one or more Member States is sufficient (taking into account e.g. availability of an interacting medicinal product in only a few Member States or differences in medical practice).
 - The CHMP will normally request recommendations on DHPCs from its Pharmacovigilance Working Party (PhVWP).
 - With regard to Member States’ requirements in relation to the communication texts, recipients and the proposed dissemination mechanism, the Marketing Authorisation Holder should contact the relevant pharmacovigilance contact points at the national Competent Authorities in a timely manner for discussion and finalisation of the Communication Plan and communication texts including relevant translations (see Chapter IV.2, Section 6.3).
- For products authorised through the mutual recognition or decentralised procedures:
 - Where a CMS considers dissemination of a DHPC is necessary, this CMS should contact the RMS to liaise with the Marketing Authorisation Holder prior to dissemination.

- Rarely, it may only be necessary to send a DHPC in one/some Member States. However, the RMS and the CMS should always keep each other informed of any proposed action.
- The PhVWP should provide recommendations at the request of a Member State.
- Member States may have approval procedures for DHPCs for nationally authorised products in place, which may also apply to products authorised through the mutual recognition or decentralised procedures.
- For purely nationally authorised products:
 - Member States may have approval procedures for DHPCs in place. Also for purely nationally authorised products, Member States should inform the other Member States and the Agency using the Rapid Alert/Non-Urgent Information System (see Chapter II.4). At the request of a Member State, a synchronised timetable for communication throughout the EU may be agreed by the PhVWP for purely nationally authorised products. Such agreement may be of particular importance in the case of DHPCs planned for purely nationally authorised products containing the same active substance as a product authorised through the mutual recognition or decentralised procedures.
- For products subject to an ongoing referral procedure:
 - The review of comments on the proposed Communication Plan and communication texts will be undertaken by the Agency (CHMP) if such communications refer to outcomes of discussion at the level of the CHMP and subsequent Commission Decisions, i.e. in particular to CHMP Referral Opinions and review of monitoring conditions for marketing set out in the Commission Decision. Otherwise, the (post-referral) RMS co-ordinates DHPCs as for products authorised through the mutual recognition or decentralised procedures. The RMS needs to keep the Referral Rapporteur and the Agency closely informed about any planned communication activities. The involvement of the CHMP will be considered on a case-by-case basis.

When a DHPC concerns an active substance or a class of active substances authorised through different procedures and/or involving overlapping roles and responsibilities of the Competent Authorities and the Agency, the relevant partners should co-ordinate their respective activities, as needed within the EU pharmacovigilance system. The PhVWP should provide recommendations for such co-ordination at the request of the CHMP/EMA or a Member State.

For roles and responsibilities regarding the process of translation of communication texts, see Chapter IV.2, Section 6.3.

In cases where a DHPC is disseminated by a Competent Authority in a Member State, the Competent Authority should provide the following to the Marketing Authorisation Holders concerned:

- the Communication Plan; including
- the communication text of the DHPC; and
- the texts of any related communication documents (see Chapter IV.2, Section 6.2.(2)).

Nationally established procedures should be followed in such cases, and the Communication Plan should be circulated for information to the other Member States and the Agency using the Rapid Alert/Non-Urgent Information System (see Chapter II.4).

2.6.2 Phased Approach to Processing

The processing of a DHPC consists of four phases:

1. Consideration phase: Initiation of the process

The process may be initiated by the Marketing Authorisation Holder or a national Competent Authority/the Agency/the European Commission.

When the Marketing Authorisation Holder considers that a DHPC may be necessary, the national Competent Authority/the Agency should be contacted and the documents required for the preparation of the DHPC submitted, as set out below. When a Competent Authority in a Member State, the European Commission or the Agency (CHMP) considers that a DHPC may be necessary, it is recommended that the national Competent Authority/the Agency sends a request letter (in case of urgency the Marketing Authorisation Holder may additionally be contacted by telephone and/or e-mail) requesting preparation of a draft DHPC and a Communication Plan. This request letter should provide the rationale for the request and the timetable for submission. When a request letter is received, the Marketing Authorisation Holder should designate a contact point within the company for liaison with the national Competent Authority/the Agency.

If the Marketing Authorisation Holder considers that a DHPC is not appropriate or requires additional clarification, a written request may be submitted to the national Competent Authority/the Agency/ the European Commission. In cases where agreement cannot be reached regarding dissemination of a DHPC by the Marketing Authorisation Holder, a DHPC and/or a Public Statement may be issued by the national Competent Authority/the Agency/the European Commission.

There may be situations in which more than one Marketing Authorisation Holder is involved in the dissemination of a DHPC, e.g. where an interaction, a class-effect or generic medicinal products are concerned. In such situations, the objective is to provide consistent information to Healthcare Professionals and to avoid multiple DHPCs on the same safety concern from different Marketing Authorisation Holders which may lead to confusion. Where the number of Marketing Authorisation Holders involved is limited to two or three, they should work together to issue a single DHPC. For a larger number of Marketing Authorisation Holders or if a single joint DHPC is not agreed, the national Competent Authority may opt to issue the DHPC.

2. Pre-communication phase: Preparation of a DHPC

Once the intention to disseminate a DHPC is confirmed, the Marketing Authorisation Holder should submit a draft Communication Plan including the following:

- the objective of the DHPC and the draft DHPC and other communication texts (including amendments to the Product Information (SPC, Package Leaflet and Labelling), either mentioned in the DHPC text or, preferably, appended to the draft DHPC, if the final revised Product Information is available) as well as the key message to the public;
- a proposed timetable covering the pre-communication, communication and post-communication phases with regard to all communication and other relevant documents including translations (see Chapter IV.2, Section 6.3). This timetable should include:
 - timelines for comments on the Communication Plan and draft communication texts by national Competent Authority(ies) and/or the Agency (CHMP);
 - timelines for agreement on final texts between the Marketing Authorisation Holder and the Competent Authority(ies)/the Agency (CHMP);
 - timelines for agreement on the date and time of release of the DHPC and information to the general public (synchronised across the EU).
- any draft Communication Plans and communication texts under discussion with other Competent Authorities (outside the EU for centrally authorised products and products authorised through the mutual recognition or decentralised procedures; within and outside the EU for purely nationally authorised products);
- a list of proposed recipients (target groups, e.g. general practitioners, specialists, coroners, pharmacists, nurses; hospitals/ambulatory care/other institutions), including Member States' specificities, if appropriate;
- a description of the dissemination mechanism in the Member State(s) where the DHPC is planned to be disseminated (e.g. by post);

- a plan for user testing of the communication text, if appropriate;
- a list of related communication documents, if appropriate, e.g. press release, questions & answers document, patient information sheet, and a description of their dissemination mechanisms in each Member State where the DHPC is planned to be disseminated;
- a description of the strategy for the post-communication phase, including the evaluation of the effectiveness of the DHPC, as outlined below in this Section, No 4.;
- an outline of proposed follow-up action and a draft Letter of Undertaking from the Marketing Authorisation Holder on further investigations, if applicable; and
- a list of contact details of relevant partners.

The proposed time and date for distribution should be considered carefully, with dissemination of a DHPC at the beginning of a week considered ideal; however the release of urgent information should not be delayed for this reason.

Usually, any planned press release/Public Statement from either national Competent Authority(ies), the Agency or the Marketing Authorisation Holder should be disseminated at the same date in all Member States, ideally at an agreed time of the day specified as London time.

When defining the target groups of recipients, it should be recognised that it is not only important to communicate with those Healthcare Professionals who will be able or likely to prescribe or administer the medicinal product, but also to those who may diagnose adverse reactions, e.g. emergency units, poison centres, or to appropriate specialists, e.g. cardiologists. It is also important to consider provision of DHPCs to relevant pharmacists who serve as information providers within healthcare systems and provide assistance and information to Patients, Healthcare Professionals, including hospital wards and poison centres, as well as the general public, in particular where media interest has arisen. The national professional associations of physicians, nurses and pharmacists should systematically receive DHPCs for further dissemination of the information to their members beyond the primary target groups of recipients.

The dissemination mechanism should take into account national policies for prompt identification of DHPCs, such as specific identifiers on the envelope (e.g. prominent red box warning) or use of a specific colour of notepaper. The use of such specific identifiers is encouraged to facilitate identification and focus Healthcare Professionals' attention.

3. Communication phase: Dissemination of the DHPC

Implementation of the communication phase should adhere to the Communication Plan agreed between the Marketing Authorisation Holder and the national Competent Authority(ies)/the Agency and should be accompanied by close monitoring of events by all partners. Any significant event or problem occurring during the communication phase should be communicated immediately between all relevant partners. If this reveals a need to change the Communication Plan or a need for further communication to Healthcare Professionals, this should be agreed between the Marketing Authorisation Holder and the national Competent Authority(ies)/the Agency.

4. Post-communication phase: Follow-up of the DHPC

After dissemination of a DHPC, a closing review should be performed by the Marketing Authorisation Holder, identifying any event or problem occurring during the communication phase requiring a change to the Communication Plan, any non-adherence to the Communication Plan as well as any difficulties experienced during any of the above phases. Such difficulties may relate e.g. to the list of recipients or the date and mechanism of dissemination. The national Competent Authority(ies)/the Agency should be informed of the outcome of this closing review and should also inform the Marketing Authorisation Holder of difficulties they identified. If the national Competent Authority/the

Agency is not satisfied, a written request should be made to the Marketing Authorisation Holder to correct the situation. On the basis of this information, action should be taken to prevent or anticipate similar problems in the future. All partners should also perform internal reviews of their performance as part of integrated quality management and take appropriate action for improvement as needed. In general, evaluation of the public health impact and the effectiveness of DHPCs should be performed in order to evaluate if the DHPCs have been received in a timely manner (check in a small sample of the target population) and if the recommendations and key messages have been understood and followed (e.g. by means of healthcare professional surveys or other study designs). This evaluation should be performed by the Marketing Authorisation Holder and is specifically relevant where DHPCs are part of risk minimisation activities in accordance with the applicable Risk Management Plan (see Chapter I.3).

2.6.3 Translations

For centrally authorised products and in most cases also for products authorised through the mutual recognition or decentralised procedures, the proposed communication texts will be submitted in English as working language. For products authorised through the mutual recognition or decentralised procedures, the working language could be another official Community language if agreed by the RMS and all CMSs.

Once the communication texts are agreed with the Agency/RMS+CMS(s), the Marketing Authorisation Holder should prepare translations of the DHPC in all official EU languages, of the Member States where the product is marketed or, if appropriate, is made available by other means (e.g. compassionate use).

The draft translations should be submitted to all Member States/RMS+CMS(s) for a language review within a reasonable time (minimum of one working day). The Marketing Authorisation Holder should take account of comments from the national Competent Authorities/the Agency and discuss any outstanding issues when finalising translations.

In the case of a centrally authorised product, the Marketing Authorisation Holder should provide the Agency with a complete set of all final language versions of the DHPC and any related communication documents.

In Member States with more than one official language, similar processes for language review by the national Competent Authority may be in place for nationally authorised products.

ANNEXES

1. Glossary

1.1 General

Abuse of a medicinal product, synonym: Drug abuse

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects (Article 1(16). of Directive 2001/83/EC).

Adverse event (AE), synonym: Adverse experience

Any untoward medical occurrence in a patient or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment (Article 2(m) of Directive 2001/20/EC). An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction, synonym: Adverse drug reaction (ADR), Suspected adverse (drug) reaction

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function (Article 1(11) of Directive 2001/83/EC)⁶⁴.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see ICH-E2A Guideline⁶⁵).

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

See also under Adverse event, Serious adverse reaction, Unexpected adverse reaction, Listed adverse reaction, Reportable adverse reaction, Unlisted adverse reaction

Clinical trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the objective of ascertaining its (their) safety and/or efficacy; This includes clinical trials carried out in either one site or multiple sites, whether in one or more Member State (Article 2(a) of Directive 2001/20/EC).

An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form (Article 2(d) of Directive 2001/20/EC).

⁶⁴ Please note that for the reporting of adverse reactions occurring in clinical trials all untoward and unintended responses to an investigational medicinal product related to any dose administered are considered adverse reactions (Article 2(n) of Directive 2001/20/EC).

⁶⁵ Available on EMEA website <http://www.emea.europa.eu>.

Consumer

A person who is not a Healthcare Professional such as a Patient, lawyer, friend or relative/parents/children of a Patient.

Company Core Data Sheet (CCDS)

A document prepared by the Marketing Authorisation Holder containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI)

All relevant safety information contained in the company core data sheet prepared by the Marketing Authorisation Holder and which the Marketing Authorisation Holder requires to be listed in all countries where the company markets the product, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Data lock point

The date designated as the cut-off date for data to be included in a Periodic Safety Update Report.

Drug abuse

See under Abuse

EU Birth Date (EBD)

The date of the first marketing authorisation for a medicinal product granted in the EU to the Marketing Authorisation Holder:

- For medicinal products authorised through the centralised procedure, the EU Birth Date is the date of the marketing authorisation granted by the European Commission, i.e. the date of the Commission Decision.
- For medicinal products authorised through the mutual recognition or decentralised procedure, the EU Birth Date is the date of the marketing authorisation granted by the Reference Member State.
- For medicinal products authorised through purely national procedures (outside the mutual recognition or decentralised procedure), the Marketing Authorisation Holder may propose a birth date which can be applied to reporting requirements across the Member States.

See also International Birth Date

Healthcare Professional

For the purposes of reporting suspected adverse reactions, Healthcare Professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners.

Individual Case Safety Report (ICSR), synonym: Safety report

A document providing the most complete information related to an individual case at a certain point of time. An individual case is the information provided by a primary source to describe suspected adverse

reaction(s) related to the administration of one or more medicinal products to an individual Patient at a particular point of time⁶⁶.

International Birth Date (IBD)

The date of the first marketing authorisation for a medicinal product granted to the Marketing Authorisation Holder in any country in the world. For a medicinal product for which the International Birth Date is not known, the Marketing Authorisation Holder can designate an International Birth Date to allow synchronisation of submission of Periodic Safety Update Reports.

Invented name

The name of a medicinal product as it appears in the Product Information, or the common or scientific name together with a trademark or the name of the Marketing Authorisation Holder followed by the strength and the pharmaceutical form of the product.

See also Name of the medicinal product.

Listed adverse reaction

An adverse reaction whose nature, severity, specificity and outcome are consistent with the information in the company core safety information.

Medicinal product

- Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
- Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis (Art 1(2) of Directive 2001/83/EC).

Name of the medicinal product

The name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder (Article 1(20) of Directive 2001/83/EC).

The common name is the International Non-proprietary Name (INN) recommended by the World Health Organization, or, if one does not exist, the usual common name (Article 1(21) of Directive 2001/83/EC).

See also Invented name.

Non-interventional trial

A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within the current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data (Article 21 of Directive 2001/20/EC).

⁶⁶ In the context of a clinical trial, an individual case is the information provided by a primary source to describe suspected unexpected serious adverse reactions related to the administration of one or more investigational medicinal products to an individual patient at a particular point of time.

Periodic Safety Update Report (PSUR)

Periodic safety update reports mean the periodical reports containing the records referred to in Article 104 of Directive 2001/83/EC and in Article 24(3) of Regulation (EC) No 726/2004.

Post-authorisation study

Any study conducted within the conditions laid down in the Summary of Product Characteristics and other conditions laid down for the marketing of the product or under normal conditions of use. A post-authorisation study falls either within the definitions of a clinical trial or a non-interventional study and may also fall within the definition of a post-authorisation safety study.

See also under Clinical trial, Non-interventional trial and Post-authorisation safety study

Post-authorisation safety study (PASS)

A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product (Article 1,15. of Directive 2001/83/EC).

See also under Clinical trial and Non-interventional trial

Risk-benefit balance

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (any risk relating to the quality, safety or efficacy of the medicinal product as regards Patients' health or public health) (Article 1,28a. of Directive 2001/83/EC).

See also under Risks related to use of a medicinal product

Risk management system

A risk management system shall comprise a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions (Article 34 of Regulation (EC) No 1901/2006).

Risks related to use of a medicinal product

Any risk relating to the quality, safety or efficacy of the medicinal product as regards Patients' health or public health and any risk of undesirable effects on the environment (Article 1(28) of Directive 2001/83/EC).

Serious adverse reaction

Serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect (Article 1(12) of Directive 2001/83/EC).

Life threatening in this context refers to a reaction in which the Patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the Patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive

treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

See also under Adverse reaction

Solicited sources of Individual Case Safety Reports

Organised data collection schemes which include clinical trials, registries, named-patients use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance.

For the purpose of safety reporting, solicited reports should be classified as Individual Case Safety Reports from studies and therefore should have an appropriate causality assessment by a Healthcare Professional or the Marketing Authorisation Holder.

See also under Clinical trial, Non-interventional trial and Post-authorisation safety study

Spontaneous report, synonym: Spontaneous notification

An unsolicited communication by a Healthcare Professional or Consumer to a company, regulatory authority or other organisation (e.g. WHO, a regional centre, a poison control centre) which fulfills the following three conditions:

- it describes one or more suspected adverse reactions in a patient
- the patient was given one or more medicinal products
- it does not derive from a study or any organised data collection scheme.

Healthcare Professionals or Consumers may be stimulated to report a suspected adverse reaction by several situations including:

- a Direct Healthcare Professional Communication
- Early Post-Marketing Phase Vigilance (EPPV), e.g. in Japan
- a report in the press
- direct questioning of Healthcare Professionals by company representatives.

In these circumstances, provided the report meets the three conditions above, it should be considered a spontaneous report.

Unexpected adverse reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of Product Characteristics (SPC) (Article 1(13) of Directive 2001/83/EC)⁶⁷. This includes class-related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product. For products authorised nationally, the relevant SPC is that approved by the Competent Authority in the Member State to whom the reaction is being reported. For centrally authorised products, the relevant SPC is the SPC authorised by the European Commission. During the time period between a CHMP Opinion in favour of granting a marketing authorisation and the Commission Decision granting the marketing authorisation, the relevant SPC is the SPC annexed to the CHMP Opinion.

⁶⁷ Please note that for investigational medicinal products an unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable Product Information (e.g. the investigator's brochure for an unauthorised investigational product or the Summary of Product Characteristics for an authorised product) (Article 2(p) of Directive 2001/20/EC).

Unlisted adverse reaction

An adverse reaction that is not specifically included as a suspected adverse effect in the Company Core Safety Information (CCSI). This includes an adverse reaction whose nature, severity, specificity or outcome is not consistent with the information in the CCSI. It also includes class-related reactions which are mentioned in the CCSI but which are not specifically described as occurring with this product.

1.2 Terms in Relation to Risk Management

Additional risk minimisation activity

A risk minimisation activity put in place to reduce the probability of an adverse reaction occurring or its severity should it occur which is not a routine risk minimisation activity – e.g. additional educational material or use of one of the other risk minimisation activities in [Table I.3.A](#).

Identified risk

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples of identified risks include:

- An adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data
- An adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest suggests a causal relationship
- An adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

Important identified risk, important potential risk or important missing information

An identified risk, potential risk or missing information that could impact on the risk-benefit balance of the product or have implications for public health.

Missing information

Information about the safety of a medicinal product which is not available at the time of submission of the EU Risk Management Plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.

Potential risk

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples of potential risks include:

- Non-clinical safety concerns that have not been observed or resolved in clinical studies
- Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship
- A signal arising from a spontaneous adverse reaction reporting system
- An event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product.

See also Adverse event

Risk management system

A risk management system shall comprise a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions (Article 34 of Regulation (EC) No 1901/2006).

Risk minimisation

This is a set of activities used to reduce the probability of an adverse reaction occurring or its severity should it occur.

Routine pharmacovigilance

Pharmacovigilance activities as specified in Regulation (EC) No 726/2004 and Directive 2001/83/EC that should be conducted for all medicinal products.

Routine risk minimisation activities

The warnings and information contained within the Summary of Product Characteristics and Patient Leaflet, and the careful use of labelling and packaging, which aim to reduce the probability of an adverse reaction occurring or its severity should it occur.

Safety concern

An important identified risk, important potential risk or important missing information.

Target Population

The Patients who might be treated by the medicinal product according to the indication(s) and contraindication(s) in the Summary of Product Characteristics.

1.3 Terms in Relation to Electronic Exchange of Pharmacovigilance Information

Acknowledgement message (ICSRACK)

An EDI Message with the information on the result of the Acknowledgement of Receipt procedure to acknowledge the receipt of one Safety Message and the Safety Report(s) contained in the Safety File.

Acknowledgement message (MPRACK)

An EDI Message with the information on the result of the Acknowledgement of Receipt procedure to acknowledge the receipt of one Medicinal Product Report Message and the Medicinal Product Report(s) contained in the Medicinal Product File.

Acknowledgement of receipt

The procedure by which on receipt of the Safety Message/Medicinal Product Report Message the syntax and semantics are checked.

Applicant

A pharmaceutical company applying for a marketing authorisation in the EEA.

Electronic data interchange (EDI)

Electronic transfer, from computer to computer, of commercial and administrative data using an agreed standard to structure an EDI message. EDI is based on the use of structured and coded messages, the main characteristic of which is their ability to be processed by computers and transmitted automatically and without ambiguity. This makes EDI specific in comparison with other data exchange such as electronic mail.

EudraVigilance database management system (DBMS)

The pharmacovigilance database defined in Community legislation.

EudraVigilance gateway

The data-processing network as defined in the Community legislation that provides a single point of contact between Marketing Authorisation Holders, Applicants, sponsors and Competent Authorities in the EEA. By doing so, the EudraVigilance Gateway is considered a hub and all connections to the EDI Partners are known as spokes. Safety, Acknowledgement and Medicinal Product Report Messages are routed through the hub to the desired spoke.

Extensible markup language (XML)

A subset of SGML that is completely compatible with SGML.

Gateway

A data exchange service, which consists of all core standards and functionality required for supporting the ICH standards (e.g. Simple Mail Transfer Protocol (SMTP)/Secure Multipurpose Internet Mail (SMIME)).

Individual case

The information provided by a primary source to describe suspected adverse reaction(s)/suspected unexpected serious adverse reactions related to the administration of one or more medicinal products/investigational medicinal products to an individual patient at a particular point of time.

Investigational medicinal product (IMP)

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form (Art 1(d) of Directive 2001/20/EC).

Medicinal product file

The electronic file transmitted in one Message Transaction between one Sender and one Receiver containing one Medicinal Product Report Message.

Medicinal product report (MPR)

An electronic report with a defined set of data elements to populate and update the EudraVigilance Medicinal Product Dictionary (EVMPD). A Medicinal Product Report may contain information on an authorised medicinal product/investigational medicinal product.

Medicinal product report message (MPRM)

An EDI Message including the information provided for one/more Medicinal Product Reports contained in one Medicinal Product File exchanged between one Sender and one Receiver in one Message Transaction.

Medicinal product report transaction

The complete set of actions in the electronic reporting of Medicinal Product Messages, which routinely includes the following:

- Creation of a Medicinal Product Report Message
- Transmission of the Medicinal Product Report Message to the Report Receiver
- On receipt of the Medicinal Product Report Message by the Receiver's Gateway return of an MDN
- This MDN will be referred to as MPR-MDN
- The MPR-MDN is received and stored by the Report Sender to document the success of the Medicinal Product Report Message transmission
- The Medicinal Product Report Message is subjected to the Acknowledgement of Receipt procedure by the Report Receiver
- The Acknowledgement Message is created
- The Acknowledgement Message is returned to the Report Sender (technically the Report Receiver is a Message Sender for this part of the transaction)
- On receipt of the Acknowledgement Message by the Report Sender's Gateway return of an MDN
- This MDN is referred to as MPRACK-MDN
- The MPRACK-MDN is received and stored by the Report Receiver to document the successful transmission of the Acknowledgement Message
- The Acknowledgement Message is evaluated to document the success of the Report Transaction

Message

An EDI Message consists of a set of segments, structured using an agreed standard, prepared in a computer readable format and capable of being automatically and unambiguously processed.

Message disposition notification (MDN)

A notification on the receipt of an EDI Message returned by the Receiver's Gateway to the Sender's Gateway. The MDN concludes a Message Transaction performed between two parties in a Gateway-to-Gateway communication.

Message transaction

A set of actions encompassing the electronic transmission of an EDI Message (Safety Message, Acknowledgement Message, Medicinal Product Message) between a Sender and a Receiver including the return of the Message Disposition Notification for that message.

Partner

An organisation exchanging EDI Messages in the area of pharmacovigilance in the pre- or post-authorisation phase with another organisation. For the purpose of this guideline, EDI partners in the pre- and post-authorisation phase in pharmacovigilance are as follows:

- Competent Authorities in the EEA
- Marketing Authorisation Holders in the EEA
- Applicants
- Sponsors in the EEA

Receiver

Intended recipient of the EDI Message.

Receiver identifier

Identification or combined EDI qualifier and ID of the recipient.

Report receiver

Intended recipient of the transmission of a Safety Message, which for the purpose of these Guidelines is an EDI Partner. The Receiver is also the intended recipient of the transmission of a Medicinal Product Report Message, which for the purpose of these Guidelines is an EDI Partner being the Agency.

Report sender

Person or entity creating a Safety Message as EDI Message in order to submit a Safety Report, which for the purpose of these Guidelines is an EDI Partner. In the Report Transaction the Report Sender will always remain the same, whereas with the exchange of messages the "Sender" and "Receiver" roles will change. The same concepts apply to the organisation creating a Medicinal Product Message as EDI Message in order to submit a Medicinal Product Report, which for the purpose of these Guidelines is an EDI Partner being an Applicant, a Marketing Authorisation Holder or a sponsor.

Report transaction

The complete set of actions in the electronic reporting of Safety Messages to comply with regulatory requirements which routinely includes the following:

- Creation of a Safety Message
- Transmission of the Safety Message to the Report Receiver
- On receipt of the Safety Message by the Receiver's Gateway return of an MDN
- This MDN will be referred to as ICSR-MDN
- The ICSR-MDN is received and stored by the Report Sender to document the success of the Safety Message transmission
- The Safety Message is subjected to the Acknowledgement of Receipt procedure by the Report Receiver
- The Acknowledgement Message is created
- The Acknowledgement Message is returned to the Report Sender (technically the Report Receiver is a Message Sender for this part of the transaction)
- On receipt of the Acknowledgement Message by the Report Sender's Gateway return of an MDN
- This MDN is referred to as ICSRACK-MDN
- The ICSRACK-MDN is received and stored by the Report Receiver to document the successful transmission of the Acknowledgement Message

The Acknowledgement Message is evaluated to document the success of the Report Transaction.

Safety file

The electronic file transmitted in one Message Transaction between one Sender and one Receiver containing one Safety Message.

Safety message

An EDI Message including the information provided for one/more Individual Case Safety Reports contained in one Safety File exchanged between one Sender and one Receiver in one Message Transaction.

Sender

Person or entity creating an EDI Message for transmission.

Sender identifier

Identification (ID) or combined EDI qualifier and ID of the Sender.

Sponsor

An individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial (Art 2(e) of Directive 2001/20/EC).

Standard generalized markup language (SGML)

International Standard (ISO 8879) computer language for describing a document in terms of its content (text, image) and logical structure (chapters, paragraphs, etc.). It is a standard for how to specify a document markup language or tag set. Such a specification is itself a document type definition (DTD). SGML is not in itself a document language, but a description of how to specify one. It is a metalanguage.

SGML is based on the idea that documents have structural and other semantic elements that can be described without reference to how such elements should be displayed.

2. Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical-Therapeutic-Chemical Classification
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination Group for Mutual Recognition and Decentralised Procedures (human)
CMS	Concerned Member State(s)
CV(s)	Curriculum (Curricula) Vitae
DHPC(s) commonly called “DDL(s)”	Direct Healthcare Professional Communication(s) commonly called “Dear Doctor Letter(s)”
DCP	Decentralised procedure
DUS	Drug utilisation studies
EBD	EU Birth Date
EC	European Commission
EDI	Electronic data interchange
EEA	European Economic Area
EMA	European Medicines Agency; “the Agency”
EU	European Union
EVMPD	EudraVigilance Medicinal Product Dictionary
EVPM	EudraVigilance Post-Authorisation Module
FDA	US Food and Drug Administration
IBD	International Birth Date
ICH	International Conference on Harmonisation
ICSR(s)	Individual Case Safety Report(s)
IMP	Investigational medicinal product
INN	International Non-Proprietary Name
IT	Information Technology
ISPE	International Society for Pharmacoepidemiology
LLTs	Lowest Level Terms (of MedDRA)
MAH(s)	Marketing Authorisation Holder(s)
MedDRA	Medical Dictionary for Regulatory Activities
MPR	Medicinal Product Report
MRP	Mutual recognition procedure
NUI	Non-Urgent Information
PAR	Public Assessment Report
PASS	Post-authorisation safety study
PhVWP	CHMP Pharmacovigilance Working Party
PL	Package Leaflet
PSUR(s)	Periodic Update Safety Report(s)
PUMA	Paediatric Use Marketing Authorisation
QPPV	Qualified Person Responsible for Pharmacovigilance
RA	Rapid Alert
RMS(s)	Reference Member State(s)
SOCs	System Organ Classes (of MedDRA)
SPC	Summary of Product Characteristics
SUSAR(s)	Suspected unexpected serious adverse reaction(s)
USR	Urgent safety restriction
WHO	World Health Organization

3. Other EU Guidelines and Relevant Terminology

3.1 Other EU Pharmacovigilance Guidelines

3.1.1 Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance During the Pre- and Post-Authorisation Phase in the European Economic Area (EEA)

Adopted at Community level in September 2004.

This Guideline is published under document reference number EMEA/115735/2004 on the EudraVigilance website www.eudravigilance.emea.europa.eu.

3.1.2 Technical Documentation – EudraVigilance Human Version 7.0 Processing of Safety Messages and Individual Case Safety Reports (ICSRs)

Adopted at Community level in July 2004.

This Guideline is published under document reference number EMEA/H/20665/04 on the on the EudraVigilance website www.eudravigilance.emea.europa.eu.

3.1.3 Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data

This Guideline (EMEA/CHMP/313666/2005) is available on the EMEA website <http://www.emea.europa.eu>.

3.1.4 Guideline on the Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population

This Guideline (EMEA/CHMP/PhVWP/235910/2005) is available on the EMEA website <http://www.emea.europa.eu>.

3.1.5 Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System

This Guideline (EMEA/106464/2006, latest version) is available on the EMEA website <http://www.emea.europa.eu>.

3.2 Relevant Terminology

3.2.1 Medical Terms

See Annex 4.5 for Dictionary for Regulatory Activities (MedDRA).

3.2.2 Standard Terms on Pharmaceutical Dosage Forms, Routes of Administration and Containers

These Standard Terms are published by the Council of Europe and are available on the website of the European Pharmacopoeia <http://www.pheur.org>.

3.2.3 Controlled Vocabulary for Routes of Administration

See Annex 4.7.1.

3.2.4 Controlled Vocabulary for Units and Measurements

See Annex 4.7.2.

3.3 Other Relevant Guidelines Specific to Similar Biological Medicinal Products

The following guidelines are not specific to pharmacovigilance but contain specific pharmacovigilance information. They are not referenced elsewhere in Volume 9A.

3.3.1 Guideline on Similar Biological Medicinal Products

This Guideline (CHMP/437/04, latest version) is available on the EMEA website <http://www.emea.europa.eu>.

3.3.2 Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Products as Active Substance: Non-clinical and Clinical Issues

This Guideline (EMA/CHMP/BMWP/42832/2005, latest version) is available on the EMEA website <http://www.emea.europa.eu>.

3.3.3 Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Products as Active Substance: Non-clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Recombinant Erythropoietins

This guidance (EMA/CHMP/BMWP/94526/2005, latest version) is available on the EMEA website <http://www.emea.europa.eu>.

3.3.4 Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Products as Active Substance: Non-clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-colony Stimulating Factor

This guidance (EMA/CHMP/BMWP/31329/2005, latest version) is available on the EMEA website <http://www.emea.europa.eu>.

3.3.5 Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Products as Active Substance: Non-clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Recombinant Human Soluble Insulin

This guidance (EMA/CHMP/BMWP/32775/2005, latest version) is available on the EMEA website <http://www.emea.europa.eu>.

**3.3.6 Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Products as Active Substance: Non-clinical and Clinical Issues:
Guidance on Similar Medicinal Products Containing Somatropin**

This guidance (EMA/CHMP/BMWP/94528/2005, latest version) is available on the EMA website <http://www.ema.europa.eu>.

3.3.7 Guideline on Comparability of Biotechnology-derived Medicinal Products after a Change in the Manufacturing Process: Non-clinical and Clinical Issues

This Guideline (EMA/CHMP/BMWP/94528/2005, latest version) is available on the EMA website <http://www.ema.europa.eu>.

3.4 Other Relevant Guidelines

The following guidelines are not specific to pharmacovigilance but contain specific pharmacovigilance information. They are not referenced elsewhere in Volume 9A.

3.4.1 Guideline on the Clinical Investigation of Human Anti-D Immunoglobulin for Intravenous and/or Intramuscular Use

This Guideline (EMA/CHMP/BPWG/575/99, latest version) is available on the EMA website <http://www.ema.europa.eu>.

3.4.2 Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins

This Guideline (EMA/CHMP/BMWP/14327/2006, latest version) is available on the EMA website <http://www.ema.europa.eu>.

3.4.3 Guideline on the Clinical and Non-Clinical Evaluation During the Consultation Procedure on Medicinal Substances Contained in Drug-Eluting (Medicinal Substance-Eluting) Coronary Stents

This Guideline (EMA/CHMP/EWP/110540/2007, latest version) is available on the EMA website <http://www.ema.europa.eu>.

4. ICH Guidelines

4.1 ICH-E2B(R2) - Maintenance of the Clinical Safety Data Management Including: Data Elements for Transmission of Individual Case Safety Reports

This Guideline is published under document reference number CPMP/ICH/287/95 modification corr. on the EMEA website www.emea.europa.eu. Please note that this Guideline was previously coded as ICH-E2B(M).

4.1.1 ICH-E2B Q&As (R5): Questions and Answers Data Elements for Transmission of Individual Case Safety Reports

This Guideline is published under document reference number CPMP/ICH/3943/03 on the EMEA website www.emea.europa.eu.

4.2 ICH-E2C(R1): Clinical Safety Data Management - Periodic Safety Update Reports for Marketed Drugs including Addendum to ICH-E2C

This Guideline is published under document reference number CPMP/ICH/288/95 for ICH-E2C and CPMP/ICH/4679/02 for ICH-E2C Addendum on the EMEA website www.emea.europa.eu as a combined document.

4.3 ICH-E2D: Post-Approval Safety Data Management - Definitions and Standards for Expedited Reporting

This Guideline is published under document reference number CPMP/ICH/3945/03 on the EMEA website www.emea.europa.eu.

4.4 ICH-E2E: Pharmacovigilance Planning

This Guideline is published under document reference number CPMP/ICH/5716/03 on the EMEA website www.emea.europa.eu.

4.5 ICH-M1: Medical Terminology - Medical Dictionary for Regulatory Activities (MedDRA)

Reference to the recommendations can be found on the EMEA website www.emea.europa.eu.

4.6 ICH-M2: Electronic Standards for Transmission of Regulatory Information (ESTRI) - Individual Case Safety Report (ICSR)

Reference to the recommendations can be found on the EMEA website www.emea.europa.eu.

4.7 ICH-M5: Data Elements and Standards for Drug Dictionaries

4.7.1 Routes of Administration Controlled Vocabulary

This Guideline is published under document reference number CHMP/ICH/175860/05 on the EMEA website www.emea.europa.eu.

4.7.2 Units and Measurements Controlled Vocabulary

This Guideline is published under document reference number CHMP/ICH/175818/05 on the EMEA website www.emea.europa.eu.

5. Templates

5.1.1 Template for EU Risk Management Plan (EU – RMP)

See document reference number EMEA/192632/2006 on EMEA website www.emea.europa.eu.

5.2.1 Template for Cover Page for PSUR Submission

<Serial number> **PERIODIC SAFETY UPDATE REPORT**
for

ACTIVE SUBSTANCE(S): <INN>

ATC CODE(S): <Code(s)>

MEDICINAL PRODUCTS COVERED:

Invented Name of the Medicinal Product(s)	Marketing Authorisation Number(s)	Date(s) of Authorisation (Underline (Harmonised) EU Birth Date)	Marketing Authorisation Holder
<>	<>	<>	<>
<>	<>	<>	<>

AUTHORISATION PROCEDURE in the EU:

<Centralised/Mutual Recognition/Decentralised/Purely National>

INTERNATIONAL BIRTH DATE (IBD): <Date>

PERIOD COVERED BY THIS REPORT: from <Date> to <Date (i.e. data lock point)> DATE OF THIS REPORT: <Date>
--

VOLUME: <Number>/<Total number of volumes>

OTHER INFORMATION:

<Other identifying or clarifying information if necessary>

DATA LOCK POINT OF NEXT PSUR: <Date>

MARKETING AUTHORISATION HOLDER'S NAME AND ADDRESS:

<Name>

<Address>

NAME AND CONTACT DETAILS OF THE QPPV:

<Name>

<Address>

<Telephone number>

<Fax number>

<E-mail address>

SIGNATURE: <Signature>

LIST OF SERIAL NUMBERS

<Serial number>	<Period covered>

DISTRIBUTION LIST⁶⁸

<Competent Authority in the EU>	<Number of copies>

⁶⁸ For medicinal products authorised through the mutual recognition or decentralised procedure the Reference Member State and the Concerned Member States should be indicated.

5.2.2 Template for PSUR section "Worldwide Marketing Authorisation Status"

This table is has been completed with fictitious data.

Country	Action-Date	Launch Date	Invented Name(s)	Comments
Sweden	A - 7/90	12/90	Bacteroff	-
	AR - 10/95	-	-	-
Brazil	A - 10/91	2/92	Bactoff	-
	A - 1/93	3/93	Bactoff-IV	IV dosage form
United Kingdom	AQ - 3/92	6/92	Bacgone	Elderly (> 65) excluded
	A - 4/94	7/94	Bacgone-C (skin infs)	(PK) Topical cream
Japan	LA - 12/92	-	-	To be refilled
France	V - 9/92	-	-	Unrelated to safety
Nigeria	A - 5/93	7/93	Bactoff	-
	A - 9/93	1/94	Bactoff	New indication
Etc.				

Abbreviations: A = authorised; AQ = authorised with qualifications; LA = lack of approval; V = voluntary marketing application withdrawal by company; AR = authorisation renewal.

5.2.3 Template for PSUR section "Line-listings of Individual Case Histories"

MAH NO	COUNTRY	SOURCE	AGE/ SEX	DAILY DOSE mg/day	DATE OF ONSET OF REACTION or time to onset	DATES OF TREATMENT or treatment duration	REACTION DESCRIPTION	OUTCOME	COMMENT

5.2.4 Template for PSUR section "Summary Tabulations"

This table is only one example of different possible data presentations which are at the discretion of the Marketing Authorisation Holder (e.g.: serious and non-serious in the same table or as separate tables, etc.).

Number of Reports by Term (Signs, Symptoms and Diagnoses) from Spontaneous (Medically Confirmed), Clinical Study and Literature Cases:
All Serious Reactions

An * indicates an unlisted reaction

Body system/Adverse reaction term	Spontaneous/ Regulatory bodies	Clinical studies	Literature
CNS			
hallucinations*	2	0	0
etc.	-----	-----	-----
etc.			

Sub-total			
CV			
etc.			
etc.			
-----	-----	-----	-----
Sub-total			
Etc.			
TOTAL			

In a footnote (or elsewhere), the number of patient-cases that represent the tabulated terms should be given (e.g.: x-spontaneous/regulatory, y-clinical study, and z-literature cases)

5.3.1 Template for Rapid Alert in Pharmacovigilance

<Logo and name of the Competent Authority of the Member State/EMA>

RAPID ALERT IN PHARMACOVIGILANCE		
REFERENCE: <doc.nr.>	N° of pages: <> N° of attachments: <>	DATE: <dd/month in words/yy>
FROM: <Member State/Agency>		
TO: ALL EU MEMBER STATES EFTA COUNTRIES CONCERNED EMA EUROPEAN COMMISSION CHMP CHAIRPERSON RAPPORTEUR (if applicable)		
TYPE OF RAPID ALERT: Concern about a change in the risk-benefit balance based on: <select/delete below> ☐ A series of report(s) of unexpected serious adverse reactions ☐ Occurrence of vCJD in a donor of blood used for human blood- and plasma derived medicinal products; ☐ Reports of an expected adverse reaction suggesting greater severity than known, new long-term sequelae or identifying new risk factors ☐ A significant increase in the reporting rate of expected serious adverse reaction ☐ Evidence from studies (clinical trials or epidemiological studies) indicative of unexpected risk or a change in frequency or severity of a known risk ☐ Knowledge that the efficacy of a medicinal product is not established as assumed to date ☐ Evidence that the risks of a particular product are greater than alternatives with similar efficacy ☐ Other reason: <specify>		
SUBJECT: <Complete as appropriate, using key words/short description of safety concern> International Non-proprietary Name (INN) or Class: <> Invented name(s): <> Procedure(s) of marketing authorisation: <select/delete below> ☐ Centrally authorised (or applied for) product(s) ★ ☐ Product(s) authorised through mutual recognition or decentralised procedure ✚ ☐ Purely nationally authorised product(s) □ ☐ Product(s) which has (have) been subject to a referral procedure ◆ ☐ Other: <specify> Strength(s): <> Pharmaceutical Form(s) and Dosage(s): <> Route of Administration(s): <> Anatomical-Therapeutic-Chemical Classification (ATC code): <> Marketing Authorisation Holder(s): <> Manufacturer(s): <complete/delete if not relevant> Indication(s): <>		

REASON FOR RAPID ALERT:

<summarise relevant evidence for the safety concern>

SOURCE OF INFORMATION: <select/delete below>

- ☐ Spontaneous reports
- ☐ Post-authorisation study
- ☐ Clinical trial
- ☐ Pre-clinical study
- ☐ Other: <specify>

PLANNED ACTIONS/ACTIONS TAKEN <delete ACTIONS TAKEN, if not applicable. If both categories are applicable, identify which actions have been taken and which are planned>:
<select/delete below>

- ☐ Suspension/withdrawal <delete as applicable> of the marketing authorisation
- ☐ Suspension of use of a product
- ☐ Recall of the medicinal product from the market at Marketing Authorisation Holder/Pharmacy/Patient level <delete as applicable>
- ☐ Action for human blood- and plasma derived medicinal products following occurrence of vCJD in a blood donor <specify action and concerned batches on the market as well as expired batches>
- ☐ Urgent safety restriction/variation <delete as applicable>
- ☐ Changes in the Summary of Product Characteristics (SPC) <select/delete below>
 - ☐ Introduction of new contraindications
 - ☐ Introduction of new warnings
 - ☐ Reduction in the recommended dose
 - ☐ Restriction in the indications
 - ☐ Restriction in the availability of a medicinal product
 - ☐ Other: <specify>
- ☐ Urgent need to inform Healthcare Professionals or Patients about an identified risk
- ☐ Other: <specify>

DETAILS ON PROPOSED ACTION AND/OR ACTION TAKEN:

<complete/delete if not applicable>

<

ADDITIONAL INFORMATION: <complete/delete if not applicable>

<

The issue could affect (an)other Member State(s): ☐ YES ☐ NO**INFORMATION REQUESTED:** <complete/delete if not applicable>

<

PLEASE RESPOND BY: <dd/month in words/yy>**NAME OF PERSON RESPONSIBLE FOR SENDING THIS MESSAGE:**

<

5.3.2 Template for Non-Urgent Information in Pharmacovigilance

<Logo and name of the Competent Authority of the Member State/EMA>

NON-URGENT INFORMATION IN PHARMACOVIGILANCE		
REFERENCE: <doc.nr.>	N° of pages: <> N° of attachments: <>	DATE: <dd/month in words/yy>
FROM: <Member State/Agency>		
TO: ALL EU MEMBER STATES EFTA COUNTRIES CONCERNED EMA EUROPEAN COMMISSION CHMP CHAIRPERSON RAPPORTEUR (if applicable)		
TYPE OF NON-URGENT INFORMATION: <select/delete below> ☐ Pre-signal information ☐ Information on status of implementation of regulatory action ☐ Information which might be of interest to other Member States, but does not require a response <i>e.g. withdrawal of a product for reasons other than safety, the outcome of discussions from national safety committees, when to expect an Assessment Report on certain items, current media activity</i> ☐ Request for information ☐ Organisational matters ☐ Interaction with external party ☐ Planned communication at national level ☐ Other reason: <specify>		
SUBJECT: <Complete as appropriate, using key words/short description of safety concern> International Non-proprietary Name (INN) or Class: <> Invented name(s): <> Procedure(s) of marketing authorisation: <select/delete below> ☐ Centrally authorised (or applied for) product(s) ★ ☐ Mutual recognition or decentralised procedure ✚ ☐ Purely nationally authorised product(s) □ ☐ Product(s) which has (have) been subject to a referral procedure ◆ ☐ Other: <specify> Strength(s): <> Pharmaceutical Form(s) and Dosage(s): <> Route of Administration(s): <> Anatomical-Therapeutic-Chemical Classification (ATC code): <> Marketing Authorisation Holder(s): Manufacturer(s) (if essential): Indication(s):		

REASONS FOR NON-URGENT INFORMATION:

<summarise relevant evidence for safety concern>

SOURCE OF INFORMATION: <select/delete below>

- ☐ Spontaneous reports
- ☐ Post-authorisation study
- ☐ Clinical trial
- ☐ Pre-clinical study
- ☐ Other: <specify>

PROPOSED ACTION AND/OR ACTION TAKEN:

<>

ADDITIONAL INFORMATION: <complete/delete if not applicable>

<>

The issue could affect (an)other Member State(s): ☐ YES ☐ NO**INFORMATION REQUESTED:** <complete/delete if not applicable>

<>

PLEASE RESPOND BY <dd/month in words/yy>**NAME OF PERSON RESPONSIBLE FOR SENDING MESSAGE:**

<>

5.4.1 Template for Direct Healthcare Professional Communications

<Date>

<Document reference number>

*Direct Healthcare Professional Communication on the association of <INN and Invented Name(s)>
with <safety concern>*

Summary

<A brief description of the safety concern, recommendations for risk minimisation (e.g. contraindications, warnings, precautions of use) and, if applicable, switch to alternative treatment, preferably in bullet points>

<Recall information, if applicable (e.g. pharmacy or patient level, date of recall)>

<A statement indicating that the information has been endorsed by a national Competent Authority/the Agency/the Marketing Authorisation Holder, if applicable>

Style guide: The Summary section should be in larger font size than the other sections of the DHPC.

Further information on the safety concern

<Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, e.g. the pharmacodynamic mechanism, temporal relationship, positive re-challenge or de-challenge, risk factors), also indicating the reason for disseminating the DHPC at this point in time>

<Placing of the risk in the context of the benefit>

<Revised Product Information text or, preferably, reference to revised Product Information in Annex>

<An estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure>

<A statement indicating any association between the adverse reaction and off-label use, if applicable>

<A statement indicating the context in which the assessment has been conducted (national procedure/CHMP procedure/European consensus)>

<A schedule for follow-up action(s) by the Marketing Authorisation Holder/Competent Authority, if applicable>

Further information on recommendations to healthcare professionals

<If needed, details on the recommendations for risk minimisation >

<If needed, additional detailed instructions on how to use the new safety or therapeutic effectiveness information>

Call for reporting

<A reminder of the need to report adverse reactions in accordance with the national spontaneous reporting system>

<Details (name, postal address, fax number, website address) on how to access the national spontaneous reporting system/Details on how to report to the Marketing Authorisation Holder>

Communication information

<Date and key messages of communication to the public>

<Content and dissemination mechanism of information to the general public or Patients, if applicable>

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes:

<Text of the revised Product Information (with changes made visible), if applicable>

<Detailed scientific information, if necessary>

<List of literature references, if applicable>

6. Distribution Requirements and Address Lists for Data Submission

6.1 Requirements for Expedited Reporting in Member States

Abbreviations:

AU: Austria, Bundesamt für Sicherheit im Gesundheitswesen / Agentur für Gesundheit und Ernährungssicherheit
BE: Belgium, Directorate-General Public Health Protection: Medicinal Products
BG: Bulgaria, Bulgarian Drug Agency
CY: Cyprus, Pharmaceutical Services
CZ: Czech Republic, State Institute for Drug Control
DE-BfArM: Germany, Federal Institute for Drugs and Medical Devices
DE-PEI: Germany, Paul-Ehrlich-Institut
DK: Denmark, Danish Medicines Agency
EE: Estonia, Estonian State Agency of Medicines
ES: Spain, Agencia Española de Medicamentos y Productos Sanitarios
EV: EudraVigilance
FI: Finland, National Agency for Medicines
FR: France, AFSSAPS
GR: Greece, National Organisation for Medicines
HP: Healthcare Professional
HU: Hungary, National Institute of Pharmacy
IE: Ireland, Irish Medicines Board
IS: Iceland, Lyfjastofnun (The Icelandic Medicines Control Agency)
IT: Italy, Agenzia Italiana del Farmaco
LI: Liechtenstein, Kontrollstelle für Arzneimittel
LT: Lithuania, State Medicines Control Agency
LU: Luxembourg, Division de la Pharmacie et des Médicaments
LV: Latvia, State Agency of Medicines of the Republic of Latvia
MS: Member State
MT: Malta, Medicines Authority
NCA: National Competent Authority
Non-HP: Non-medically confirmed reports as defined in this document.
NL: Netherlands, College ter beoordeling van geneesmiddelen
NO: Norway, Norwegian Medicines Agency
PL: Poland, The Office For Registration Of Medicinal Products, Medical Devices And Biocidal Products
PT: Portugal, Instituto Nacional da Farmacia e do Medicamento
RO: Romania, National Medicines Agency
SE: Sweden, Medical Products Agency
SI: Slovenia, Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
SK: Slovak Republic, State Institute for Drug Control
UK: United Kingdom, Medicines and Healthcare Products Regulatory Agency

6.1.1 Specific Expedited (15-days) Reporting Requirements in Member States for ICSRs from Spontaneous Reporting and Non-Interventional Studies Occurring in the Territory of a given Member State

Authorisation Procedure	Seriousness		All suspected serious ICSRs		All suspected non-serious ICSRs
	Time frame and reporting		15 days reporting		Periodic
			ICSRs to be sent to NCA	ICSRs to be sent to EV EMEA post-authorisation module only	ICSRs to be sent to NCA
Centrally approved	Spontaneous report	HP	AU, BE, BG, CZ, DE-BfArM, DE-PEI, DK, EE, ES, FI, FR, GR*, HU, IE, IS ¹ , IT, LT, LU, LV, MT, NL, NO, PL*, PT, RO, SE, SI, SK, UK	CY, IS ¹ , LI	PL ¹ , RO ¹
		Non HP	DK, HU	LI	
	Reports from non interventional studies	HP	AU, BE, BG, CZ, DE-BfArM, DE-PEI, DK, EE, ES, FI, FR, GR*, HU, IE, IS ¹ , IT, LT, LU, LV, MT, NL, NO, PL*, PT, RO, SE, SI, SK, UK	IS ¹	PL ¹
		Non HP	DK, HU		
Purely National	Spontaneous report	HP	AU, BE, BG, CZ, DE-BfArM, DE-PEI, DK, EE, ES, FI, FR, GR*, HU, IE, IS ¹ , IT, LT, LU, LV, MT, NL, NO, PL*, PT, RO, SE, SI, SK, UK	CY, IS ¹ , LI	PL ¹ , RO ¹
		Non HP	DE-BfArM, DK, HU	LI	
	Reports from non interventional studies	HP	AU, BE, BG, CZ, DE-BfArM, DE-PEI, DK, EE, ES, FI, FR, GR*, HU, IE, IS ¹ , IT, LT, LU, LV, MT, NL, NO, PL*, PT, RO, SE, SI, SK, UK	IS ¹	PL ¹
		Non HP	DE-BfArM, DK, HU		
MRP, Decentralised, Ex-Referral	Spontaneous report	HP	AU, BE, BG, CZ, DE-BfArM, DE-PEI, DK, EE, ES, FI, FR, GR*, HU, IE, IS ¹ , IT, LT, LU, LV, MT, NL, NO, PL*, PT, RO, SE, SI, SK, UK	CY, IS ¹ , LI	PL ¹ , RO ¹
		Non HP	DE-BfArM, DK, HU	LI	
	Reports from non interventional studies	HP	AU, BE, BG, CZ, DE-BfArM, DE-PEI, DK, EE, ES, FI, FR, GR*, HU, IE, IS ¹ , IT, LT, LU, LV, MT, NL, NO, PL*, PT, RO, SE, SI, SK, UK	IS ¹	PL ¹
		Non HP	DE-BfArM, DK, HU		

*: Cases should be submitted to NCA both electronically and in hard copy (CIOMS I form). IS¹: Cases to be sent electronically to both the Icelandic Medicines Control Agency and to EV EMEA post-authorisation module. PL¹: Cases recommended to be reported to Polish NCA in a timeframe convenient for MAH. RO¹: Cases to be reported to Romanian NCA on a monthly basis.

6.1.2 Specific Expedited (15-days) Reporting Requirements in Member States for ICSRs from Spontaneous Reporting and Non-Interventional Studies Occurring in the Territory of Another Member State

<u>Authorisation Procedure</u>	Seriousness		All suspected serious ICSRs		
	Time frame and reporting		15 days reporting		
			ICSRs to be sent to NCA	ICSRs to be sent to NCA when RMS or Rapporteur MS	ICSRs to be sent to EV EMEA post-authorisation module only *
<u>Centrally approved</u>	Spontaneous report	HP	UK ¹	CZ, IE, UK	BG, CY, EE, IS, IT, LT, SK
		Non HP			
	Reports from non interventional studies	HP	UK ¹	CZ, IE, UK	BG, EE, IS, IT, LT, SK
		Non HP			
<u>Purely National</u>	Spontaneous report	HP	UK ¹		BG, CY, EE, IE, IS, LT, SK
		Non HP			
	Reports from non interventional studies	HP	UK ¹		BG, EE, IE, IS, LT, SK
		Non HP			
<u>MRP, Decentralised, Ex-Referral</u>	Spontaneous report	HP	UK ¹	AU ¹ , BE, BG ¹ , CZ, DE-BfArM, DE-PEI, EE ¹ , ES, FI, FR, GR, HU, IE, IS ¹ , LU, LV, MT, NL, PL, PT, RO, SE, SI, SK ¹ , UK	AU ¹ , BG ¹ , CY, EE ¹ , IS ¹ , IT, LT, SK ¹
		Non HP			
	Reports from non interventional studies	HP	UK ¹	AU ¹ , BE, BG ¹ , CZ, DE-BfArM, DE-PEI, EE ¹ , ES, FI, FR, GR, HU, IE, IS ¹ , LU, LV, MT, NL, PL, PT, RO, SE, SI, SK ¹ , UK	AU ¹ , BG ¹ , EE ¹ , IS ¹ , IT, LT, SK ¹
		Non HP			

*: ICSRs should not be sent to EV EMEA post-authorisation module by the MAH as they are made available by the NCA where the reaction occurred. AU¹, BG¹, EE¹, IS¹, SK¹: Cases to be sent electronically to EV EMEA post-authorisation module and in addition to the NCA if country is RMS. UK¹: For Black Triangle products in United Kingdom (new products under intensive monitoring).

6.1.3 Specific Expedited (15-days) Reporting Requirements in Member States for ICSRs from Spontaneous Reporting and Non-Interventional Studies Occurring Outside the EU

<u>Authorisation Procedure</u>	Seriousness / Expectedness		All suspected serious ICSRs	Suspected unexpected serious ICSRs only	
	Time frame and reporting		15 days reporting	15 days reporting	
			ICSRs to be sent to EV EMEA post-authorisation module only *	ICSRs to be sent to NCA	ICSRs to be sent to EV EMEA post-authorisation module only *
<u>Centrally approved</u>	Spontaneous report	HP	CY	BE, CZ ¹ , DE-BfArM, DE-PEI, DK, FR, IE, LU, MT ¹ , PL ² , RO ² , SE, UK	AU, BG, CZ ¹ , EE, ES, FI, GR, HU, IS, IT, LI, LT, LV, MT ¹ , NL ¹ , NO, PT, SI, SK
		Non HP		DK	
	Reports from non interventional studies	HP		BE, CZ ¹ , DE-BfArM, DE-PEI, DK, FR, IE, LU, MT ¹ , PL ² , RO ² , SE, UK	AU, BG, CZ ¹ , EE, ES, FI, GR, HU, IS, IT, LT, LV, MT ¹ , NL ¹ , NO, PT, SI, SK
		Non HP		DK	
<u>Purely National</u>	Spontaneous report	HP	CY, IT	BE, DE-BfArM, DE-PEI, DK, FR, IE, LU, PL ² , RO ² , SE, UK	AU, BG, CZ, EE, ES, FI, GR, HU, IS, LI, LT, LV, MT, NL ¹ , NO, PT, SI, SK
		Non HP		DK	
	Reports from non interventional studies	HP	IT	BE, DE-BfArM, DE-PEI, DK, FR, IE, LU, PL ² , RO ² , SE, UK	AU, BG, CZ, EE, ES, FI, GR, HU, IS, LT, LV, MT, NL ¹ , NO, PT, SI, SK
		Non HP		DK	
<u>MRP, Decentralised, Ex-Referral</u>	Spontaneous report	HP	CY, IT	BE, CZ ¹ , DE-BfArM, DE-PEI, DK, EE ² , FR, IE, LU, MT ¹ , NL ² , PL ² , RO ² , SE, UK	AU, BG, CZ ¹ , EE ² , ES, FI, GR, HU, IS, LI, LT, LV, MT ¹ , NL ¹ , NO, PT, SI, SK
		Non HP		DK	
	Reports from non interventional studies	HP	IT	BE, CZ ¹ , DE-BfArM, DE-PEI, DK, EE ² , FR, IE, LU, MT ¹ , NL ² , PL ² , RO ² , SE, UK	AU, BG, CZ ¹ , EE ² , ES, FI, GR, HU, IS, LT, LV, MT ¹ , NL ¹ , NO, PT, SI, SK
		Non HP		DK	

*: Reporting obligations are already fulfilled when submitting to EV EMEA post-authorisation module. CZ¹, MT¹: Cases to be sent to EV EMEA post-authorisation module and in addition to NCA if country is Rapporteur-MS or RMS. EE²: Cases to be sent to EV EMEA post-authorisation module and in addition to NCA if EE is RMS. NL¹: Provided that a waiver has been obtained not to report to the NCA; all serious ICSRs allowed. NL²: ICSRs to be sent to NCA when NL are RMS; all serious ICSRs allowed. PL² and RO²: Cases to be submitted to NCAs electronically until access to EV Data Analysis System is available.

6.2 Distribution Requirements and Address Lists for Periodic Safety Update Reports

A table reflecting the requirements will be kept up-to-date on the EMEA website www.emea.europa.eu.