ECA QP ASSOCIATION
An ECA Foundation Interest Group

ECA Foundation
Fostering harmonisation of GMP/GDP regulations

EQPA Code of Practice for QPs

– Duties and Responsibilities for Qualified Persons in the EU –

A guidance document by the ECA Foundation
Version 11; December 2024

Contents

EQPA Code of Practice

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Version

Internal Draft 0.1	01 September 2006
Internal Draft 0.2	19 February 2007
Version 1.0	22. November 2007
Version 2.0	02. December 2009
Version 3.0	August 2014
Version 4.0	August 2017
Version 5.0	November 2018
Version 6.0	December 2019
Version 7.0	November 2020
Version 8.0	November 2021
Version 9.0	January 2023
Version 10.0	March 2023
Version 11.0	December 2024

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Comment Form

This Form should be used in order to send comments to the QP Association.

Paragraph	Comment	Alternative Proposal

1 Introduction/Scope

The EU Directives, EU Regulations, and the EU Guides to GMP (Eudralex Vol. 4) define detailed requirements to be met by the Qualified Person (QP). These requirements have been extracted from the relevant documents and are discussed here. However, several responsibilities including requirements for continuous training for QPs are not defined in detail. This Good Practice Guide – considered to be a "living document" – gives recommendations to QPs especially in areas of less descriptive requirements.

This Good Practice Guide reflects the consolidated view of the EQPA board and is recognized as a reference of an appropriate interpretation of the concept and role of the Qualified Person in EU. EQPA is promoting this view in conferences, trainings and comments to existing legislation.

Overview on used abbreviations.

Acronym	Long text
ATMP	Advanced Therapy Medicinal Product
ATIMP	Advanced Therapy Investigational Medicinal Product
CAPA	Corrective action and preventive action
EDQM	European Directorate for Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
EQPA	European Qualified Person Association
EU	European Union
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HMA	Health Medicines Authorities
ICH	International Convention of Harmonization
IMP	Investigational Medicinal Product
KPI	Key Performance Indicator
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MIA	Manufacturing and Importation Authorization
MIAH	Manufacturing and Importation Authorization Holder
MRA	Mutual Recognition Agreement
NCA	National Competent Authority
OOS	Out of Specification
PSF	Product Specification File
PQR	Product Quality Review
PQS	Pharmaceutical Quality System
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RP	Responsible Person (for Wholesale)
SOP	Standard Operating Procedure

WDA	Wholesale Distribution Authorization

The following table gives an overview on the codes for each country used throughout this document in texts, tables and graphs.

EQPA - Countries							
Countries addressed							
EU member states							
AT	Austria	EE	Estonia	IE	Republic of Ireland	PL	Poland
BE	Belgium	ES	Spain	IT	Italy	PT	Portugal
BG	Bulgaria	FI	Finland	LT	Lithuania	RO	Romania
CY	Cyprus	FR	France	LU	Luxembourg	SE	Sweden
CZ	Czech Republic	GR	Greece	LV	Latvia	SI	Slovenia
DE	Germany	HR	Croatia	MT	Malta	SK	Slovakia
DK	Denmark	HU	Hungary	NL	The Netherlands		
EEA member states							
IS	Iceland	NO	Norway	LI	Liechtenstein		
EU candidate states							
MK	Republic of North Macedonia	TR	Turkey				
states holding MRA/ACCA with EU							
CH	Switzerland	IL	Israel				
others							
BA	Bosnia and Hercegovina	N-IE	Northern Ireland	UK	United Kingdom		

Table 1: List of countries and used abbreviations.

2 Legal Basis

2.1 The basic European Requirements

The European Union legislation is based on the Treaty of Lisbon (Treaty of the functioning of the EU) which is considered primary law.

Secondary law is based on a hierarchy of acts.[1]

Regulations

Regulations are legal acts defined by Article 288 of the Treaty on the Functioning of the European Union (TFEU). They have general application, are binding in their entirety and are directly applicable in all European Union (EU) Member States. A regulation is part of the EU's secondary law, the body of law that derives from the principles and objectives set out in the EU treaties (primary law).

[1] https://eur-lex.europa.eu/summary/glossary.html

Directives
A directive is a legal act adopted by the EU institutions addressed to the EU Member States and, as laid down in Article 288 of the Treaty on the Functioning of the European Union, is binding as to the result to be achieved. A directive is part of the EU's secondary law, the body of law that derives from the principles and objectives set out in the EU treaties (primary law).
The national authorities of each EU country to which the directive is addressed determine the form and the methods they use to incorporate the directive into their national law (formally known as 'transposition'). Generally, this needs to be done within 2 years of the directive's adoption.

Decisions
A "decision" is binding on those to whom it is addressed (e.g. an EU country or an individual company) and is directly applicable. Example: European Commission Decision to grant a centralised marketing authorisation following a scientific opinion from the European Medicines Agency.

Non-legislative acts also take the form of Regulations, Directives or Decisions and are made up of:

Delegated acts
Delegated acts are non-legislative acts delegated to and adopted by the European Commission that serve to amend or supplement the non-essential elements of the legislation. They are binding.

Implementing acts
Implementing acts aim to create uniform conditions for the implementation of the legislative act in question, if and when this is necessary. They are binding.

The legal acts may be supplemented by non-binding documents:

Guidelines
Guidelines are non-binding documents and not part of EU legislation.
Guidelines reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives. The Agency strongly encourages applicants and marketing authorisation holders to follow these guidelines.

The European Union legislation is constantly evolving. The latest status can be verified on respective homepages maintained by the European Commission.

As mentioned, interpretive guidelines often complement legislation. "The rules governing medicinal products in the European Union" (Eudralex) is a collection of both legislation and guidelines applicable to medicinal products. Volume 4 is dedicated to good manufacturing practice and includes guidelines that interpret the principles of GMP as laid down in EU legislation (see section 2.2). Guidelines are generally non-binding so alternative approaches may be taken, provided that these

are appropriately justified. Rarely, exceptions to this rule exist. Examples of direct relevance to QPs are the 3 legislative acts that lay down the principles and guidelines of GMP. Despite the word "guidelines" appearing in their titles the entire contents of these legislative acts are mandatory. Another example of importance to QPs is the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" which, according to legislation, has to be explicitly complied with.

A useful explanation of the different types of guideline that apply to medicinal products, published by European Medicines Agency can be found at:

https://www.ema.europa.eu/en/documents/scientific-guideline/status-emea-scientific-guidelines-european-pharmacopoeia-monographs-chapters-regulatory-framework_en.pdf

2.2 The legislative acts governing medicinal products within the European Union

Separate legal acts lay down the GMP rules for Investigational Medicinal Products and marketed medicinal products for both human and veterinary use. Depending on the products you are engaged with you may find the applicable legislation in different directives or regulations and interpreted in different guidelines. The following tables identify the key legislation that QPs must be familiar with:

Legislation defining the responsibilities of the Qualified Person

Document	Referred to in this guide as
EU Directive 2001/83/EC on the Community code relating to medicinal products for human use	Directive 2001/83/EC
Regulation (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC	Regulation 2019/6
REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC	Regulation 536/2014

Legislation defining the principles (and guidelines) of GMP

Document	Referred to in this guide as
Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the	Directive 2017/1572

Document	Referred to in this guide as
principles and guidelines of good manufacturing practice for medicinal products for human use	
Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products	Directive 91/412
COMMISSION DELEGATED REGULATION (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use	Regulation 1252/2014*
Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections	DR 2017/1569

*At the time of writing no corresponding legislation had been adopted on GMP for actives substances for veterinary use

Other legislation to note:

Document	Referred to in this guide as
Commission Implementing Regulation (EU) 2021/1248 of 29 July 2021 as regards measures on good distribution practice for veterinary medicinal products in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council	Regulation 2021/1248
Commission Implementing Regulation (EU) 2021/1280 of 2 August 2021 as regards measures on good distribution practice for active substances used as starting materials in veterinary medicinal products in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council	Regulation 2021/1280
REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004	Regulation* 1394/2007

*Regulation 1394/2007 empowered the European Commission to produce specific GMP guidelines for Advanced Therapy Medicinal Products (see guidelines below).

Guidelines on Good Manufacturing Practice

As mentioned above, EudraLex Volume 4, comprises a collection of relevant legislation and guidelines on GMP for medicinal products for both human and veterinary use. There are also a number of miscellaneous documents related to GMP (Part 3) and a further collection of documents of relevance including legislation and guidance on Good Distribution Practice. Care should be taken to note that the Eudralex 4 webpages may not always be completely up to date. While EQPA strives to keep QPs updated on developments, QPs may find subscribing to one or more of EMA's RSS feeds beneficial.

The GMP guidelines can be summarised as follows:

Documents	Comment
Part 1	Basic Requirements for medicinal products
Part 2	Basic Requirements for active substances. ICH Q7 with minor modification adopted in EU to extend applicability to active substances used in the manufacture of veterinary medicinal products.
Annexes	Supplementary guidelines on specific aspects complementing Parts 1 and 2 as relevant. Annex 16 provides guidance specifically for the QP. "Annex 13" (Commission guideline of 8 December 2017 on good manufacturing practice for investigational medicinal products pursuant to the second paragraph of the Article 63(1) of Regulation (EU) No 536/2014) also includes guidance specific to the QP.* There is no Annex 18, which was formerly ICH Q7 (GMP for active substances), but owing to changes to its legal status now forms Part 2. Neither is there an Annex 20, which was formerly ICH Q9 (Quality Risk Management) but was removed to Part 3 as it is not a GMP guideline as such.
Part 3	Miscellaneous documents related to GMP
Part 4	Guidelines on GMP specific to Advanced Therapy Medicinal Products. This also includes guidance specifically for the QP.

*Although this includes specific guidance for QPs involved with IMPs, it recommends that QPs also take account of Annex 16. The guidance in Part 4, applicable to both ATMPs and ATIMPs, is designed to be stand-alone.

2.3 Requirements for Medicinal Products in the EU Member States

The EU requirements defined in Directives (see 2.1) must be transferred to national law by each EU Member State. For medicinal products such requirements are typically transposed into the national law on medicinal products. The transposition may result in differences between EU Member States due to the fact that each Member State can choose the form and methods for transposing directives into national law. However, they are bound by the terms of the directive as to the result to be achieved and the deadline by which the transposition should take place. Additional requirements based on national law are also possible and do exist. These

additional national requirements should not conflict with EU requirements or interfere with the free movement of goods between member states. A transposition deadline, which can be several years after a directive comes into force means that requirements may come into operation at different times in different member states. The QP must nevertheless comply with the applicable national law of the member state in which he or she operates.

The EU requirements defined in Regulations and Delegated Regulations (see 2.1) are immediately applicable law in each member state and do not need to be transferred into national law. Regulations and Delegated Regulations lead to a significantly higher degree of harmonization.

Annex 1 to this Good Practice Guide briefly summarises the minimum requirements for the nomination of a QP and further relevant specific information as available for each Member State.

2.4 Legislative basis for the Qualified Person

Human medicinal products

According to Article 48 of the Directive 2001/83/EC, a QP is a prerequisite for the granting and maintenance of a manufacturing and importation authorisation (MIA):

1) *"Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one qualified person, in accordance with the conditions laid down in Article 49, responsible in particular for carrying out the duties specified in Article 51."*

2) *"If he personally fulfils the conditions laid down in Article 49, the holder of the authorization may himself assume the responsibility referred to in paragraph 1."*

Be aware that because this is a directive it is the transposed requirement that is the legal foundation for a QP at the national level.

Articles 49 to 53 of directive 2001/83/EC define for medicinal products for human use the minimum conditions of qualification, the enforcement of QPs responsibilities, and the need for QPs to follow ethical standards. (see chapter 3).

REGULATION 1394/2007 on advanced therapy medicinal products does not make any provisions for QPs so the rules set by directive 2001/83/EC apply including those on qualifications and practical experience.

However, guidance on specific experience for QPs is defined in GMP Part 4, which applies also to ATIMPs:

11.12. In addition to having the qualification requirements provided for under Article 49 of Directive 2001/83, QPs responsible for ATMPs should have training and

experience relevant to the specific characteristics of these products, including cell and tissue biology, biotechnological techniques, cell processing, characterization and potency testing. QPs should have detailed knowledge of the type of ATMP and manufacturing steps for which they are taking responsibility.

Veterinary medicinal products

Article 97 of Regulation 2019/6 similarly requires the availability of at least one Qualified Person at the manufacturer as a prerequisite to receive a manufacturing authorization. A welcome update to the practical experience requirements laid down in directive 2001/83/EC has been made:

(article 97 (3)):

3. The qualified person referred to in paragraph 1 shall have acquired practical experience over at least two years, in one or more undertakings which are authorised manufacturers, in the activities of quality assurance of medicinal products, of qualitative analysis of medicinal products, of quantitative analysis of active substances and the checking necessary to ensure the quality of veterinary medicinal products.

Investigational Medicinal Products for human use

REGULATION 536/2014 refers in article 61 to the need for a manufacturing authorisation and cross refers to article 49 of directive 2001/83/EC with respect to the QP. Articles 62 and 63 assign responsibilities to the QP analogous to those defined for marketed products in directive 2001/83/EC.
Guidance on specific experience for QPs is given in the guideline on GMP for IMPs**:**

The qualified person that certifies the finished batch of investigational medicinal products for use in the clinical trial should ensure that there are systems in place that meet the requirements of good manufacturing practice and should have a broad knowledge of pharmaceutical development, clinical trial processes and supply chain of the batch concerned.

3 Ethics for the Qualified Person - A Professional Code of Conduct

3.1 Introduction:

The EU Directives, EU Regulations, and the EU Guide to GMP (EudraLex Vol. 4) and its Annexes define detailed requirements to be ensured by the Qualified Person (QP).
Requirements for education as well as practical experience, which need to be acquired by the QP prior to becoming eligible for the role and responsibility of a QP are described in Directive 2001/83/EC for medicinal products and in Regulation 2019/6 for veterinary medicinal products.
In addition to the educational and practical experience, Article 52 of Directive 2001/83/EC – applicable to human medicinal products - continues to state, that

"Member States shall ensure that the duties of qualified persons referred to in Article 48 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

Member States may provide for the temporary suspension of such a person upon the commencement of administrative or disciplinary procedures against him for failure to fulfil his obligations."

While Directive 2001/82/EC, which is now repealed, made identical provisions for QPs operating in the veterinary sector, no reference is made to a professional code of conduct in the replacement legislation, Regulation 2019/6.

Article 52 of Directive 2001/83 points out that there is an ethical dimension to be considered by the QP during his/her professional decision-making process. EU rules provide no further details on how such an ethical dimension is defined and ensured.
The relevant authorities of the EU/EEA member states are responsible for transposing article 52 into national legislation. As a result, many QPs may be subject to a Code of Conduct by virtue of their underlying professional status, but EQPA is unaware of a Code of Conduct published by any EU/EEA authority that applies specifically to QPs. In the United Kingdom, which is no longer a member state, QPs are required to be members of one of the Royal Societies of Biology, Chemistry and Pharmacy and are therefore bound by the relevant Code of Conduct. Again, these are not specific to QPs, but a Code of Practice for QPs has been published designed to complement the respective Codes of Conduct.
Chapter 3 of this document was developed by EQPA with the sole focus of framing the ethical borders and behaviours to meet the purpose of such a Code of Conduct. This chapter will be available to all parties across EU/EEA member states as a professional reference until EU-regulators might publish their own or European harmonized Code of Conduct for QPs.
Although ethics is a very general motif of action it is not easy to define in simple terms. For medicines and their use avoidance of any negative potential impact on patients is the absolute leading principle. Ethics is usually not an area that allows compromise.
Training on the laws in place – while very technical – is a basic asset for the QP. Training on ethics should also receive appropriate attention in basic and continued training for QPs.

3.2 Purpose of this Code:

As per Art, 52 of Dir 2001/83/EC, QPs shall be subject to a professional code of conduct.
The purpose of this EQPA QP Code of Conduct is to provide guidance to EQPA-member QPs on what constitutes professional conduct within their role. In addition, this Code of Conduct may serve as a reference and standard to inform ethical training of QPs and underpin decision making by QPs. As noted in 3.1 above there is no mention of a code of conduct in the new veterinary legislation, Regulation 2019/6 although QPs working in the veterinary sector may be bound by a professional code

of conduct depending on their professional status. QPs working in the veterinary sector are recommended to take account of the code of conduct developed by EQPA.

3.3 Ethical Duties of the QP:

Pharmaceutical Manufacturers and the NCAs of each member state must ensure that patients are protected and that all medicinal products meet the appropriate requirements for compliance, safety, quality, and efficacy.
QPs have the professional duty to decline certifying any batch of a product for which they have ethical concerns.
The following ethical duties of the QP have been identified:

3.3.1 Selflessness:

- Always put the interest of the patient first
- Motif of action should be aligned with the benefit of the patient at lowest risk to the patient
- Whenever in doubt on compliance, quality, safety, or efficacy, a batch should not be certified by the QP.

3.3.2 Integrity:

- Act at the highest level of integrity and avoid any fraud or negligence.
- Fulfil all duties and responsibilities towards the employer. However, when conducting statutory duties, the sole obligation is the correct performance of those duties in accordance with the law.
- Avoid placing themselves under any obligation to any person or organisation that might inappropriately try to influence them in their statutory duties.
- Undertake the statutory duties of the QP only in relation to product types for which you do have sufficient competence.
- Establish a collegial relationship with other QPs.

3.3.3 Objectivity:

- Act and take decisions impartially based on legislation, official guidance, best science, facts, quality risk management principles, and without bias.
- Constantly keep abreast of new developments in science, technology, legislation, and official guidance that have an impact on their work.

3.3.4 Responsibility:

- Take full responsibility for their decisions and subject themselves to the scrutiny of their employer, MAH and regulatory authorities, or any legal investigation.
- Do not take any decision, which may compromise compliance, quality, safety, or efficacy of the product batch.

3.3.5 Transparency:

- Act and take decisions in an open and transparent manner.

- Information should not be withheld from the employer, marketing authorisation holder (observing any confidentiality considerations) or regulatory authorities.
- Explain decisions professionally and transparently, communicate clearly.
- Share information and opinion.
- Ensure proper documentation of decisions.

3.3.6 Honesty:

- Act with respect and be truthful.

3.3.7 Leadership:

- Exhibit these principles in their own behaviour and treat others with respect.
- Actively promote and robustly support the professional ethical principles and challenge poor behaviour wherever it occurs.
- Lead by example by constantly exhibiting the above behaviours in your work.
- Actively support work colleagues who do the same and call out poor behaviour when it occurs while always maintaining courtesy and respect for others.
- Address shortcomings
- Take the first step, when necessary

3.3.8 Knowledge:

- Maintain up to date skills and assist the development of others.
- Do not knowingly accept or perform work which they are not competent to undertake.
- Perform certification only once the registered requirements and the details of manufacturing and testing processes are sufficiently understood and assessed.

3.3.9 Prevent professional misconduct:

- Take steps to prevent corrupt practices and professional misconduct.
- Do not knowingly mislead, or allow others to be misled, about scientific and professional matters (e.g., by inappropriate use of risk management)
- Do not act or take decisions in order to gain financial or other material benefits for themselves, family members, or friends.

3.3.10 Rigour and Robustness:

- Stay focused.
- Behave to maintain consistency in words and actions.
- Apply risk management principles appropriately Do the right professional thing, rather than simply following the opinion of the majority or those in authority.
- Build positions on comprehensive assessment.
- Form a rationale based on different perspectives.
- Consider other people's arguments and views.

3.3.11 General Duties:

Any indication or suspicion of fraud or negligent violation of professional or legal rules by others needs to be followed-up by the QP. Only after complete clarification that fraud or negligence has not occurred may continuation of certification be considered.

QPs should ensure that senior management is sufficiently aware of the roles and responsibilities of the QP including matters of ethics. This Code of Conduct is recommended for use in this situation.

The QP should consult other experts to reinforce knowledge where required.

Ultimately, the QP must be satisfied either directly or, more usually, by the proper operation of the PQS. Each delegated task should rely on provisions made by the PQS including immediate escalation to the QP in case of deviations and the possibility for the QPs to personally involve themselves as needed.

Batch certification without such adequate steps may be regarded as professional and therefore ethical misconduct.

The QP depends on many colleagues and different functions/organizations. It is therefore of paramount importance that the QP achieves good working relationships with others.

The QP should take necessary steps to inform other functional groups of the legal role and responsibilities of the QP and help them to understand how they can provide effective support.

What cannot be over emphasized is the QP's need to regularly meet with professional colleagues in all functional groups to achieve mutual understanding of their contribution to and impact upon quality.

3.4 Professional and Ethical Conduct:

QPs have duties not only to their employer but also to the NCA and specifically to the patient.

When there is any aspect of the PQS or its implementation which is not in accordance with ethical norms, then the QP has a duty to bring this to the attention of Senior Management and Senior Management has to ensure that appropriate corrective measures are taken. Depending on the level of severity the QP has to consider refusing to certify batches until correction is effective based on his/her professional and ethical assessment.

QPs should establish a good working relationship with Regulatory Inspectors of the member state and participate in site-inspections as far as possible.

In cases where undue pressure to depart from professional, ethical, and technical standards cannot be counterbalanced by reference to this and other relevant guidance, QPs should contact the appropriate authority of the member state to mutually settle the issue(s), preferably having informed the employer first.

3.5 Disciplinary Procedures:

Article 52 of Directive 2001/83/EC requires that NCAs of member states put in place administrative disciplinary measures (e.g., temporary suspension of such person) in case of misconduct. In Regulation 2019/6 the equivalent powers are expressed in general terms in Chapters 8 and 9 rather than having specific provisions for QPs.

The QP has a personal and professional responsibility for ensuring that the tests and checks have been carried out. In certifying into the register or equivalent document the QPs are indicating that they have satisfied themselves that the necessary steps have been carried out and that the batch complies with all relevant requirements to the benefit of the patient.
If undue risks to the patient not related to the inherent risk of the product itself a legal investigation against the QP on negligence, gross negligence or fraud may be initiated. Disciplinary measures against the QP may be enforced. This Code intends to become a reference to QPs and NCAs to assess professional and ethical conduct.

4 Responsibilities and Duties of a Qualified Person (QP) in the EU

4.1 Personal Responsibilities

Article 51 of Directive 2001/83/EC lists the basic responsibilities of the QP for medicinal products for human use:

"1.(a) in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization;

1.(b) in the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the Community, that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation.

The qualified person referred to in Article 48 shall in the case of medicinal products intended to be placed on the market in the Union, ensure that the safety features referred to in point (o) of Article 54 have been affixed on the packaging.

The batches of medicinal products which have undergone such controls in a Member State shall be exempt from the controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.

2. In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph of paragraph 1 have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

3. In all cases and particularly where the medicinal products are released for sale, the qualified person must certify in a register or equivalent document provided for that purpose, that each production batch satisfies the provisions of this Article; the said register or equivalent document must be kept up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years."

4.2 Good Practice for QPs

4.2.1 Qualification of Suppliers of Starting Materials

The Directive 2001/83/EC (Human Medicinal Products) and Regulation 2019/6 (Veterinary Medicinal Products) require that active substances that are used for the

manufacture of medicinal products have been manufactured according to the Good Manufacturing Practices for starting materials. Delegated Regulation 1252/2014 lays down the GMP principles (and guidelines) for active substances used in medicinal products for human use. At the time of writing this update there was no corresponding legislation for active substances used in veterinary medicinal products, although expected. Nevertheless, guidelines for both human and veterinary active substances are given as Part 2 of the GMP Guide. It should be noted that the legislation explicitly requires risk management to be incorporated to the quality system whereas this is only implicit in the guidelines.

The QPs who are responsible for certification of the final production batch must satisfy themselves that the provisions of Directive 2001/83/EC or Regulation 2019/6 are met and that the manufacturer or importer has a system of supplier qualification in place to give the assurance that only GMP-compliant active substances are used for the manufacture of medicinal products. The European Medicines Agency (EMA) has published a Questions and Answers document on audits of active substance manufacturers. [2]

The measures to ensure that the active substance manufacturer is operating an adequate Quality System to ensure compliance do not have to be carried out by the QP of the MIA holder personally. What the QP requires is the "assurance" that all elements of the quality system are correctly implemented and applied. This assurance can be obtained by having the appropriate means and tools to assess their effectiveness throughout the supply chain by other suitably trained personnel, which may, or may not, include other QPs.

In order that the QP can acquire this assurance he must have the means to understand the complete supply chain. The "supply chain diagram" was a powerful tool introduced as a requirement in Annex 16 1.7.2. as well as in the GMP for IMPs 2.1.(x).

Active substances used in the manufacture of a medicinal products are not only required to be manufactured under appropriate GMP but also supplied under Good Distribution Practice (GDP). GDPs are legally binding by virtue of Directive 2001/83/EC in the case of active substances for human use. Good distribution practice guidelines 2015/C 95/01 for active substances are in force. For active substances used in veterinary medicinal products equivalent GDP rules have been put in place although in this case the requirements are laid down as legislation through Regulation 2021/1280 even though the content is almost identical.

In the case of medicinal products for human use excipients should be manufactured in accordance with appropriate GMP. The exact definition of "appropriate GMP" will depend on the material in question and will follow the Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for

[2] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers

human use. This means that the QP must be assured that the manufacturer of the medicinal product has used Risk management as defined by ICH Q9 to determine the appropriate risk classification of the excipient manufacturer and the excipient as it is used and then applied appropriate GMP controls. The level of GMP required is commensurate with the risk classification (i.e. the higher the risk the stricter the GMP requirements required).

The procurement of **all** starting materials requires the supplier to be assessed using some form of supplier qualification procedure based on ICH Q9 principles and so supplier selection and approval should include personnel from the QA, and manufacturing, QC, and other technical functions as appropriate, in addition to procurement. Although not mandatory it may help the QP in fulfilling his duties to be involved in this process. There must be contractual agreements in place between the manufacturer and its suppliers which must document what each party is responsible for with respect to change control, deviation, and complaint management, etc.. These agreements must cover all relevant GMP aspects and include the means of assessing compliance through a supplier qualification programme. The programme must include manufacturers, quality control laboratories, brokers, traders, service providers, packaging material suppliers and distributors. A "Quality Questionnaire" on its own together with testing and performance history may be appropriate for non-critical components such as most excipients, but on-site audits conducted by or on behalf of the manufacturing authorisation holder of all active substance suppliers including active substance intermediate manufacturers are mandatory. Inspection reports by regulatory authorities, including those done on behalf of EDQM. may be taken into account for risk-based prioritisation of audits but cannot replace audits done by or on behalf of the manufacturing authorisation holder. Shared audits, where it can be shown that the auditor has no conflict of interest, are accepted by regulatory authorities as complying with this requirement.
The question of distant assessments of manufacturers including the active substance-manufacturers arose during the COVID-19 pandemic. EMA and the EU Heads of Medicines Agencies (HMA) published a statement, that all member states would support and accept distant assessments during the pandemic if the pandemic risk level dictated. In this situation the QP should expect to see justification for the controls in place based on science as well as a documented risk assessment on a product specific basis. This approach does not support the selection of suppliers of unknown compliance status. An audit of active substance suppliers remains mandatory. Responsibilities for medicinal product quality and safety remains unchanged even under the circumstances of a pandemic.

4.2.2 QP Declarations

There are 2 types of QP declaration. The first is provided by the QP on behalf of the Manufacturing Authorisation Holder to the Marketing Authorization Holder (MAH) or MA applicant to confirm that the relevant active substance manufacturers have been audited and found to comply with GMP. The MAH uses this in support of an application for a new marketing authorisation, relevant variation or renewal. A QP declaration is required for each manufacturer in the active substance supply chain from the first use of the designated starting material.

The second type of QP declaration is provided to a clinical trial sponsor or applicant for a clinical trial authorisation. For further information please refer to chapter 4.2.5. QP declarations for active substances should be signed by the QP of each manufacturing site in the EEA that uses the active substance or imports the product containing the active substance. It is however common for the declaration to be delegated to one QP in accordance with a relevant technical agreement.

Templates published by EMA provide formats considered suitable for submission of both types of declaration and in the case of active substances detailed guidance also exists.

QP declarations for active substances are based on audit reports and the audits are expected to be no more than 3 years old.

QPs should be aware that new audit reports on any active substance manufacturer mentioned in QP declarations are notifiable variations (Type A8) as they are a change to the details submitted in accordance with Art 8ha of directive 2001/83. This is avoided in the new veterinary legislation although the relevant submission guidelines still require a QP declaration in the original MA application and subsequent relevant variations.

4.2.3 Written Confirmation

Each consignment of active substances for marketed human medicinal product imported into EU must be accompanied by a written confirmation issued by the third country authorities confirming that the manufacturer concerned complies with GMP rules equivalent to those of the EU. According to Article 111b of Directive 2001/83/EC, this requirement doesn´t apply to countries which - following prior assessment - have been placed on a "white list" by the European Commission. Countries where no written confirmation is needed can be found in Implementing Decisions published by the European Commission.[3]

The EU Commission has created a Questions & Answers document addressing the most important questions with regards to the Written Confirmation for active substance imports from non-EU Countries.[4]

The written confirmation must be available to active substance importers and manufacturers using the active substance. It should also be available to the certifying QP -where he/she operates from a different site.

It is important that all QP's are knowledgeable about the integrity of the supply chain. If any QP becomes aware of any issues relating to the manufacture or distribution of an active substance entering the EU which might suggest that the Written Confirmation is not an accurate representation of the compliance status of the active substance manufacturer, the QP should notify his/her Supervisory Authority. You should be prepared to provide as much information as possible

[3] https://health.ec.europa.eu/medicinal-products/falsified-medicines/importation-active-substances-listing-third-countries_en
[4] https://ec.europa.eu/health/sites/health/files/files/gmp/qa_importation.pdf

about the company, the active substance in question and the nature of any documented anomaly to ensure the relevant authorities can follow up properly.

4.2.4 Contract Manufacture and Analysis

Chapter 7 "Outsourced Activities" of Part I of the EU Guide to GMP states that contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. To realise this objective, the QP needs to have the assurance that:

- A written contract is in place "*covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.*".
- The Contract Giver should "*ensure, either by himself, or based on the confirmation of the Contract Acceptor's Qualified Person, that all products and materials delivered to him by the Contract Acceptor have been processed in accordance with GMP and the marketing authorisation.*"
- *"The Quality Management System of the Contract Giver must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility."*
- Any proposed changes in technical or other arrangements should be in accordance with the marketing authorisation for the product concerned.
- A system to assess the competence of the Contract Acceptor to fulfil compliance to the principles of GMP is in place.
- The Contract Acceptor *"must be able to carry out satisfactorily the work ordered by the Contract Giver"* and is fully aware of any problems associated with the product or the work which might pose hazard to his premises, equipment, personnel, other materials or other products.

4.2.5 QPs and Investigational Medicinal Products (IMPs)

The nature of clinical trials and IMPs define specific areas to consider corresponding to the stage of development of the IMP. In general, less focus is given on the active substance) and active substance supply chain, with more focus given on the drug product and packaging including blinding. EudraLex Vol 4 GMP Part II section 19 outlines the GMP requirements for active substances for use in clinical trials.

EudraLex Volume 10 of the publication "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials. The Clinical Trial Regulation 536/2014 together with its Delegated Regulation 2017/1569 define specific requirements for clinical trials and respective IMPs. They build the legal background to issue specific GMP guidelines for IMPs, the Detailed Commission Guidelines on good manufacturing practice for IMPs for human use C(2017) 8179 . The interface to the sponsor is regulated by the "Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice", EMA/INS/GMP/258937/2022.

Chapter 3 of GMP for IMPs provides a precise definition of the QP responsibilities:

The responsibilities of the qualified person are set out in Article 62 of Regulation (EU) No 536/2015 and further elaborated in Article 12 of Commission Delegated Regulation (EU) No 2017/1569.

and

The qualified person that certifies the finished batch of investigational medicinal products for use in the clinical trial should ensure that there are systems in place that meet the requirements of good manufacturing practice and should have a broad knowledge of pharmaceutical development, clinical trial processes and supply chain of the batch concerned.

The Qualified Person for IMPs is in particular responsible for:

- Ensuring that there are systems in place that meet the requirements of *Delegated Regulation (EU) No 2017/1569 and the Detailed Commission Guidelines on GMP for IMPs for IMPs for human use*.
- Maintaining a broad and product specific knowledge of pharmaceutical development and clinical trial processes.
- Ensuring that a release of IMPs should not occur until after the QP has certified that the relevant requirements are met.
- Ensuring that the certification is documented in a register available to the competent authorities and appropriately archived.

The batch certification is performed through assessment of each batch as defined by the Detailed Commission guidelines on GMP for IMPs chapter 8 and has to consider all conditions and the source of the materials introduced into a clinical trial.

The QP is responsible for safeguarding that the importer has ensured compliance of 3rd country manufacturers with EU GMP (or equivalent). This is part of each imported batch certification. Similarly, a declaration signed by a QP using the template in EudraLex Vol 10 is required to accompany any clinical trial application in which an IMP manufacturer located in a third country is named, unless a MRA applies.

The IMP release procedure is defined in the "Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice",
The release process consists of the batch certification by the Qualified Person (QP) according to Annex 16 *followed by the regulatory release of the IMP by the sponsor to the sites for use in a clinical trial.*
The regulatory release is the verification of completion of batch certification by the QP and that the necessary authorisations are in place for the clinical trial, before supply of IMP to the clinical trial site.
Where the manufacturer is delegated by the sponsor to perform the regulatory release of the IMP to the trial sites in addition to certification by the QP, the arrangements should be defined in an agreement between the sponsor and the manufacturer. The

sponsor should ensure that the details mentioned in the clinical trial application are consistent with the details actually considered by the QP. Both releases should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.

The Product Specification File (PSF) is essential for GMP compliance for IMPs. The entire chapter 2.1 of the Detailed Commission guidelines on GMP for IMPs describes the relevance and importance of keeping it up-to-date throughout the development process.

> *Products specification file, in light of Article 2(3) of Commission Delegated Regulation (EU) No 2017/1569, brings together and contains all of the essential reference documents to ensure that investigational medicinal products are manufactured according to good manufacturing practice for investigational medicinal products and the clinical trial authorisation. The products specification files is one of the essential elements of pharmaceutical quality system.*
>
> *The information in the product specification file should form the basis for assessment of the suitability for certification and release of a particular batch by the qualified person and should therefore be accessible to him or her.*

In addition, the IMP Qualified Person may be involved in other situations, e.g.,

- *Transfers of IMPs from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The product history while outside of the control of the manufacturer should be established, including review of trial monitoring reports and records of storage conditions at the original trial site. This should be part of the assessment of the product's suitability for transfer and the advice of the certifying QP should be sought* Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice", sec. 3.
- The IMP QP has to be involved in the assessment of any potential impact of a complaint and the conclusion of the investigation on the product and the clinical trial, Detailed Commission guidelines on GMP for IMPs, sec. 10.

Regulation 536/2014 marks a significant change to the legal system for IMPs. Not only is EudraLex Vol. 4 impacted but a number of documents in EudraLex Vol 10 have been revised and updated accordingly. Additionally, new documents were prepared to cover new aspects introduced by Regulation 536/2014. Both sets of documents can be accessed on the EudraLex Vol 10 website.
During the transitional period, which will last for a period of 3 years starting from 31 Jan 2022, both sets of documents in EudraLex 10 (Clinical Trial Directive 2020/20/EC and Clinical Trial Regulation 536/2014) will apply accordingly and should be referred to respectively according to the legislation under which the Clinical trial is conducted.

Source, citations and more detailed information, please refer to EudraLex Vol 10.

4.2.6 Certification and Batch Release

Guidance on certification prior to Batch Release for marketed products (principles apply also for IMPs) is provided in Annex 16 of the EU Guide to GMP. Annex 16 is formally not applicable to the certification of ATMPs, as this is detailed in section 11.2 of Chapter IV of EudraLex Volume 4, but may be used as appropriate to adapt to the ATMP QP´s needs where needed. Annex 16 also covers those cases where a batch has had different stages of production or testing conducted at different locations or by different manufacturers. In cases where the QP needs to rely on the functioning PQS of another site, the QP must ensure that a documented review of the other party´s PQS by the means of audit has taken place and that an approved audit report is available.

In this context, the QP must personally ensure that the responsibilities listed under Chapter 1.6 of Annex 16 are fulfilled. Chapter 1.7 lists many other tasks that should be undertaken in order to support certification and the QP should ensure that these are fulfilled. These tasks can be delegated and the QP normally relies on the respective quality management systems but the "QP should have on-going assurance that this reliance is well founded" (1.7). In practice the QP must be prepared to expend much of his/her time becoming familiar with the PQS as the central responsibility of a certifying QP is to hold back any certification of a batch if he/she does not have assurance that all of the 21 tasks (1.7.1 till 1.7.21) are reliably executed and completed.
It needs to be pointed out, that signing a QP declaration, the batch register, the Control Report (art. 97.6 of Regulation 2019/6) the batch certificate or batch confirmation cannot be delegated except to another QP. The QP should also ensure that the relevant authorisation (MIA, MIA(IMP), etc) covers the product type and activity and that the QP is named or otherwise formally linked to the license as appropriate according to national legislation.

To achieve appropriate control, overview and insight of the delegated tasks is especially challenging for QPs new in their role or taking responsibility for certifying a batch of a new product for the first time. In all cases delegation of tasks requires personal involvement and checks from time to time based on risk by the QP.

4.2.7 Certification of an imported batch

Annex 16 gives GMP guidance on the batch testing requirement in a Member State upon importation according to directive 2001/83/EC art 51.1.(b) or Regulation 2019/9 art. 97.7. Particular guidance is given on sampling for such testing and provisions are defined if such sampling is outsourced to the third country manufacturer. Annex 21 (in force since August 2022) defines two roles: the physical importer and the site performing QP certification. If different, both are required to hold a MIA. In addition to the tasks defined by Annex 16, Annex 21 identifies further tasks, which can be delegated, that need to be ensured and executed prior to QP certification or confirmation. These additional tasks include confirmation of customs clearance, reconciliation, ordering and transportation documentation and availability of the full batch record in a language understood by the QP. Annex 21

also gives guidance on product quality reviews and ongoing stability testing as relevant to importers.

In the case of importing medicinal products or their intermediates from a third country with which a relevant mutual recognition agreement (MRA) is in place a Batch Certificate/(Certificate of Conformance is provided by the third country manufacturing site's quality department (confirming compliance with the requirements of the Marketing Authorization, with GMP requirements and the terms in the Quality Agreement). This is needed to waive import testing. A similar document could be expected from non-MRA countries but obviously cannot be used to waive testing.

4.2.8 Release, Certification or Confirmation?

Annex 16 describes a3-step release process in its "General Principles" section. The only step mandatorily performed by the QP is certification/confirmation, which is considered the quality release of a product and the second step in the process. This step cannot be delegated and needs to be performed personally by the QP. The first step of the process is the review of manufacturing and testing documentation usually under the responsibility of the Head of Manufacturing, Head of Quality Control and in some organizations the Head of Quality Assurance may share some of these responsibilities. The third and final step of this process is the "transfer into saleable stock" (i.e. change to the release-status in a physical or electronic material management system) which can be done by someone sufficiently trained and empowered according to the Quality System. Safeguards must be in place to prevent premature transfer into saleable stock before certification by the QP.

The Glossary of Annex 16 defines the terms "Certification" as well as "Confirmation" when more than one QP is involved as they relate to "quality release" and as responsibilities which can only be assumed personally by a QP.

Discussions in industry on the topic of certification are often focused on the final step of the signature. Despite the applicable definition of certification as the (electronic) signature in the batch register, certification is often mis-interpreted as the signature itself, a signature on a certificate, or the change of the status of a batch in the material management system.

Certification is defined by giving a personal signature. Traditionally personal signatures are handwritten. If such handwritten personal signatures should be replaced by electronic signatures the appropriate security of electronic signatures has to be ensured. For the EU requirements on security on electronic signatures are defined by Regulation (910/2014) and art 25 (2.) therein defines that qualified electronic signatures are equivalent to handwritten signatures. National laws may provide more clarity upon the required electronic signatures for batch registers or batch certificates.

4.2.9 Remote QP certification

QPs should be aware, that certification is a process built on continuous oversight and a significant variety of information (refer to chapter 4.2.6 of this document and Annex 16).

More and more data and information is becoming available electronically at any point of time and at any location. QPs and the law makers of the member states have therefore assessed the possibility of performing QP certification remotely. The topic received additional attention as a valid option under the circumstances of the Covid-19 pandemic.

According to directive 2001/83/EC there is no provision that rules out remote QP certification. The legislation is silent on the matter. Some national laws of member states address this topic directly and normally, restrictively.

There seem to be two general approaches to remote QP certification:

1. Not mentioned in national law, therefore (most likely) possible
2. Interpreted in national law as a manufacturing activity, which must occur physically within premises covered by the manufacturing authorization. In addition, manufacturing requires regular presence and availability of a QP at the site to ensure an appropriate level of oversight by the QP. Therefore, legally, remote certification is not allowed.

A survey performed by EQPA revealed that not all QPs are aware of the rules enforced in their member states on this specific topic. This exposes QPs to the risk of executing their responsibilities in conflict with applicable laws. If in doubt, always refer directly to your national Competent Authorities. The rules may be applied differently during a public health emergency such as a pandemic.

QPs performing or intending to perform remote QP certification should ensure that the entire process of certification is transferred to and can been executed at the remote location. This includes all elements of information, documents, and data normally reviewed and considered by them when conducting certification on-site. A combination of on-site and remote activities may be considered. . Data should be made available from an appropriate secure electronic system (compliant to Annex 11, chapter 4 of GMP Part I) forming part of the PQS. SOPs should reflect the alternative processes before execution.

Safeguards need to stay in place that no batch is transferred into saleable stock prior to certification.

The question of the possibility of remote certification became apparent during the Covid-19 pandemic which created pressures to accept remote activities of all kinds. EMA and the Heads of all EU medicines agencies (HMA) published a statement that all member states supported and accepted remote QP certification during the pandemic. Although legal relief is given under such extremes, practical implementation may take time and may need additional measures. EQPA lobbies

for a single harmonized approach on remote certification across all member states permanently.

Independent from the specific established procedure or setup the QP`s responsibilities stay unchanged. The level of involvement and the effectiveness of oversight of delegated tasks by the QP should not differ between on-site or remote certification.

4.2.10 Maintenance of a Pharmaceutical Quality (Management) System

Chapter 1 of GMP Part I requires that a comprehensively designed and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practices and Quality Risk Management is in place. It should be fully documented, and its effectiveness monitored. Similar provisions are made by GMP Part IV for ATMPs (chapter 1.2.)

The key requirement for QPs according to Chapter 1 is to ensure that Medicinal Products are not sold or supplied before a QP has certified that the batch has been produced and tested in accordance with the requirements of the marketing authorisation and any other rules relevant to the production, control, and release of medicinal products.

The QP should therefore be involved in the implementation and maintenance of the Pharmaceutical Quality System. This is a critically important activity for the QP as it can provide the necessary assurances needed in order to certify batches. The QP should also have access to monitoring data, usually referred to as key performance indicators (KPIs) and other activities such as management reviews, inspections and audits which are also important indicators of the design and functioning of the system.

4.2.11 Qualification and Validation

Under the EU GMPs, the QP is required to know the basics of qualification and validation. Details can be found in Annex 15 to the EU GMP Guide "*Qualification and Validation*". Paragraph 5.17 clearly mentions that "*the results and conclusion should be formally documented and available to the Qualified Person prior to certification of the batch*". Also refer to Annex 16 1.7.12 where a continuous validated state for all manufacturing and testing is required. ATMP manufacturers have to follow the same principles as defined by chapter 10.1 and 10.3 of GMP Part IV. In early stages of clinical trials, validation of processes and methods may only be as complete as appropriate to the stage of their development.

Therefore, the QP should have a clear understanding of what level of formalisation and documentation is necessary for the planning, the validation master plan(s), the protocols, the reports, and the associated data for process validation. The QP should be aware of the critical quality attributes and critical process parameters that are being monitored to demonstrate that a state of control is maintained. Initial process validation is followed-up with ongoing process validation, a term that covers both traditional revalidation and more advanced approaches. Enhanced

process development, an aspect of Quality by Design, can lead to Continuous Process Verification or Real Time Release Testing although a hybrid of both conventional validation and continuous verification is most commonly seen. In all cases the QP must understand what the acceptable parameters are to assure that the validated state is maintained.

The QP should also be familiar with and understand the vocabulary of Annex 15. The QP should be able, based on the conclusion of the validation master plan as a whole, and based on the specific qualification and validation reports, to determine whether a batch complies with the Annex 15 requirements. Furthermore, the QP should:

- have a good understanding of the critical aspects of the product realisation through the qualification of equipment & utilities and through the validated status of the product (principle)
- be aware of any potential external sources that could impact the reliability of the data under review
- should understand the use of the quality risk management principles (Annex 15 chapter 1; GMP Part IV chapter 2)
- know who is responsible for the review, approval and authorisation of the qualification and validation documentation (Annex 15 chapter 2)
- either participate or be represented during the definition of the User Requirements Specifications (URS) (Annex 15 chapter 3)
- have the possibility to trigger an evaluation of the need for re-qualification of any equipment or re-validation of a process where the review of the successive batch records indicates such a need (Annex 15 chapter 4 and chapter 5)
- understand and, where relevant, should have access to full details of the process validation and be satisfied that it is in conformance with the relevant MA dossier submission, or submitted process validation scheme, as appropriate
- be aware of the risk assessments made for the transportation of products that the QP is going to certify (chapter 6)
- be aware of the requirements for the validation of packaging (qualification of the primary packaging equipment and materials). (Annex 15 chapter 7)
- know what the required quality is for the utilities used in the different manufacturing processes and ensure that he/she is informed without any delay of occurrence(s) that may affect the quality of water, steam, air, etc. coming into direct contact with the products to be certified (Annex 15 chapter 8)
- ensure that the methods used in product testing and cleaning validation are validated and that the former is in compliance with the methods described in the product dossier (Annex 15 chapter 9)
- ensure that cleaning validation or verification limits are based on the Permitted Daily Exposure for each product determined by suitably qualified experts to ensure there is no unacceptable cross-contamination (Annex 15 chapter 10)
- be aware of any change-control requests, especially where an impact on the quality of the product or compliance with the dossier may be compromised before batch certification is carried out (Annex 15 chapter 11).

4.2.12 Deviation Management

Annex 16 of the EU Guide to GMP, Chapter 3 clarifies the role of the QP with regards to deviations. This chapter describes the "handling of unexpected deviations". A batch with an unexpected deviation concerning the manufacturing process may be certified if the result of a risk analysis performed shows that "the potential impact of the deviation on quality, safety or efficacy of the batch(es) concerned and conclusion that the impact is negligible." It is important to point out that in case of a repetition of an event this cannot be classified as unexpected anymore. Correction is needed and if necessary, a variation submitted. In some cases, to avoid supply disruption of a critical product, the relevant competent authorities should be consulted where a risk assessment could justify a decision to certify. In cases where a deviation concerns specifications defined in the marketing authorisation as essential for the release (OOS; out of specification), there is no discretion available to the QP, refer to 1.7.13 of Annex 16.

Chapter 1.7.16 of Annex 16 requires that *"all investigations pertaining to the batch being certified … have been completed to a sufficient level to support certification"*. It is not explicitly required that for any deviation correction of the root cause should be completed, and the deviation closed, prior to certification by the QP. The QP has the discretion (based on risk assessment and existing SOPs), to accept a deviation as sufficiently completed to support certification provided the conditions of Annex 16 chapter 3 are met. This can be important in the case of longer lasting CAPAs. This however needs to be appropriately documented and should comply with the requirements of GMP Part I Chapter 4.

The QP does not need to assess and formally sign off each individual deviation report but can rely on the pharmaceutical quality system. However, it should be clearly defined (in the relevant SOPs) when, how and in which cases the QP should be directly involved and notified. The QP must have access to all deviations in connection with any batch to be certified. The QP may challenge the rationale and investigation. Special attention should be taken when there are multiple QPs involved in the certification/confirmation of the batch concerned. The QP performing certification of a batch of medicinal product should be aware of and take into consideration any deviations which have the potential to impact compliance with GMP and/or compliance with the MA.

4.2.13 Supply Chain Overview and Diagram

Chapter 1.7.2 of Annex 16 and GMP for IMPs chapter 2.1.(x) introduce the concept of a document providing an overview of the entire supply chain of the active substance and medicinal product, "*preferably in the format of a comprehensive diagram*". This document should include not only the manufacturing sites of starting materials and packaging materials and any other materials deemed critical through a risk assessment, but also subcontractors of critical (manufacturing) steps. When establishing a process for preparing such diagrams and keeping them updated, it is important to carefully detail not only the process flowchart but also the outcome of documented risk assessments (starting materials, packaging materials, any other materials deemed critical) as well as subcontractors of critical

steps (e.g. sterilization of components and equipment for aseptic processing, testing).

This document is a powerful tool not only for QPs. It is a comprehensive overview bringing together data and information to support the comprehensive assessment of a batch and (planned) changes to the supply chain including changes in responsibilities.

The supply chain diagram concept is included in the GMP for IMPs guidelines where testing sites are included. It is recommended that testing sites should also be included in the supply chain diagrams for marketed products.

As stated above, the supply chain diagram is a powerful tool particularly if widened in scope to identify critical raw materials and excipients for both the active substance and the finished product, the relevant transport/courier companies, hubs, temporary storage facilities, brokers, wholesalers. It can be an important tool when (re-)issuing the QP-declaration or in identifying which companies need to be audited. Ideally, from a glance the QP should have a comprehensive understanding of how the finished product reaches the location upon QP certification.

4.2.14 Safety feature and Serialization

The Falsified Medicines Directive, Directive 2011/62/EC (amending Directive 2001/83/EC) introduces requirements for protection of the legal supply chain. This included specific requirements for safety features, both the unique identifier, known as the serialization code and the anti-tampering device - their application and associated responsibilities are defined in delegated regulation 2016/161.

Article 51 of amended Directive 2001/83/EC assigns the responsibility personally to the QP to ensure that safety features are affixed to each pack:

> *The qualified person referred to in Article 48 shall in the case of medicinal products intended to be placed on the market in the Union, ensure that the safety features referred to in point (o) of Article 54 have been affixed on the packaging.*

The GMP rules reflect this task within the certification guidance in Annex 16 1.7.21 as well as in GMP Part IV 11.27(xiv).

The responsibility for ensuring implementation and compliance with the serialisation system is clearly assigned to the MAH and a required affiliate to the MAH called an onboarding partner according to delegated regulation 2016/161. Tasks may be delegated by the MAH. In many organizations tasks have been delegated to the QP. QPs should note that no duties are assigned to QPs in delegated regulation 2016/161. In fact, it does not mention the Qualified Person at all. If QPs accept any task beyond confirming as part of batch certification that the safety features have been affixed, they should be aware that these are responsibilities that are added to and separate from his/her statutory QP duties.

EQPA has issued a position paper (together with EIPG) clarifying that QPs as such do not have a personal role or responsibility for assuring data correctness, data accuracy, or data handling in relation to the serialization codes. Successful data upload (controlled by the call-back messages provided by EMVS) must be ensured prior to transfer to saleable stock but not necessarily prior to certification. It is acknowledged that the time gap between both steps should normally not be excessive for practical reasons and business interest of the company. If we look at the typical ERP systems, these are usually 2 different transactions in the system due to the requirement to have separate signatures audit trails for the action of certification vs action of transfer to saleable stock. However, the transfer to saleable stock could be done by the QP if this is written into their batch certification / release procedure.

The QP retains responsibility for oversight of the procedures that ensure appropriate safeguards are in place such that certification, including confirmation of affixed safety features and documentation in the register are reliably completed prior to the transfer into saleable stock (or simultaneously).

4.2.15 Product Quality Review

The requirement of the Product Quality Review (PQR) for marketed products is defined in GMP Part I Chapter 1.10. and for ATMPs in GMP Part IV paragraph 1.26. Additional guidance applicable in the case of importation is given in Annex 21.

According to GMP Part 1 Chapter 1 the aim of PQRs requirement is to verify

- the consistency and appropriateness of the existing process,
- the adequacy of current specifications for starting material and finished product and
- the presence and initiation of product and process improvements.

The frequency of PQRs is not stated in the guidelines as flexibility is allowed for products that are only manufactured infrequently. Normally it is expected that they are conducted and documented annually and should cover all aspects of the supply chain: starting materials, the process, process environment and the final product.

The manufacturer and marketing authorisation holder, where different, should evaluate the results of this review and an assessment should be made whether corrective and preventative actions or any revalidation should be undertaken. The MAH is responsible for any regulatory filings should any corrective or preventive action introduce notifiable changes. The same product in bulk may be packed for different markets and even within EU national or decentralized authorizations may be held by different MAHs. Because each EU MAH assumes overall responsibility for placing their products on the market, each MAH should be equally involved in the review and approval process of PQRs. In larger organizations some tasks may be delegated to a corporate function including those located in a third country, but responsibility lies with the EU MAH(s).

The manufacturer, together with the marketing authorisation holder(s) should ensure that the quality review is performed in a timely manner and is accurate. It is necessary to understand the aim and basic principles of the PQR to assume responsibility. The generation of the PQR can be done by any company function but it is recommended that QA takes the lead in interpreting the data and defining any follow-up. There is no specific requirement that QPs must sign or approve PQRs within EU GMPs but it should be noted that in some countries (e.g. Austria) national law may require this. This has the merit of ensuring that the QP is aware of their content but as a minimum PQRs should be accessible to the QP at any given time and especially at the time of certification.

4.2.16 Reference and Retention Samples

The requirements on the taking and holding of **reference** samples of starting materials, packaging materials or finished products and **retention** samples of finished products are defined in Annex 19 to the EU GMP Guide. Reference to Annex 19 is made in chapter 6.14 ("Quality Control") of the GMP Part I. The requirements for such samples for IMPs are defined differently in GMP for IMPs. GMP Part IV includes specific guidance in this respect for ATMPs.

The guidance clearly distinguishes between

- **Reference** samples of starting materials or finished products intended to be re-analysed in case of any complaint, dispute, or discrepancy and
- **Retention** samples of a fully packaged unit from a batch of finished product stored for identification purposes.

It is possible to keep retention samples as reference samples but be aware that according to the different purposes the amounts to be stored are different – **reference** samples usually in a sample size sufficient to allow at least two full analytical controls on the batch (this includes sterility testing if applicable) – **retention** samples are usually only one package per packaging presentation. Reference and retention samples may be combined if conditions are met.

Reference and **retention** samples from finished marketed products must be retained for at least one year after the expiry date. Storage of such samples for IMPs are defined differently in GMP for IMPs. GMP Part IV includes specific guidance in this respect for ATMPs. Unless a longer retention period is required under national law, samples of starting materials (other than solvents, gases or water used in the manufacturing process) must be retained for at least two years after the release of the product.

Storage conditions must be in accordance with the conditions submitted in the marketing authorisation.

In all cases including cases where a product has been manufactured (partially) outside the European Union, **reference** samples must be on hand in the European

Union, unless there is an applicable operational Mutual Recognition Agreement (MRA) in place.

As retention samples represent a batch of finished product as distributed in the EU and may need to be examined to confirm compliance with the marketing authorisation or EU legislation the Annex strictly advises that **retention** samples should be located within the EU, preferably at the site where the Qualified Person (QP) certifying the finished product batch is located.

The Qualified Person who certifies a batch for sale is responsible for ensuring that all relevant **reference** and **retention** samples are accessible at all reasonable times. If necessary, the arrangements for such access must be defined in a written agreement.

4.2.17 QP of a Manufacturing and Importation Authorisation Holder (MIAH) and RP of a Wholesaler

According to Article 1(17) of Directive 2001/83/EC,

> *´wholesale distribution of medicinal products is 'all activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned'.*
> According to Article 77(3) of EU Directive 2001/83/EC
> *´Possession of a manufacturing authorization shall include authorization to distribute by wholesale the medicinal products covered by that authorization. Possession of an authorization to engage in activity as a wholesaler in medicinal products shall not give dispensation from the obligation to possess a manufacturing authorization and to comply with the conditions set out in that respect, even where the manufacturing or import business is secondary´.*

Possession of a manufacturing and importation authorisation (MIA) includes authorisation to distribute the medicinal products manufactured under this authorization. Manufacturers performing any distribution activities with their own products must therefore comply with GDP. They do not need a separate Wholesale Authorization.

Manufacturers engaging in wholesale activities for products which they do not manufacture require a separate wholesale authorisation.

In the sequence of activities manufacturing encompasses all steps up to certification by the QP. Therefore, storage of uncertified product requires a MIA and this MIAH must also be registered in the corresponding MA(s) of the product(s).

After certification by the QP wholesale activities start and the rules on Good Distribution Practices (GDP) of medicinal products for human use or for veterinary use apply respectively.

In today's pharmaceutical industry, many activities in the supply chain are routinely outsourced to suitable service providers; product storage and transport and distribution of medicinal products are often outsourced to 3rd parties. Chapter 9 of the GDP Guidelines for human medicinal products applies to transportation and respective 3rd parties who do not hold their own MIA or wholesale license – normally called logistics providers. Responsibility for compliance with medicines legislation stays with the Contract Giver according to GMP Part I chapter 7, or chapter 7 of the GDP Guidelines for wholesalers for human medicinal products, or chapter 8 of implementing Regulation 2021/1248 for wholesalers of veterinary medicinal products. Technical Agreements should clarify the respective tasks and responsibilities.

Good distribution practice rules require the nomination of a Responsible Person (RP). It is the personal responsibility of the RP to establish the Quality System related to GDP activities. There is no requirement that an RP must be appointed by a MIAH that does not require a WDA but a MIAH may choose to appoint one. Neither is it a requirement that a QP should fulfil the role. In most cases the functions of the RP will be built into the PQS but If a MIAH decides to appoint a QP to assume RP responsibilities the QP should note that this is in addition to his or her QP responsibilities and thereby properly reflected in the job description.

Regardless as to whether a MIAH appoints an RP or not the QP should ensure that the PQS provides efficient exchange of information on any unusual event that occurs after batch certification. According to GMP Part 1 Chapter 8, QPs should be made aware of any investigations involving potential quality defects, any risk-reducing actions and any recall operations. When the MAH is different from the MIAH this should be included within the relevant contractual agreements.

4.3 Specific Situations

4.3.1 Contracted QPs

Some companies may engage Contracted QPs, sometimes operating under their own company name who provide their service as the only QP to the organization or in addition to QPs hired by the organization. The duties and responsibilities do not differ by virtue of the contractual arrangement. In such cases it is necessary to have a detailed contract that ensures that all duties and responsibilities are met.
Not all EU member states allow such Contracted QP services under national law. The following table 2 shows us the different legal environments by country according to feedback from a survey on Contract QPs:

Analysed countries															
EU member states															
	A: allowed; NS: not supported, P: prohibited														
	A	NS	P		A	NS	P		A	NS	P		A	NS	P
AT				ES				IT				RO			
BE				FI				LV				SE			
BG				FR				MT				SI			
CY				GR				NL				SK			
CZ				HR				NO							
DE				HU				PL							
DK				IE				PT							
EEA member states															
IS															
EU candidate states															
MK				TR											
states holding MRA/ACAA with EU															
CH				IL	?										
others															
BA				N-IE				UK				Canada			
A: allowed; NS: not supported, P: prohibited															

Table 2: Acceptance of contracted QPs by country.

4.3.2 Delegation of Tasks/Absence of a QP

Batch certification cannot be delegated except to another QP under the same MIA who in this case takes the responsibility in full.

Several member states have introduced via national law an additional category of "delegate QP". The term delegate QP is not used in or defined by directive 2001/83/EC. Delegate QPs must usually fulfil qualification requirements identical to the nominated QP.

Differences among member states exist as to whether none, some or all QPs (including delegate QPs) are listed by name in the MIA document (or an annex to it). In some member states QPs become registered in a national QP registry as persons fulfilling the requirements and eligible to be a QP, in other member states such national QP registries do not exist and QPs are only QPs as long as they are hired as such, although their qualification status would remain intact irrespective of their appointment as QPs.

Within a manufacturing supply chain, several QPs may share responsibilities by providing QP confirmation for their area of responsibility as defined in SOPs or Technical Agreements as appropriate to the QP who finally certifies the finished product batch. In several member states such contractual arrangements may be called QP to QP agreements (or arrangements).

Each confirmation or certification process is built upon the execution of a variety of tasks (refer to Annex 16 and Annex 21 in case of import or GMP for IMPs and GMP Part IV for ATMPs). Such tasks may include batch record review, assessment of changes or deviations, etc. Tasks can be delegated by each QP within his area of responsibility. In all but the very smallest of organisations these tasks are embedded in the PQS and done by a range of functions. The QP must continuously be satisfied that the tasks are properly defined and executed though routine involvement in the design, establishment and monitoring of the PQS and spot checks as he/she feels fit.

4.3.3 Mutual Recognition Agreements and similar arrangements[5]

The EU has established Mutual Recognition Agreements to support the exchange of goods including medicinal products when both parties operate according to comparable standards. MRAs are today established with Switzerland, Canada, New Zealand, Australia, Japan, and USA. A more comprehensive agreement exists with Israel called Agreement on Conformity Assessment and Acceptance (ACAA) whereby Israel has transposed the EU pharmaceutical acquis into its own legislation. Another example is the EU-UK Trade and Cooperation agreement.

In terms of Medicinal Products MRAs primarily conclude bilateral acceptance of comparable supervision systems by the respective Health Authorities. On this basis inspectorates accept the result of GMP inspections of the other party performed within their territory. In some agreements extra-territorial inspections are included. With the exception of the EU-UK Trade and Cooperation agreement EU import testing is waived when an MRA is applicable.

For QPs three basic requirements change because of an existing and applicable MRA:

- QPs are typically relieved of ensuring full release testing within EU/EEA territory according to directive 2001/83/EC and Regulation 2019/6. Testing in the country of origin may be accepted. Such testing needs to be fully compliant with the MA and compliant with GMP and needs to be ensured before importation testing can be waived.
- QPs can delegate batch assessment to the person responsible for batch release in the third country by the acceptance of a batch certificate, and
- According to Annex 19 under some provisions reference samples may be stored in that third country. See also paragraph 4.2.16 of this document.

In practice, specific care must be taken to ensure whether an existing MRA is actually applicable under any particular circumstance. Applicability of MRAs is limited by certain preconditions:

- Each MRA has a different scope of product classes, which may be widened over time. Ensure that your particular product is covered by the scope.

[5] On current status of MRAs please refer to of MRAs: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra

- The MRA with USA differentiates a scope and an operational scope of product classes. The MRA can only be applied to the operational scope. It is expected that over time the operational scope will widen and become identical with the overall scope of this MRA.
- Each MRA may apply differently to different manufacturing stages per product class. Often API manufacturing is not covered by the scope.
- Most confusing for people trained in GMP is that MRAs use a different definition of manufacturing. MRAs only apply in scenarios of industrial manufacturing within the territory of the MRA country. Industrial manufacturing for medicinal product comprises the drug product formulation only (forming the tablet, filling the vial, etc.). No other GMP manufacturing activity or combination thereof (packaging, testing, release, etc.) is considered industrial manufacturing.
- MRAs are usually strictly bilateral. This means that material exchange which has been industrially manufactured within the other country´s territory needs to be direct between the two territories. The only exception currently is the MRA between Switzerland and EU, which allows importation testing for EU on Swiss territory even if no industrial manufacturing is executed on Swiss territory.
- MRAs do not apply if more than two countries are involved. Any active role in the supply chain of a party in a third country other than the two MRA partner countries places the whole supply chain out of scope of the MRA so the MRA cannot be applied at all.
- The terms of one MRA cannot be applied to or combined with another MRA.
- For any export of medicinal product without further manufacturing in the MRA country directly followed by re-import, the MRA applies only to the first step never for both.

It is advisable to carefully read through the terms of the MRA in question. An overview of the current status of all MRAs is provided on the EMA website.[6]

The reliance on the other country's responsible person for release is in addition sometimes difficult to establish. The other country may have a distinct way to define and execute the release process (no QP involved) and may qualify the personnel assigned the responsibility for release very differently. The QP of the importer should establish reliance only on full understanding of the other party´s system.

The relief from importation testing provided by MRAs often leads to the belief that importation activities between the two territories is simplified. This is not fully the case. Customs rules applicable to importation of medicinal products continue to apply under an MRA. Provisions of Annex 21 apply to any certification and release of imported batches irrespective of whether an MRA applies.

[6] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra

4.3.4 UK departure from EU and consequences

The United Kingdom (UK) left the European Union (EU) on 31 January 2020 although there was a transition period until 31 December 2021 when the UK continued to follow EU law and so provided a grace period for companies that had not already done so, to bring affected EU MAs and routes of supply into line with EU rules.

The UK is the "United Kingdom of Great Britain and Northern Ireland". The former, composed of England, Scotland and Wales is differentiated from the latter in the EU withdrawal agreement. This was because any physical border infrastructure between Northern Ireland (NI) and the Republic of Ireland (RoI) had to be avoided in recognition of the Good Friday Peace Agreement of 1998 between the UK and RoI. The withdrawal agreement therefore included a protocol on Ireland/Northern Ireland, under which NI continued to follow EU rules for goods thereby allowing them to move freely on the island of Ireland (and consequently, EU's single market).

The withdrawal agreement is lengthy and complex, with sector-specific provisions as well as rules on customs, excise, VAT and state aid. It is not expected that QPs are familiar with these so this chapter will focus solely on the impact on goods only in so far as pharmaceutical legislation is concerned. The term "European Economic Area" (EEA) is deliberately used in places throughout the chapter because the EU legislation here is also relevant to Iceland, Norway and Liechtenstein.

As a result of the Protocol, even though NI is part of the UK, for most practical purposes NI can be handled as if it were an EEA member state although there are some significant differences, which must be understood as outlined later. On the other hand, Great Britain (GB) must be handled as a third country, although again, there are some differences. UK medicines legislation reflects this dual regulatory scenario. The most significant change at the time of UK withdrawal was the introduction of new territorial marketing authorisations (MAs) for NI (NI MA) and GB (GB MA) alongside UK-wide MAs and since NI MAs and UK MAs allowed product to be placed on the market in NI they were required to conform to EU rules. Centrally authorised MAs continued to be automatically valid in NI. However, as we will see later the situation with marketing authorisations was subsequently changed by way of the Windsor Framework, but only in the case of products for human use at the time of publishing this updated chapter of the EQPA Good Practice Guide.

A feature of the new UK legislation applicable to GB, is the creation of lists of "Approved Countries" for various purposes. All EEA countries were included in these lists by default. Others may be added in future:

- Import. Allows import via a Wholesale Distribution Authorisation Holder (WDAH) with a nominated Responsible Person for Import (RPi).
- Batch testing. Allows recognition of batch testing and includes countries with whom the EU had Mutual Recognition Agreements (MRA) with on 31 January 2022, i.e. Australia, Canada, Israel, Japan, New Zealand, Switzerland and the USA, as the agreements were rolled-over with identical product scope as new bilateral agreements with the UK.

- Equivalent standards for the manufacture of active substances. Provides exemptions for the need of Written Confirmations when importing active substances and includes those countries on the EU's "White List" as on 31 January 2020, i.e. Australia, Brazil, Israel, Japan, Republic of Korea, Switzerland and the USA.
- Marketing authorisation. This relates to products used in clinical trials in accordance with a marketing authorisation. It has no impact on the role of QPs
- Countries where a sponsor can be established responsible for a clinical trial in the UK.
- Countries where QP certification for Investigational Medicinal Products (IMPs) is recognised. Relieves the GB QP from recertification.

The Northern Ireland/Ireland Protocol was unpopular in the UK because, in order to protect the integrity of EU's single market, customs, excise, VAT and other border checks applied to goods moving between GB and NI because they could potentially then move into EU's single market. Furthermore, almost all medicines on the NI market are sourced from GB, even if originally manufactured in or imported into the EEA. According to the Protocol these were being imported from a third country (GB) with all the related consequences. To avoid resultant shortages in NI the UK authorities created the Northern Ireland Marketing Authorisation Route (NIMAR) to allow products with a GB MA to be distributed in NI provided they were included on a shortages list drawn up by the authorities for this purpose. Some EU member states, most notably Cyprus, Malta and RoI, which were also dependent on supply from GB, experienced similar problems.

The European Commission published a Notice, 2021/C 27/08, announcing an amendment to Art. 22 of Regulation (EU) 2016/161, exempting EEA distributors from decommissioning EU unique identifiers when exporting to GB as well as other temporary derogations until 31 December 2022. These temporary derogations allowed practices in place to continue in Cyprus, Malta, NI and RoI when sourcing from GB until the respective changes could be made to affected MAs and supply chains. It was later found necessary to extend these temporary derogations until 31 December 2024, with some aspects extended to 31 December 2026. Directive 2001/83/EC and Regulation (EU) 536/2014 were amended accordingly. In the latter case, the derogations were permanent for NI for investigational medicinal products (IMPs). In the case of veterinary medicinal products, the derogations were extended until 31 December 2025. See Commission Notice 2022/C 9653.

The Windsor Framework, agreed in 2023, provided a long term solution for NI in the case of products for human use only. It made changes to the Ireland/Northern Ireland Protocol relaxing "border" controls for goods moving between GB to NI destined exclusively for the NI market. The temporary derogations referred to above became permanent or irrelevant, as appropriate, in respect of NI. Also, GBMAs, NI MAs and EU centralised MAs were replaced by UK-wide MAs issued by MHRA.

A summary of the practical overall outcome of UK's withdrawal from EU taking account of the Windsor Framework follows. We will look initially from the UK perspective and then from the EEA perspective, which includes some overlaps. QPs

in either location involved in EEA-UK trade should nevertheless be interested in both perspectives:

- Although now repealed in the EEA, Directive 2003/94/EC, as transposed into UK legislation, remains the legal basis of GMP in the UK for both marketed products and IMPs although for GB it has been modified, but only as necessary to reflect GB's status as no longer being an EU member state. Nevertheless, there appears to be a mismatch here since according to the Ireland/Northern Ireland Protocol, Chapter IX of Regulation (EU) 536/2014 (dealing with manufacture and import of IMPs) still applies to NI.
- Despite the above, GMP guidance remains the EU GMP Guide for the whole of the UK, which throws up a number of anomalies. There are some published UK guidelines covering the GMP- and GDP-related changes as a result of new UK legislation such as the role of the RPi mentioned earlier.
- A batch of marketed product QP-certified in any part of UK in accordance with the relevant MA permits release into all parts of the UK.
- A batch of marketed product imported into UK from the EEA, including a batch imported into EEA from a third country, can continue to be imported by a WDAH provided that they have been tested (if necessary) and QP-certified in the EEA. If the WDAH is located in GB, an RPi has to be nominated on the WDA whose function is to ensure that a QP within EEA has certified the batch in accordance with UK requirements prior to importation into GB. In all other cases, import can only occur through a UK manufacturing/Import Authorisation Holder (MIAH) and subject to QP certification in the UK.
- A batch of marketed product imported from a non-EEA country has to be imported by a MIAH and must be tested in the UK unless an MRA waiver applies.
- A batch of marketed product exported from the UK must continue to be QP certified in the UK although certification in GB no longer allows release onto the EEA market. A batch manufactured in, or imported and tested (if necessary) in, NI can be released onto the EEA market if it has been certified by a QP located in NI in accordance with the relevant MA.
- Official Control Laboratory "Batch Release" (OCABR) still applies in UK for relevant products. Only certificates from the National Institute of Biological Standards and Control (NIBSC) or an MRA partner (currently Israel and Switzerland) are accepted in UK. Batches of product subject to OCABR exported from any part of UK to EEA will require a certificate from an EEA or MRA partner official laboratory prior to release in EEA.
- The MAH for a UK MA can be established in the UK or the EEA. This applies also for veterinary products including NI MAs or GB MAs noting that establishment in GB is one of the temporary derogations mentioned earlier.
- In the case of products for human use, EU safety features (in practice the unique identifier) must **not** appear on the packaging destined for any part of UK. Other coding may be permitted in the MA.
- All product subject to a MA for human use and placed onto the UK market must be labelled "UK only".

- Joint packs between UK and EEA are not allowed in the case of products for human use. Any shared information on the outer packaging must be removed although shared information is permitted for the inner packaging.
- The placing of "UK only" labelled product onto the market of an EEA member state is subject to penalties.
- A batch of IMP QP-certified in any part of UK in accordance with the relevant Clinical Trial Application (CTA) can be supplied to trial sites in all parts of the UK, subject to regulatory release by the sponsor. An anomaly exists here because according to Regulation (EU) 2014/536, as amended in order to provide a permanent derogation for supply between GB and NI, batches destined for NI explicitly require certification in accordance with art. 63(1) of the same Regulation, whereas UK legislation still refers to Directive 2003/94/EC.
- A MIA is required to import IMPs from EEA into GB but if the batch has been QP-certified in EEA, the QP on the GB MIA can rely on that certification and so be relieved from re-certifying.
- In the case of NI, IMPs imported from the EEA can be move directly to sponsors or trial sites (subject to regulatory release by the sponsor) without a MIA provided batches have been QP-certified in EEA.
- IMPs imported into UK from non-EEA countries must be through a MIAH.
- A batch of IMP exported from UK must continue to be QP certified in the UK although certification by a QP in GB no longer allows release to sponsors or trial sites in the EEA. A batch manufactured in, or imported into NI can be released directly to trial sites in the EEA if they have been certified by a QP located in NI in accordance with the relevant CTA (but see the anomaly mentioned above).
- The QP on a UK MIA must reside in UK but an exception applies in the case of a MIAH whose role is limited to importation of IMPs from EEA. In this case the QP can reside in EEA. Product specific flexibilities may also apply in this regard in the case of the UK's Early Access to Medicines Scheme.
- A sponsor for a clinical trial in the UK can be established in the UK or EEA.
- Exports to EEA of active substances manufactured in GB need to be accompanied by a Written Confirmation from the UK authorities. This is not required for active substances manufactured in NI and supplied from a registered manufacturer or distributer in NI.

The MHRA has published a number of useful guidelines which give much more detail on many of the topics above. Despite the changes outlined in this chapter, the role of the UK QP remains fundamentally the same as before given the GMP rules themselves are essentially unchanged. There has been a recent minor modification to UK legislation that permits product specific modifications to QP duties with respect to the Early Access to Medicines Scheme. MAs will be different, especially with respect to labelling. A confounding aspect is that GMP legislation applicable to UK is still based on Directive 2003/94/EC whereas the current EU GMP Guide remains the official guidance. This may present some anomalies although it is unclear whether this will cause significant problems in practice. It does however present a conundrum for certification by a QP in NI when exporting to EEA or for QPs in GB certifying IMPs which could be supplied to NI. The UK labelling requirements for IMPs are adaptable because UK legislation still refers to art. 15 of

Directive 2003/94/EC. This provides flexibility for supply to UK trial sites but obviously does not extend to IMPs destined for trials in the EEA.

Looking now at the practical outcome from the perspective of QPs operating in the EEA and supplying or receiving product from the UK (some of the rules with respect to labelling are repeated as responsibilities are likely to be shared):

- In general NI can be handled in the same way as a member state with some key exceptions:
    - EU unique identifiers do not apply and must not appear on the outer packaging as with the rest of the UK.
    - There is no NI official laboratory recognised by EEA for OCABR.
    - NI can receive products from GB without NI QP oversight or import testing in NI, unlike an EEA member state, but only on condition that the goods remain exclusively in NI. Such products cannot then move to EEA without QP certification and testing (where necessary) in NI or the EEA.
    - QP certification in NI allows release into GB without oversight by an RPi or a QP in GB, unlike an EEA member state.
- Marketed product and IMPs imported into the EEA from GB must be done through a MIAH and must be batch tested (where applicable) in EEA, QP certified in EEA and, where necessary, given an EEA OCABR certificate. The Mutual Recognition Agreement provided in Annex 12 of the EU-UK Trade and Cooperation agreement does not extend to recognition by EU of batch testing carried out in UK including by its official laboratory, NIBSC.
- Regulation (EU) 2023/1182, amending Directive 2001/83/EC, requires QPs in EEA who certify batches of marketed product for human use destined for any part of the UK to ensure that no EU unique identifier is visible on the packaging. **This is a new legal responsibility of the EEA QP**. It would be expected that the risk of non-compliance will diminish over time as legacy packaging components are consumed. It is permissible for a barcode to appear on the packaging provided it is not one recognised by the EU repositories system. Distributors exporting to the UK should be aware that the derogation made in 2022 has been reversed and that now Unique Identifiers appearing on the packaging of product destined for any part of the UK must be removed. Decommissioning is insufficient.
- "UK Only" labelled packs must not be stored in EU after the batch is physically placed onto the UK market.
- Joint packs between UK and EEA are not allowed for products for human use. Any shared information on the outer packaging must be removed although shared information is permitted for the inner packaging.
- The placing of "UK only" labelled product onto the market of an EEA member is subject to penalties.
- At the time of writing there is no long term solution for veterinary medicinal products being supplied from GB to Cyprus, Malta, NI and RoI. Derogations apply until 31 December 2025. This means that unless an alternative solution is negotiated, MAs and supply chains must be brought into line. Practices in place before UK's departure from EU can only continue until the new deadline.

While it is important for any EEA QP involved in the supply of medicinal products to or from the UK to be aware of the above changes, again it can be said that with the exception of the new duty concerning the unique identifier, the responsibility of the QP is unchanged although practices, will have changed when dealing with GB, since it is now a third country with no MRA covering batch certification or testing. There is however, a subtle difference that comes into play affecting QPs certifying batches destined for UK compared to certifying batches destined for other third countries. EEA QP certification is recognised in UK and allows marketed product and IMPs to be to be released onto the NI market or supplied directly to trial sites (subject to regulatory release by the sponsor), as applicable. For GB the RPi of a WDAH is responsible for ensuring that the EEA QP has met the relevant UK MA requirements. In the case of IMPs the QP of the UK MIAH fulfils a similar role. This will require certification that a third country MA or CTA has been complied with so EEA QPs should be familiar with the supply chain and liaise with the relevant UK counterparts to ensure that the GMP contractual arrangements are fit for purpose.

New UK rules will doubtless be introduced as time progresses. Significant further changes in the regulation of clinical trials in UK are already foreseen. It is unlikely that there will be significant divergence in GMP guidelines given that the UK remains in PIC/S. In the meantime, developments involving the EU to address the continuing problems in Cyprus, Malta, NI and the RoI with veterinary medicinal products are anticipated. Meanwhile, Regulation (EU) 2019/4, although applicable to NI, is not actually implemented there. Finally, there are still political objections to the Ireland/Northern Ireland Protocol unresolved by the Windsor Framework so this chapter may need to be updated again in future.

4.3.5 Importation from third country and QP responsibilities

Importation of medicinal products falls under the definition of manufacturing. In doing so a MIA and a QP is required for all parties involved in activities related to importation from third countries.

Annex 21 is the applicable GMP guidance for importation into EU/EEA. Importation is defined in Annex 21 as

> *… the term importation refers to the action of physically bringing a medicinal product, from outside the territory of EEA/EU; …*

As far as EU is concerned there is an exception to this rule with respect to Northern Ireland as a result of the Northern Ireland/Ireland Protocol. More information on the impact of the departure of UK from EU is given in section 4.3.4. In addition, UK based on the shared history and GMP rules with the EU classifies importation from EU/EEA differently than importation from other countries. Although Annex 21 is not applicable for importation into Great Britain, it is applicable for imports into Northern Ireland although some temporary derogations, which will become permanent (see section 4.3.4), apply to movement of medicinal products from Great Britain to Northern Ireland.

Fiscal imports defined as solely cross-border financial transactions are out of scope of Annex 21. EU is not harmonized (yet) on whether GMP rules apply to fiscal imports or not. National rules apply and the legislation of several member states requires QP certification of fiscal importation.

Annex 21 requires that a batch must be physically on EU territory and cleared by customs before certification may happen:

> *Qualified Person (QP) certification or confirmation, as appropriate, of a batch of a medicinal product takes place only after physical importation and custom clearance into the customs territory of an EU/EEA State.*

If the imported product is not yet the final product and imported for additional manufacturing activities within the EU, QP confirmation upon importation is required prior to further manufacturing.

Importation rules including Annex 21 apply even when the supply chain starts within EU but then leaves the EU and is later imported back into the EU. Importation may therefore happen more than once with the same batch and all Annex 21 requirements need to be met prior to certification or confirmation each time, as appropriate.

Importation activities include holding and storage of product, sampling for and performing of importation testing, storage of retention and references samples and certification by a QP after completion of testing. If these (and other) tasks upon importation are executed in different legal entities each legal entity must hold its own MIA. The roles and responsibilities of each MIA holder must be defined in a technical agreement agreed by all parties involved.

Annex 21 defines only two potential parties with associated responsibilities involved in importation activities, the real set-up may be more complicated:

> *a) Site of Physical Importation.*
>
> *b) Site of QP certification of imported medicinal products or QP confirmation for bulk or intermediate products undergoing further processing, as appropriate.*

Other requirements defined by Annex 21 specific for importers and their QPs include documentation of transportation up to the point of physical importation, procurement documentation, customs clearance documentation, availability of full batch records in a language understood by the QP and additional considerations for product quality reviews.

5 Organisational Duties to be established by the Company of the QP

To perform the duties and the responsibilities, a QP needs support from the company and its senior management. The following organisational tasks should be implemented:

1) The senior management should be actively involved in the implementation, maintenance, and further development of the Pharmaceutical Quality System ensuring access to all relevant documentation, data, and information to the QP.
2) A clear job description should be in place defining the responsibilities of the QP and the relationship to senior management, other departments, responsible managers and especially to the Head of Production and the Head of Quality Control and – if appropriate – the Head of Quality Assurance and other QPs. Any responsibilities in addition to the statutory duties of the QP should be clearly identified.
3) The QP should always have access to the Marketing Authorisation Dossier(s) and should be informed about all dossier changes that have a bearing on the QP's responsibilities.

6 Professional Development/Training

6.1 Knowledge, Skills, and Continuous Training

The requirement for ongoing training for QPs is given in Annex 16 to the EU GMP Guide

> *"1.2 Any QP involved in the certification, or confirmation of a batch must have detailed knowledge of the steps for which they are taking responsibility. The QPs should be able to prove their continuous training regarding the product type, production processes, technical advances and changes to GMP."*

QPs taking responsibility for certification for clinical trials have to consider GMP for IMPs and should

> *"be appropriately trained in the requirements specific to these types of product"*

In addition

> *"The qualified person that certifies the finished batch of investigational medicinal products for use in the clinical trial should […] have a broad knowledge of pharmaceutical development, clinical trial processes and supply chain of the batch concerned."*

Also, GMP Part IV for ATMPs is very specific on the knowledge requirements for the type of product within the many different types of ATMP covered by the definition of ATMPs:

> *11.12. In addition to having the qualification requirements provided for under Article 49 of Directive 2001/83, QPs responsible for ATMPs should have training and*

experience relevant to the specific characteristics of these products, including cell and tissue biology, biotechnological techniques, cell processing, characterization and potency testing. QPs should have detailed knowledge of the type of ATMP and manufacturing steps for which they are taking responsibility.

Last but not least, it is the QP's personal professional responsibility and decision to ensure that he/she has the appropriate level of knowledge and up-to-date training to accept a QP assignment and to maintain training once assigned and accepted.

However, there are no specific requirements regarding the content of the continuous training defined in the EU rules.

Please be aware about national expectations in member states on continuous training to maintain professional status and specifically QP professional development.

It is important that a Qualified Person should have a detailed knowledge of Quality Control.

In addition to these skills several additional areas are also relevant for a Qualified Person in order to fulfil the duties defined within Directive 2001/83/EC, Regulation 2019/6 and Regulation 536/2014 as well as the guidance given in Annex 16 to the EU GMP Guide.

The following table lists proposed knowledge and skills. This list serves as a basis for defining the elements of a QP's continuous training and we recommend that 3-5 of the "Basic knowledge and skills training" areas in the following table are covered per year – in-house or by external trainers or through participation in public professional courses and conferences. A limitation of the QP´s training to elements of the PQS as defined and implemented by the QP´s employer cannot be considered sufficient to maintain an appropriate level of current knowledge.

Training requirements	**Training on a regular basis (at least annually)**	**Basic knowledge and skills: training needs and frequency depending on main tasks and responsibilities (at least once)**
Applicable international GMP guidance and legislation	**X**	
Applicable national GMP guidance and legislation	**X**	
General and specific GMP requirements	**X**	

Training requirements	Training on a regular basis (at least annually)	Basic knowledge and skills: training needs and frequency depending on main tasks and responsibilities (at least once)
Marketing and manufacturing authorisation systems and their relationship/ regulatory affairs		x
Microbiology		x
Process engineering/ HVAC Systems		x
Utilities		x
Analytical equipment and instrumentation		x
Analytical methods and validation		x
Computer systems and validation		x
(New) Pharmaceutical technologies and production		x
Manufacturing, quality control, release and distribution of IMPs		x
active substance: technology, equipment, processes		x
Process validation		x
Instrument and equipment qualification, calibration, maintenance		x
Storage and distribution		x
Pharmacovigilance		x
Import and export of medicinal products		x
Complaint handling and recalls		x
OOS/ Deviation handling and failure investigation		x
Change Management/ Change Control		x
Risk analysis and risk management		x
Stability testing		x

Training requirements	Training on a regular basis (at least annually)	Basic knowledge and skills: training needs and frequency depending on main tasks and responsibilities (at least once)
Good documentation practice and review		x
Serialization		x
Product Quality Review		x
Data Integrity/ Data Governance		x
Auditing techniques		x
Inspection preparation		x
Communication skills, time and conflict management		x
basic knowledge and skills related to statistics, monitoring and trending		X
Electronic data/computer systems/cloud, etc.		X
Structure, content and variation procedures on Marketing Authorization and Clinical Trial Application		X

As one of their main tasks, the European QP Association supports its members with their continuous professional development.

6.2 Continuous Training Needs Assessment

For all QPs the environment and legal references are under continuous change and development. Irrespective from QPs changing their assignment continuous training needs arise from fast changes in regulations, supply chain, or technology.

Training needs may be adapted or even increased if a Qualified Person faces other tasks or assignments in their daily business. Taking over QP responsibilities for the first time or getting new responsibilities for different products, other areas of pharmaceutical technology or different dosage forms will call for additional training.

For example, if a QP was responsible for the release of solid oral drugs and then takes responsibility with respect to parenteral or biotech products, new training activities should meet the needs of the new tasks.

Training must be completed prior to execution of the first certification. Appropriate and sufficient time for such training should be ensured. This must be assessed

based on the personal experience of the QP and is a central responsibility of the QPs themselves. It is therefore a misconception that a QP can routinely execute certification the day after assignment without completing appropriate training activities beforehand.

7 QPs for manufacturers of active substance

The QP's responsibilities embrace not only the finished medicinal product but also matters related to starting materials including active substances. The legally binding requirements for active substance manufacturers are laid down in Regulation 1252/2014, which covers active substances for human use. Part 2 of the EU GMP Guide provides interpretive guidelines based on ICH Q7 but also applicable to veterinary active substances in EU. The EU implementation of ICH Q7 includes additional expectations on applied risk management. No QP is required for active substance manufacturers according to EU legislation and neither is there any defined role for the QP. In regulatory procedures the QP of the finished product manufacturer or importer (for marketed products) signs QP declarations and when certifying batches takes responsibility for GMP compliance of the active substance supply chain.

Despite this several member states have introduced at the national level the requirement of a manufacturing license for biotech active substances and in some cases also for chemical active substances including the requirement for a QP. Batches of such APIs have to be certified by the respective QP at the stage of API manufacture (see also FAQ for country specific information).

This provides several unresolved areas of contradiction:

- QPs taking responsibility for partial manufacturing according to definitions given in Annex 16 perform confirmation not certification. This means that batch confirmation may follow an API batch certification,
- Annex 16 as the guideline for certifying batches cannot be easily applied to API batches. A GMP Guideline to support the activity of certification of API batches does not exist.
- Shipments of API batches between member states with unharmonized rules may be accompanied/not accompanied by a QP batch certificate although the recipient in the neighbouring country may expect the opposite based on local law.
- Importation from outside EU/EEA of such API batches may require QP certification upon importation in one member state and no such formal step in another member state.

Annex 16 can be taken as a feasible although not mandatory guide for developing a local process for certification of API batches. In case of cross-border shipments within EU, upfront clarification between the parties within Technical Agreements is highly recommended.