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## ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

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## GDP for APIs:

### “How to do” Document

Interpretation of the WHO Guideline GOOD TRADE AND DISTRIBUTION PRACTICES FOR PHARMACEUTICAL STARTING MATERIALS and the EU GUIDELINES ON THE PRINCIPLES OF GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE

*Version 2 – March 2019*

## Preamble

The original version of this guidance document has been compiled by a subdivision of the APIC Good Distribution Practice Task Force on behalf of the Active Pharmaceutical Ingredient Committee (APIC) of CEFIC.

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## **Chapter 1 Introduction**

### **1.1 Objective**

#### **APIC Good Distribution Practices for Active Pharmaceutical Ingredients "How to do" Document**

##### **Historical Background**

In the past there have been no separate regulations on GDP for distributors of APIs.

The GMP Part II /ICH Q7 for the manufacturers of API have been the only Guidelines partially covering GDP for API. These affect more the handling of APIs at the manufacturing site, but not the distribution outside the site.

The WHO Guide on GTDP for Pharmaceutical Starting Materials has been a reference document with broad acceptance in industry on a voluntary basis.

With the EU Falsified Medicines Directive (Directive 2011/62/EU), the application of GDP for APIs is becoming mandatory. The EU Commissions Guideline on principles of Good Distribution practices of active substances for medicinal products for human use issued on 19 March 2015 is the first regulatory binding document specifically for distribution activities of APIs.

##### **ACKNOWLEDGEMENTS**

This document was developed by representatives of member companies of the Active Pharmaceutical Ingredients Committee (APIC).

##### **Purpose of the Document**

This document was written by experts from the European Industry (CEFIC APIC).

It is essentially an interpretation of "how to" implement the EU Commissions Guideline on principles of Good Distribution Practices (GDP) of active substances for medicinal products for human use, published by the European Commission DG SANCO on 19 March 2015, based on practical experience.

This guide provides in particular additional explanatory notes to the EU Commissions Guideline on principles of Good Distribution practices of active substances for medicinal products for human use.

The explanatory notes in this guide are the views of The Active Pharmaceutical Ingredients Committee (APIC) and not necessarily those of the European Commission or WHO.

This document does not intend to provide an exhaustive list of "how to" comply with the requirements and recommendations mentioned above.

It does provide examples of potential solutions and more detail on how requirements and recommendations can be met and /or interpreted.

The word « should » is used several times in the EU Guideline on the Principles of GDP for APIs. It indicates requirements and recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative that can be shown to provide at least an equivalent level of quality assurance. Hence, « should » does not mean that because it is only a «should», and not a «must», then this requirement does not have to be met.

This document is meant to be a "living document" to describe current practice and to help with the implementation of the EU Commissions Guideline on principles of GDP of active substances for medicinal products for human use. Suggestions and/or questions from industry or regulators to CEFIC APIC (<http://apic.cefic.org>) are welcomed. These will be discussed regularly by the industry experts and clarifications and improvements incorporated into the document.

This document has been written to provide guidance for those companies involved in the distribution of active pharmaceutical ingredients.

Examples based on practical experience are provided to facilitate the application of GDP. However, alternative approaches may be acceptable.

### **Regulatory Requirements**

According to Article 46 of Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, companies should be aware to apply the following to prevent the entry into the legal supply chain of falsified medicinal products.

The holder of a manufacturing authorization shall at least be obliged to use only active substances, which have been manufactured in accordance with good manufacturing practice for active substances and distributed in accordance with good distribution practices for active substances. Distributors of active substances may, according to Article 111 of the same directive, become subject to inspections by the competent authority.

Furthermore, the holder of the manufacturing authorization shall verify compliance with good manufacturing practices and good distribution practices by conducting audits at the manufacturer and distributors sites of active substances.

## **1.2 Regulatory applicability**

EU guideline is applicable to distribution\* of active substances for human use within EA countries since 21 September 2015.

*\*See paragraph 1.2 of the EU Commissions Guideline on principles of Good Distribution practices of active substances for medicinal products for human use*

## **Chapter 2 Scope**

According to the European Falsified Medicines Directive, Manufacturing Authorization Holders are responsible to use only active substances which have been distributed in accordance with Good Distribution Practices for active substances. This is one significantly new requirement in the EU Falsified Medicines Directive.

In the EU Commissions Guideline on principles of Good Distribution Practices of active substances for medicinal products for human use, the scope is defined as follows:

- 1.** These guidelines apply to distribution of active substances, as defined in Article 1(3a) of Directive 2001/83/EC, for medicinal products for human use. According to that provision, an active substance is any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.
- 2.** In view of these guidelines, the distribution of active substances for medicinal products for human use (hereafter 'active substances') is defined as the procuring, importing, holding, supplying or exporting active substances.
- 3.** Activities consisting of re-packaging, re-labelling or dividing up of active substances are manufacturing activities and as such are subject to the guidelines on Good Manufacturing Practice of active substances."

### **Chapter 3 General Considerations**

This document is based on the EU Commissions Guideline on principles of Good Distribution Practices of active substances for medicinal products for human use, and therefore it follows the same structure.

This APIC document provides guidance on practical approaches with examples on the application of EU Commissions GDP guideline for API principles.

The APIC document applies to steps in the distribution/supply chain starting from the point at which an API is transferred outside the control of the original manufacturer's material management system.

Some sections and/or sub-sections in this document may not apply to all involved parties. This document is meant to provide guidance in the application of the GDP; however, alternative approaches may be acceptable.

Specific guidance on storage conditions are described in regulatory documents as USP chapter <659> Packaging and Storage Requirements and EMEA Guideline on Declaration of Storage Conditions CPMP/QWP/609/96/Rev 2 EMEA 2007.

### **Chapter 4 Good Distribution Practices for API**

#### **4.1 How to use the "How to do" - Document**

The requirements have been interpreted for APIs by APIC taking into consideration the requirements given in ICH Q7 / APIC "How to do" Document on ICH Q7. Reference has also been made to the WHO technical report annex 6 on Good trade and distribution practices for starting materials.

The interpretation of APIC must be read and considered in conjunction with the requirements of the EU GDP guideline. The references in the other columns should help the user of this document to find the respective paragraphs in the APIC "How to do" document on ICH Q7 and WHO TRS report

The application of the interpretations in this table should always take in consideration the potential inherent risks related to the API or the conditions under which the API is handled and distributed. The risk assessments should be based on sound scientific evaluation and appropriate risk management tools, as referenced for example in ICH Q9.

## 4.2 "How to do" - Document

EU Guidelines on GDP 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use	APIC	ICH Q7 / APIC „How to do” Document on ICH Q7	WHO TRS 886 annex 06
<b>Introduction</b>			
These guidelines are based on the fourth paragraph of Article 47 of Directive 2001/83/EC (1). (1) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67)			
They follow the same principles that underlies the guidelines of Eudralex Volume 4, Part II, Chapter 17, with regard to the distribution of active substances and the Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use (2). (2) OJ C 343, 23.11.2013, p. 1	Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use reference is to provide overall definition of the good distribution practices, similarity not applicable to API		
These guidelines provide stand-alone guidance on Good Distribution Practice (GDP) for importers and distributors of active substances for medicinal products for human use. They complement the rules on distribution set out in the guidelines of EudraLex Volume 4, Part II, and apply also to distributors of active substances manufactured by themselves.			
Any manufacturing activities in relation to active substances, including re-packaging, re-labelling or dividing up, are subject to Commission Delegated Regulation (EU) No 1252/2014 (3) and EudraLex Volume 4, Part II. (3) 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 (OJ L 337, 25.11.2014, p1	Repackaging/relabeling or dividing-up activities made during distribution should comply with requirements from Commission Delegated Regulation (EU) No 1252/2014 and EudraLex Volume 4, Part II.		
Additional requirements apply to the importation of active substances, as laid down in Article 46b of Directive 2001/83/EC.	It is recommended to describe specific requirements (e.g. national requirements) to import API		
Distributors of active substances for medicinal products for human use should follow these guidelines as of 21 September 2015.			



EU Guidelines on GDP 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use	APIC	ICH Q7 / APIC „How to do“ Document on ICH Q7	WHO TRS 886 annex 06
<b>Chapter 1 - Scope</b>			
<p><b>1.1</b> These guidelines apply to distribution of active substances, as defined in Article 1(3a) of Directive 2001/83/EC, for medicinal products for human use. According to that provision, an active substance is any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.</p>	<p>Transportation companies do not need to be certified by authorities. However, they should follow parts of the GDP guideline relevant to their activities.</p> <p>It is the responsibility of distributors (GDP certified parties contracting transporters) to verify that selected transporting companies are able to apply these requirements like quality system, appropriate personnel, good documentation practices.... In relation to the criticality of their activities.</p>		
<p><b>1.2</b> For the purpose of these guidelines, distribution of active substances shall comprise all activities consisting of procuring, importing, holding, supplying or exporting active substances, apart from brokering.</p>	<p>This guideline only applies to distribution activities including transportation (meaning that no container of product is opened during such activities).</p> <p>Brokering activities definitions provided in the EU guideline: All activities in relation to the sale or purchase of active substances that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.</p>		
<p><b>1.3</b> These guidelines do not apply to intermediates of active substances.</p>	<p>The guideline does not apply to intermediates or starting materials. It only applies to active substances.</p> <p>According to EU Guideline on GMP for medicinal products for human and veterinary use; volume 4 part 1 chapter 5 (5.29) supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance</p> <p>However, this requirement should be referred to as Manufacturing Supply Chain traceability up to</p>		

EU Guidelines on GDP 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use	APIC	ICH Q7 / APIC „How to do” Document on ICH Q7	WHO TRS 886 annex 06
	starting material and should not be considered Distribution Supply Chain Traceability starting from final API.		
<b>Chapter 2 – Quality System</b> Damage management – responsibility for material to be distributed			
<b>2.1</b> Distributors of active substances should develop and maintain a quality system setting out responsibilities, processes and risk management principles. Examples of the processes and applications of quality risk management can be found in EudraLex Volume 4, Part III: GMP related documents, ICH guideline Q9 on Quality Risk Management (ICH Q9).	Parties involved in the distribution of APIs should establish a Quality Management System to man- age the quality of their products and services, to maintain the original quality of the APIs. As an es- sential prerequisite for any Quality Management System, the top management should elaborate a corporate quality policy. Parties involved should share responsibility for assuring that the API pro- vided by the distributor conforms to the mutually agreed specification requirements of the pharma- ceutical manufacturer and/or is suitable for the intended use of the API. Quality Risk Management principles should be in- tegrated into the quality management system.	2. QUALITY MANAGEMENT 2.1 Principle Chapter 2.11 Chapter 17.30 Chapter 17.11	Chapter1 with 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9 Chapter 2.2
<b>2.2</b> The quality system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. It should ensure that: <b>(i)</b> active substances are procured, imported, held, sup- plied or exported in a way that is compliant with the re- quirements of GDP for active substances;	A system should be in place to control documents and data that relate to the requirements of the applicable Quality System. The Quality Manual should include as a minimum the following ele- ments: - scope of the Quality Management System, - organizational structure including description of responsibility of top management, - written procedures, processes and resources or reference to them, and - a description of the sequence and interaction between the procedures and departmental func- tions. The Quality Management System should also in- clude a procedure to verify that any supplier of APIs, or relevant service providers has the capa-	Chapter 17.3 Chapter 2.1 Chapter 3.1	Chapter 1.4 Chapter 13.4 (contract activities) Chapter 4.1 Chapter 6 with 6.1, 6.2 Chapter 1.6, 1.7

EU Guidelines on GDP 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use	APIC	ICH Q7 / APIC „How to do” Document on ICH Q7	WHO TRS 886 annex 06
	<p>bility to consistently meet previously agreed re- quirements. This may include periodic audits of the service providers. The related computerized system ensuring the required traceability and data integrity should be properly installed, qualified and controlled.</p>		
<b>(ii)</b> management responsibilities are clearly specified;	Refer to chapter 3 for personnel	Chapter 2.10 Chapter 2.13 Chapters 2.2 and 2.3	Chapter 13.4 (contract activities) Chapter 1.4, 1.5 Chapter 1.2 Chapter 2.2
<b>(iii)</b> active substances are delivered to the right recipi- ents within a satisfactory time period;	There should be an organization in place to en- sure the product is shipped to the right customer. Note: Satisfactory time outlined in the supply agreement or following service level agreement should be determined considering the customer will not be into shortage (refer to chapter 6 oper- ations).	Chapter 17 Chapter 10.24	Chapter 13.4 (contract activities)
<b>(iv)</b> records are made contemporaneously;	Compliance with good documentation practices, refer to <b>chapter 4</b> Documentation.	Chapter 2.15 <b>Chapter 6.10 (APIC):</b> ALL data generated should follow ALCOA (At- tributable, Legible, Current, Original, Accurate) principles	Chapter 6 with 6.1, 6.2
<b>(v)</b> deviations from established procedures are docu- mented and investigated;	<p>The conclusions of deviations with impact on the product should be risk based. If there are deviations with potential impact on the product quality (e.g. the storage conditions, damages .....,) the API manufacturer should pro- vide support as needed. There should be a communication process in place between the distributor and the API manu- facturer regarding deviations occurring at distribu- tor level, to ensure that the reporting of the de- viation is performed in a timely manner. Quality agreements should be in place to cover such re- quirements and responsibilities. Investigations should typically be performed by the distributor.</p>	<p>Chapter 2.16, chapter 2.13 <b>Chapter 10.21 (APIC):</b> Appropriate protective outer packaging and a reliable shipper should be chosen to avoid damage during transport. For sensitive prod- ucts special shipping conditions should also be specified. Records of those conditions should be available to the manufacturer on demand and at any time. The shipping conditions records should be re- viewed for compliance to the acceptance crite- ria on arrival. If deviations occurred an investi- gation should be initiated and actions justified and documented.</p>	Chapter 11.1, chapter 11.2

EU Guidelines on GDP 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use	APIC	ICH Q7 / APIC „How to do” Document on ICH Q7	WHO TRS 886 annex 06
	Drug product customer involvement at this step may be needed depending on the INCOTERM conditions regarding deviations during the distribution of APIs. Management of deviations and damages during storage and transport should be handled with all of the relevant parties in the supply chain lane.		
<b>(vi)</b> appropriate corrective and preventive actions, commonly known as ‘CAPA’, are taken to correct deviations and prevent them in line with the principles of quality risk management;	Self-explanatory	Chapter 2.16 Chapter 2.17	Chapter 1.9 Chapter 11.2
<b>(vii)</b> changes that may affect the storage and distribution of active substances are evaluated.	There should be a communication process in place to ensure that any change at distributor level (changes to what has been committed and agreed in the quality agreement) will be assessed by the manufacturer of the API prior to implementing the change and communicated to the customer in a timely fashion.	Chapter 17.60 Chapter 13	Chapter 6.1 Chapter 7.8
<b>2.3</b> The size, structure and complexity of the distributor’s activities should be taken into consideration when developing or modifying the quality system.	Appropriate organisation in place with adequate number of resources	--	Chapter 12.3 Chapter 13 with 13.1, 13.2, 13.3, 13.4, 13.5
<b>Chapter 3 – Personnel</b>			
<b>3.1</b> The distributor should designate a person at each location where distribution activities are performed who should have defined authority and responsibility for ensuring that a quality system is implemented and maintained. The designated person should fulfil his responsibilities personally. The designated person can delegate duties but not responsibilities.	There should be an organization in place to implement and maintain the quality system with a designated representative at each location. The main quality responsibilities should not be delegated. These responsibilities should be described in writing e.g. in form of a contract/agreement between the concerned parties.	<b>Chapter 2.10</b> : Company management should empower Quality responsibility <b>Chapter 2.2:</b> Responsibilities of the Quality Unit(s)	<b>Chapter 1.2:</b> an independent quality unit (or designee), which is responsible for all quality-related matters
<b>3.2</b> The responsibilities of all personnel involved in the distribution of active substances should be specified in writing. The personnel should be trained on the requirements of GDP for active substances. They should have the appropriate competence and experience to ensure	The organization should be documented in an organizational chart with clear indication of personnel responsible for distribution activities. Levels of authorization should be clearly defined in job descriptions.	<b>Chapter 3.1:</b> Personnel qualifications <b>Chapter 3.11:</b> the responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing	<b>Chapter 2.1:</b> There should be an adequate organizational structure Chapter 2.2: Individual responsibilities should be clearly defined

EU Guidelines on GDP 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use	APIC	ICH Q7 / APIC „How to do“ Document on ICH Q7	WHO TRS 886 annex 06
that active substances are properly handled, stored and distributed.	There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise activities concerning API distribution. A system for planning, documentation and follow up of the training should be in place.	<b>Chapter 3.12:</b> Training should range from “basic introduction” training through to job specific training	<b>Chapter 2.3:</b> All personnel should be aware of the principles of the appropriate guidelines, including but not limited to GTDP
<b>3.3</b> Personnel should receive initial and continuing training relevant to their role, based on written procedures and in accordance with a written training program.	Involved personnel should be trained in the handling of the material taking the requirement of the material safety data sheet into account. Personnel should be trained on the GDP principles and the chapters relevant for their field of responsibility. For transport companies, the training program should fit the intended activities within their responsibility All involved personnel should receive initial and regular follow-up training according to the potential impact of the activities on the API. Quality standards applied should be part of a regular training program provided by qualified individuals and the training should be documented.	<b>Chapter 3.12:</b> The need for GMP training should be periodically evaluated, conducted if needed and documented as part of the individual training program of the employee	<b>Chapter 2.2:</b> Personnel should be suitably qualified, trained <b>Chapter 2.4:</b> Personnel should receive initial and continuing training relevant to their tasks. <b>Chapter 2.5:</b> Personnel dealing with hazardous materials (...) should be given specific training
<b>3.4</b> A record of all training should be kept, and the effectiveness of training should be periodically assessed and documented.	Records should be maintained listing the name, address, and qualifications of any contracted service provider and the type of service they provide.	<b>Chapter 3.12:</b> GMP training should be scheduled regularly and conducted according to a plan. Training records should indicate names of the people trained, subject of the training in keywords, date of the training and name of the trainer.	<b>Chapter 2.4:</b> Training records should be maintained
<b>Chapter 4 - Documentation</b>			
<b>4.1</b> Documentation comprises all written procedures, instructions, contracts, records and data, in paper or in electronic form. Documentation should be readily available or retrievable. All documentation related to compliance of the distributor with these guidelines should be made available on request of competent authorities.	Self-explanatory If computerized systems are used at distributor level, then the computer systems should be validated.	<b>Chapter 6.15 (ICH Q7)</b> During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.	<b>Chapter 6.10</b> Records must be kept and must be readily available upon request in accordance with GSP (2).

EU Guidelines on GDP 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use	APIC	ICH Q7 / APIC „How to do“ Document on ICH Q7	WHO TRS 886 annex 06
		<p><b>Chapter 6.16 (ICH Q7)</b> Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records...</p> <p>Chapter 6.11 and 6.12 (APIC)</p>	
<p><b>4.2</b> Documentation should be sufficiently comprehensive with respect to the scope of the distributor's activities and in a language understood by personnel. It should be written in clear, unambiguous language and be free from errors.</p>	Self-explanatory	--	<p><b>Chapter 6.2</b> Documents should have unambiguous contents: their title, nature and purpose should be clearly stated. They should be laid out in an orderly manner and be easy to check.</p>
<p><b>4.3</b> Any alteration made in the documentation should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.</p>	Self-explanatory Refer to good documentation practices for data in paper and in electronic form.	<p><b>Chapter 6.14 (APIC)</b> No pencil, no white out and no crossing out and no obliteration of an original entry that is subsequently corrected.</p> <p><b>Chapter 6.18 (ICH Q7)</b> If electronic signatures are used on documents, they should be authenticated and secure.</p>	--
<p><b>4.4</b> Each employee should have ready access to all necessary documentation for the tasks executed.</p>	Self-explanatory	--	--
<p><b>Procedures</b></p>			
<p><b>4.5</b> Written procedures should describe the distribution activities which affect the quality of the active substances. This could include receipt and checking of deliveries, storage, cleaning and maintenance of the premises (including pest control), recording of the storage conditions, security of stocks on site and of consignments in transit, withdrawal from saleable stock, handling of returned products, recall plans, etc.</p>	Comment: Written procedures need to be in place and respective processes implemented.	Chapter 10.2 (APIC)	<p><b>4.5</b> Written procedures should describe the distribution activities which affect the quality of the active substances. This could include receipt and checking of deliveries, storage, cleaning and maintenance of the premises (including pest control), recording of the storage conditions, security of stocks on site and of consignments in transit, withdrawal from saleable stock, handling of returned products, recall plans, etc.</p>
<p><b>4.6</b> Procedures should be approved, signed and dated by the person responsible for the quality system.</p>	Self-explanatory	Chapter 2.21	<p><b>4.6</b> Procedures should be approved, signed and dated by the person responsible for the quality system.</p>

EU Guidelines on GDP 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use	APIC	ICH Q7 / APIC „How to do“ Document on ICH Q7	WHO TRS 886 annex 06
<p><b>4.7</b> Attention should be paid to the use of valid and approved procedures. Documents should be reviewed regularly and kept up to date.</p> <p>Version control should be applied to procedures. After revision of a document a system should exist to prevent inadvertent use of the superseded version.</p> <p>Superseded or obsolete procedures should be removed from workstations and archived.</p>	<p>(APIC 2014):</p> <p>Procedures on document control should be established.</p> <p>A revision history of documents should be readily available.</p> <p>Changes to procedures should be considered in the training program</p>	<p><b>6.11 (ICH Q7)</b> The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.</p> <p><b>Chapter 6.11 (APIC):</b> Regarding revision of documents, the company should define e.g. in a SOP when and how documents are revised.. If an electronic system is used to control the revision and approval of SOP's the system should be validated and found in compliance with data integrity principles including audit trail.</p> <p>If a paper based system is used this must be managed in a controlled manner with Quality Unit oversight. During the document life cycle the periodical review of its content should be performed and documented. If needed the document should be revised. The revision history of the document shall be traceable over the retention period. Where electronic document management systems are used the details of the document history can be retained in the metadata and so does not have to appear on the document itself</p>	--
<b>Records</b>			
<p><b>4.8</b> Records should be clear, be made at the time each operation is performed and in such a way that all significant activities or events are traceable.</p> <p>Records should be retained for at least 1 year after the expiry date of the active substance batch to which they relate.</p> <p>For active substances with retest dates, records should be retained for at least 3 years after the batch is completely distributed.</p>	<p>Comment:</p> <p>Retention periods of documents should be established. The security and methods of archiving and retrieval of such records should be ensured. Record retention schedule and practices for distribution records should be specified in the quality agreement.</p>	<p><b>6.12 (APIC)</b> It is good industry practice to consider retaining records for the period of time the drug product(s) in which the API was used may be available on the market. )</p>	--
<p><b>4.9</b> Records should be kept of each purchase and sale, showing the date of purchase or supply, name of the active substance, batch number and quantity received or</p>	<p>Comment:</p> <p>Recommendation: In addition to records requested by EU Guidelines on GDP: <u>Quantity of</u></p>	<p><b>6.30 (ICH Q7)</b> Records should be maintained including:</p>	--

EU Guidelines on GDP 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use	APIC	ICH Q7 / APIC „How to do“ Document on ICH Q7	WHO TRS 886 annex 06
<p>supplied, and name and address of the supplier and of the original manufacturer, if not the same, or of the shipping agent and/or the consignee. Records should ensure the traceability of the origin and destination of products, so that all the suppliers of, or those supplied with, an active substance can be identified. Records that should be retained and be available include:</p> <ol style="list-style-type: none"> <li>I. identity of supplier, original manufacturer, shipping agent and/or consignee;</li> <li>II. address of supplier, original manufacturer, shipping agent and/or consignee;</li> <li>III. purchase orders;</li> <li>IV. bills of lading, transportation and distribution records;</li> <li>V. receipt documents;</li> <li>VI. name or designation of active substance;</li> <li>VII. manufacturer's batch number;</li> <li>VIII. certificates of analysis, including those of the original manufacturer;</li> <li>IX. retest or expiry date.</li> </ol>	<p><u>each shipment of each batch</u> should also be retained and be available.</p>	<p>— The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; ...</p> <p><b>Chapter 10.24 (APIC)°:</b> Full traceability for all shipments from the manufacturer to its external customer(s) has to be in place. If APIs or intermediates are delivered to a broker, full traceability has to be ensured by the broker as well according to chapter 17. (Remarks: In this case the final user of the API is unknown to the API producer, therefore full traceability to the end customer should be the duty of the broker).</p> <p>Chapter 17.2</p> <p>Chapter 11.4</p>	
<p>--- (NEW LINE ADDED FOR WHO REQUIREMENTS) ---</p>	<p>A distributor should not change the original title and data of the CoA or other quality documents. Whenever possible, the original manufacturer's documentation should be used, or transcription of data should be verified.</p> <p>The original manufacturing site should be identified by name or unique identifier on the CoA or any other document agreed upon with the customer</p> <p>Comment: Records should be readily available and ensure traceability of supply chain of products/APIs from the origin (manufacturer), via suppliers/distributors, to the destination (purchaser)</p>	<p><b>6.30 (APIC)</b> The objective of this record keeping is to trace the above Materials back to the suppliers production records and trace forward until the API-batch delivered to individual customers in case of any failure occurring in the supply chain.</p>	<p>6.3 Original Certificates of Analysis (COAs) should accompany materials supplied by manufacturers to suppliers. COAs issued by the manufacturer should indicate which results were obtained by testing the original material and which results came from skip lot testing. The use of the Model COA as adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations is recommended (1).</p> <p>6.5 The original manufacturer and intermediaries handling the material</p>



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			should always be traceable and the information available to authorities and end-users, downstream and upstream.
--- (NEW LINE ADDED FOR WHO REQUIREMENTS) ---	API should normally be released according to their specification for shipment. In case of API pending final release testing, API could be shipped under quarantine when authorized by the quality unit, in agreement with customer and according to local legislation. Appropriate controls and documentation should be in place. API should remain in quarantine until full release CoA is obtained by manufacturer.	<b>Chapter 10.20 (APIC):</b> The process of transfer under quarantine should be established. Quality unit of both sites need to approve the shipment under quarantine and the receiving site cannot use the material before a CoA of the batch in scope is issued. Before shipment under quarantine the manufacturing batch record should be reviewed and approved by the quality unit	6.4 Before any material is sold or distributed, the supplier should ensure that the COAs and results are available and that the results are within the required specifications. Alternatively the customer should be informed without delay of the results as soon as these become available. For each shipment the COA should be forwarded to the pharmaceutical product manufacturer.
<b>Additionally:</b>	--	--	6.9 Relevant storage, handling and safety data sheets should be available.
<b>Chapter 5 – Premises and Equipment</b>			
<p><b>5.1</b> Premises and equipment should be suitable and adequate to ensure proper storage, protection from contamination, e.g. narcotics, highly sensitising materials, materials of high pharmacological activity or toxicity, and distribution of active substances. They should be suitably secured to prevent unauthorised access. Monitoring devices that are necessary to guarantee the quality attributes of the active substance should be calibrated according to an approved schedule against certified traceable standards.</p>	<p>Buildings and facilities used in the <u>distribution of APIs</u> should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of handling. Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the product, such equipment can be located outdoors. Equipment should be qualified before use to ensure that it is functioning as intended.</p> <p>There should be defined areas or other control systems for the following activities: receipt, identification and quarantine of incoming products. Sufficient spaces should be available in the warehouses to allow efficient movements without damaging the packaged products as well as to allow for cleaning.</p> <p>Proper access control of the premises should be ensured.</p>	<p><b>Chapter 4.11</b> Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.</p> <p><b>Chapter 4.12</b> Where the equipment itself (e.g. closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.</p> <p><b>Chapter 4.13</b> the flow of materials and personnel through the building or facilities should be designed to prevent mix ups or contamination.</p> <p><b>Chapter 4.14</b> there should be defined areas or other control systems for the following activities :</p> <p>-receipt, identification of materials Quarantine before release or rejection of intermediates and APIs; Holding rejected materials before further disposition (e.g., return, reprocessing or destruction); Storage of released materials;</p>	<p>Premises, including laboratory facilities, must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, cross-contamination, mix ups, build-up of dust, dirt or waste and, in general, any adverse effect on the quality of materials.</p> <p>Measures should be in place to prevent unauthorized persons from entering the premises.</p> <p>Suitable supporting facilities and utilities (such as air control, ventilation and lighting) should be in place and appropriate to the activities performed, in</p>

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	<p>Adequate lighting should be provided in all areas to facilitate cleaning, maintenance and proper operations.</p> <p><i>Comment : also applicable for 6.7 and 6.8</i></p>	<p><b>4.20</b> All utilities that could impact product quality (e.g. heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utilities should be available.</p> <p><b>Chapter 4.50</b> adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.</p> <p><b>Chapter 4.21</b> Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms, dust, humidity and temperature, as appropriate</p> <p><b>Chapter 10.11 (APIC):</b> Acceptable separate storage areas for such activities may solely be marked shelving or floor spaces with the exception of areas for rejected or recalled products in which physical barriers should be utilised to prevent unauthorised use, e.g. locked cages, are-as or rooms. Alternative systems may be computerised stock control with restricted access. These do not require separated areas. Physical separation of non-conforming (e.g. returned material) product is necessary. Separate identified areas should be used.</p> <p><b>Chapter 10.10 (APIC)</b></p>	<p>order to avoid contamination, cross-contamination and degradation of the material. Utilities that could affect product quality should be identified and monitored.</p>
--- (NEW LINE ADDED FOR WHO REQUIREMENTS) ---	Facilities should also be designed to minimize potential contamination. The risk of contamination	<b>Chapter 7.4 storage</b>	<b>Chapter 4.10</b> Where special storage conditions are required (e.g. particular

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	and mix up should also be considered in respect to the flow of products and personnel through the buildings or facilities.	Materials should be stored in a way that the quality of the raw material cannot be negatively influenced taking into account light, time, temperature and humidity. Sufficient space should be available in the warehouses to allow efficient movements without damaging the packaged materials as well as to allow for cleaning. It is good practice to store the material at sufficient distances from walls. The floor of the warehouses should be easy to clean.	<p>temperature, humidity or protection from light) these should be provided, monitored and recorded as appropriate.</p> <p><b>Chapter 4.11</b> Highly active materials, narcotics, other dangerous drugs and substances presenting special risks of abuse, fire or explosion should be stored in safe, dedicated and secure areas. In addition and where applicable, international conventions and national legislation are to be adhered to.</p> <p><b>Chapter 4.12</b> Special attention should be given to the design, use, cleaning and maintenance of all equipment for bulk handling and storage, such as tanks and silos.</p>
--- (NEW LINE ADDED FOR WHO REQUIREMENTS) ---	A set of current drawings should be maintained for facilities and critical installations (e.g. instrumentation and utility systems). Schedules and procedures (including responsibilities) should be established for the preventive maintenance and calibration program of the facility.	<p><b>Chapter 5.16</b> A set of current drawings should be maintained for equipment and critical installations (e.g. instrumentation and utility systems).</p> <p><b>Chapter 5.2 Equipment Maintenance and Cleaning</b></p> <p><b>Chapter 5.20</b> Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.</p> <p><b>Chapter 5.3 Calibration</b></p> <p><b>Chapter 5.30</b> Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of APIs should be calibrated according to written procedures and an established schedule.</p>	<p><b>Chapter 5.1</b> Equipment must be located, designed, constructed, adapted, qualified, used, cleaned and maintained to suit the operations to be carried out.</p> <p>Its layout, design and use should aim to minimize the risk of errors and permit effective cleaning and maintenance so as to avoid cross contamination, build-up of dust or dirt and any adverse effect on the quality of materials.</p> <p><b>5.2</b> Defective equipment should not be used and should either be removed or labelled as defective. Equipment should be disposed of in such a way as to prevent any misuse.</p>

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		<p><b>Chapter 5.31</b> Equipment calibrations should be performed using standards traceable to certified standards, if existing.</p> <p><b>Chapter 5.32</b> Records of these calibrations should be maintained.</p> <p><b>Chapter 5.33</b> The current calibration status of critical equipment should be known and verifiable.</p> <p><b>Chapter 5.34</b> Instruments that do not meet calibration criteria should not be used.</p> <p><b>Chapter 5.35</b> Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the ... API(s) manufactured using this equipment since the last successful calibration.</p>	<p><b>5.3</b> The status of the equipment should be readily identifiable.</p> <p><b>5.9</b> Procedures should be in place for the operation and maintenance of equipment. Lubricants and other materials used on surfaces that come into direct contact with the materials should be of the appropriate grade, e.g. food-grade oil, and should not alter the quality of the materials.</p> <p><b>5.10</b> Washing and cleaning equipment should be chosen and used such that it cannot be a source of contamination.</p> <p><b>Chapter 5.6</b> Balances and other measuring equipment of an appropriate range and precision should be available and should be calibrated in accordance with a suitable schedule.</p>
<b>Chapter 6 – Operations</b>			
<b>Orders</b>			
<p><b>6.1</b> Where active substances are procured from a manufacturer, importer or distributor established in the EU, that manufacturer, importer or distributor should be registered according to Article 52a of Directive 2001/83/EC.</p>	<p>The EudraGMDP database provides a source to check GMP/ GDP certificates and API registrations of registered API manufacturers, importers and distributors.</p> <p>If the supplier cannot be found in the EudraGMDP database, he should be asked to provide this documentation.</p>	--	--
<b>Receipt</b>			
<p><b>6.2</b> Areas for receiving active substances should protect deliveries from prevailing weather conditions during unloading. The reception area should be separate from the storage area.</p> <p>Deliveries should be examined at receipt in order to check that:</p>	<p>Self-explanatory</p> <p>Checklist would be recommended to capture different points.</p>	<p><b>7.2 Receipt and Quarantine (ICH Q7)</b></p> <p>7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house</p>	<p><i>4. Procurement, warehousing and storage</i></p> <p>4.3 Receipt and dispatch bays should be equipped with the means to protect materials from adverse environmental conditions. Reception areas should be</p>

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<p>(i) containers are not damaged;  (ii) all security seals are present with no sign of tampering;  (iii) correct labelling, including correlation between the name used by the supplier and the in-house name, if these are different;  (iv) necessary information, such as a certificate of analysis, is available; and  (v) the active substance and the consignment correspond to the order.</p>		<p>name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.  7.2 Receipt and Quarantine (APIC)  Before acceptance of incoming materials the packaging should be checked visually. The materials should be sampled, tested and released. As long as the material is not released it must be held under quarantine; this can be realised in different ways e.g. separate areas or through a validated computer system. These systems or others may also be used to identify the status of the material.  Incoming stock materials should be released before mixing them with the existing stock. This new stock should get a new lot number.</p>	<p>designed and equipped to allow containers of incoming materials to be cleaned before storage if appropriate. Upon receipt, material should be segregated until released by the quality unit.</p>
<p>6.3 Active substances with broken seals, damaged packaging, or suspected of possible contamination should be quarantined either physically or using an equivalent electronic system and the cause of the issue investigated.</p>	<p>Self-explanatory.</p>	<p>See 7.2 above</p>	<p>--</p>
<p>6.4 Active substances subject to specific storage measures, e.g. narcotics and products requiring a specific storage temperature or humidity, should be immediately identified and stored in accordance with written instructions and with relevant legislative provisions.</p>	<p>Self-explanatory  The specific storage measures should be written and communicated to relevant personnel.</p>	<p><b>10. STORAGE AND DISTRIBUTION (ICH Q7)</b>  10.1 Warehousing Procedures   <b>Chapter 10 (APIC):</b>  In general all storage conditions should be established based on stability data or suitability for use information. This data can be derived from formal stability studies for APIs.</p>	<p>--</p>
<p>6.5 Where the distributor suspects that an active substance procured or imported by him is falsified, he</p>	<p>Self-explanatory.  It is recommended to describe the process of informing the authority in a protocol or procedure.</p>	<p>--</p>	<p>--</p>

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should segregate it either physically or using an equivalent electronic system and inform the national competent authority of the country in which he is registered.			
<b>6.6</b> Rejected materials should be identified and controlled and quarantined to prevent their unauthorised use in manufacturing and their further distribution. Records of destruction activities should be readily available.	Self-explanatory	7.4 Storage (ICH Q7) 7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorised use in manufacturing.	--
<b>Storage</b>			
<b>6.7</b> Active substances should be stored under the conditions specified by the manufacturer, e.g. controlled temperature and humidity when necessary, and in such a manner to prevent contamination and/or mix up. The storage conditions should be monitored and records maintained. The records should be reviewed regularly by the person responsible for the quality system.	Self-explanatory  Non controlled storage is considered acceptable supported by a risk assessment and temperature monitoring data of the facility.  Materials should be stored under conditions and for a period that have no adverse effect on their quality and should normally be controlled to ensure the oldest stock is used first.  2013/C 343/01 EUROPEAN COMMISSION Guidelines on Good Distribution Practice of medicinal products for human use state in Chapter 9.2 last paragraph “Provision should be made to minimize the duration of temporary storage while awaiting the next stage of the transportation route.” The GDP Group of the ECA Foundation states in its FAQ that “This duration should be specified in company SOPs based on risk assessment. The current industry practice is up to 72 hours storage at temporary facilities. Longer storage periods are classed as long-term storage of product and the facility must have a license to operate.” An SOP should be in place to deal with events that lead to deviations to the temporary storage time and conditions. The fate of the product should be decided based on a risk assessment.	<b>10. STORAGE AND DISTRIBUTION (ICH Q7)</b> <b>10.1 Warehousing Procedures</b> <b>10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.</b> <b>7.4 Storage (ICH Q7)</b> 7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination. 7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection. 7.42 Materials should be stored under conditions and for a period that have no adverse effect on their quality and should normally be controlled so that the oldest stock is used first.	--

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<b>6.8</b> When specific storage conditions are required, the storage area should be qualified and operated within the specified limits.	Self-explanatory.		--
<b>6.9</b> The storage facilities should be clean and free from litter, dust and pests. Adequate precautions should be taken against spillage or breakage, attack by micro-organisms and cross-contamination.	Materials stored in fibre drums, bags or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.	--	--
<b>6.10</b> There should be a system to ensure stock rotation, e.g. 'first expiry (retest date), first out', with regular and frequent checks that the system is operating correctly. Electronic warehouse management systems should be validated.	Materials should be stored under conditions and for a period that have no adverse effect on their quality and should normally be controlled to ensure the oldest stock is used first.	<i>7.4 Storage</i> 7.42 Materials should be stored under conditions and for a period that have no adverse affect on their quality, and should normally be controlled so that the oldest stock is used first	--
<b>6.11</b> Active substances beyond their expiry date should be separated, either physically or using an equivalent electronic system, from approved stock and not be supplied.	Self-explanatory	7.2 Receipt and Quarantine (ICH Q7) 7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.	--
<b>6.12</b> Where storage or transportation of active substances is contracted out, the distributor should ensure that the contract acceptor knows and follows the appropriate storage and transport conditions. There must be a written contract between the contract giver and contract acceptor, which clearly establishes the duties of each party. The contract acceptor should not subcontract any of the work entrusted to him under the contract without the contract giver's written authorization.	Self-explanatory See templates of Quality agreements (APIC reference)	<i>10.2 Distribution Procedures (ICH Q7)</i> 10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality. 10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.	--

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		<p><b>Chapter 10.21 (APIC):</b> Logistics companies who are contracted to move API should be qualified. A quality agreement should also be in place (or equivalent) which details the key requirements for the safe and effective transportation of the API.</p>	
<b>Deliveries to customer</b>			
<p><b>6.13</b> Supplies within the EU should be made only by distributors of active substances registered according to Article 52a of Directive 2001/83/EC to other distributors, manufacturers or to dispensing pharmacies.</p>	<p>Recommendation: The EudraGMDP database provides a source to check Manufacturing and Import authorizations (MIA's), GMP/GDP certificates and API registrations of registered manufacturers and distributors.</p> <p>These should be checked prior to delivery of APIs to the customer. If none of these documents are available on the EudraGMDP database it is recommended to ask the customer to provide these prior to API dispatch.</p> <p>If Manufacturer holds a GMP certification, no separate GDP certification is required.</p>	--	--
<p><b>6.14</b> Active substances should be transported in accordance with the conditions specified by the manufacturer and in a manner that does not adversely affect their quality.</p> <p>Product, batch and container identity should be maintained at all times. All original container labels should remain readable.</p>	<p>Self-explanatory</p> <p>Refer to the APIC statement on Good distribution practices for definition of <b>Product temperature range</b> when distributing the product under non-controlled temperature.</p>	<p><i>10.2 Distribution procedures (ICH Q7)</i></p> <p>10.23 Appropriate transport and storage requirements are typically conveyed to the shipper on the bill of lading. If very special storage conditions are required to avoid alteration, it might be necessary to monitor the shipping conditions and to retain records of these conditions.</p> <p><i>17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS (ICH Q7)</i></p> <p><i>17.2 Traceability of Distributed APIs and Intermediates</i></p>	--



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		<p>17.20 Agents, brokers, traders, distributors, re-packers, or relabellers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:</p> <ul style="list-style-type: none"> <li>– Identity of original manufacturer</li> <li>– Address of original manufacturer</li> <li>– Purchase orders</li> <li>– Bills of lading (transportation documentation)</li> <li>– Receipt documents</li> <li>– Name or designation of API or intermediate</li> <li>– Manufacturer’s batch number</li> <li>– Transportation and distribution records</li> <li>– All authentic Certificates of Analysis, including those of the original manufacturer</li> <li>– Retest or expiry date</li> </ul> <p><b>Chapter 17.20 (APIC):</b> It is essential that the identity (i.e. name) and the address of the original manufacturer be given to the customer (see also § 17.61. If the Agent, Broker, Trader, Repacker, etc. does not know or cannot provide the name and address of the original manufacturer of the commercially available intermediate or API this would then be a serious violation of this GMP Guide.</p> <p>It is already known by many Brokers, Traders, Re-packers, etc. that one should not accept at face value certain names and addresses of companies provided by state controlled export agencies, as their practice of changing the source of the API depending on which state company has stocks available are well known. It should be pointed out that in the EU, if a "Qualified Person" releases a Medicinal Prod-</p>	

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		<p>uct made from an API from an unknown manufacturer this would be a serious violation of his/her ethical duties as a "Qualified Person". The inclusion of the wording "authentic" Certificates of Analysis is to indicate that it is not acceptable to photocopy the Certificate of Analysis of the original manufacturer onto the letter heading of the Agent, Broker, Trader, etc. It is a current expectation that besides the documents listed in the ICHQ7 there should be a written statement on regulatory and quality requirements such as: TSE/BSE – heavy metals/catalysts – residual solvent ... from the manufacturer if applicable</p> <p>In general the customer should receive all necessary information to fulfill his Regulatory and Legal obligations.</p>	
<p><b>6.15</b> A system should be in place by which the distribution of each batch of active substance can be readily identified to permit its recall.</p>	<p>Self-explanatory</p>	<p><i>10.2 Distribution procedures (ICH Q7)</i> 10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.</p> <p><b>Chapter 10.24 (APIC):</b> Full traceability for all shipments from the manufacturer to its external customer(s) has to be in place. If APIs or intermediates are delivered to a broker, full traceability has to be ensured by the broker as well according to chapter 17. (Remarks: In this case the final user of the API is unknown to the API producer, therefore full traceability to the end customer should be the duty of the broker).</p>	<p>--</p>
<p><b>Transfer of Information</b></p>			

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<b>6.16</b> Any information or event that the distributor becomes aware of, which have the potential to cause an interruption to supply, should be notified to relevant customers.	Recommendation: To ensure a continuous supply of the general public with medicinal products, manufacturers need to know as early as possible about anything that has the potential to disrupt the supply chain. Therefore suppliers/distributors must inform their relevant customers if they become aware of any information or event that has the potential to lead to supply disruptions as agreed in the quality agreement.	--	--
<b>6.17</b> Distributors should transfer all product quality or regulatory information received from an active substance manufacturer to the customer and from the customer to the active substance manufacturer.	Self-explanatory	<p><i>17 AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS</i>  <i>17.6 Transfer of Information</i>  17.60 Agents, brokers, distributors, repackers, or relabellers should transfer all quality or regulatory information received from an API or intermediate manufacturer</p> <p><b>Chapter 17.60 (APIC):</b>  This section is included to ensure that information which would normally be transferred by the API manufacturer to the dosage form manufacturer (In General the customer should receive all necessary information to fulfill his Regulatory and Legal obligations) as required under § 13.17 is transferred instead to the Agent, Broker, Trader, Re-packer, etc.  The meaning of "all quality and regulatory information received from the API manufacturer" means much more than the information listed in § 17.20 and would of course cover any changes made by the manufacturer to the process, the specifications (specifically the deletion of a test parameter) the test methods or the retest date.</p>	--
<b>6.18</b> The distributor who supplies the active substance to the customer should provide the name and address of the original active substance manufacturer and the	Self-explanatory	<p><i>17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS</i>  <i>17.6 Transfer of Information</i></p>	--

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batch number(s) supplied. A copy of the original certificate of analysis from the manufacturer should be provided to the customer.		<p>17.61 The agent, broker, trader, distributor, repacker, or relabeller who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.</p> <p>Chapter 17.61 (APIC): This is an unequivocal statement, specifically inserted in the ICH Q7 guide at the request of the dosage form manufacturers and supported by the authorities. It makes it clear that the process of covering up the source of APIs, ("neutralizing"), is no longer acceptable. It is a current expectation that traceability must be assured over the full supply chain and a system should be in place to control supply chain integrity.</p>	
<p><b>6.19</b> The distributor should also provide the identity of the original active substance manufacturer to competent authorities upon request. The original manufacturer can respond to the competent authority directly or through its authorised agents. (In this context 'authorised' refers to authorised by the manufacturer.)</p>	Self-explanatory	<p>17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.6 Transfer of Information 17.62 The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer.</p> <p><b>Chapter 17.62 (APIC):</b> The authorities expect that Agents, Brokers, Traders, Re-packers, etc. will not only comply with this guide but also actively cooperate with the authorities to clarify matters which only the Agents, Brokers, Traders, Re-packers, etc. may be aware of. Hence when the authorities</p>	--

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		<p>have reasons to involve Agents, Brokers, Traders, Re-packers, etc. in their investigations, the latter are obliged to respond to "a request" in a timely manner. Agents, Brokers, Traders, Re-packers, etc. should therefore, in order to minimize any risks to patients, reply promptly and fully to such requests for information from the authorities.</p>	
<p><b>6.20</b> The specific guidance for certificates of analysis is detailed in Section 11.4 of Part II of Eudralex Volume 4.</p>	<p>Self-explanatory</p>	<p><i>11.4 Certificates of Analysis</i>  11.40 Authentic: true, accurate record of results obtained, signed (also electronically) by authorised person (from Q-Unit) and dated for every batch (API and/or Intermediate) that is released from the manufacturing site.  11.41 The Certificate of Analysis requires the date of manufacture (there must be a procedure that describes how the manufacturing date is defined. Preferably be set by the final purification step of the API).  Retest and expiry dates are calculated from the manufacturing date.  11.42 Actual values should be reported if numerical results are obtained.  If the result is lower than the limit of detection (LOD) the result is reported as "not detected" (ND).  If the result is between the LOD and limit of Quantification (LOQ) the result is re-ported as &lt; LOQ.  Results above the LOQ must be reported with the actual numerical result.  Non-numeric results can be reported as "Conforms or complies".  Certificates should make reference to the analytical test methods used. This can be done by referring each individual test ID on the CoA or</p>	<p>--</p>

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		<p>by making a reference to the overall specification used.</p> <p>Certificates of Analysis for blended batches should be based on the results of sampling and testing the blend and not just taken from one of the components.</p> <p>11.43 The signature can be a manual signature or produced by a validated computer system which provides a degree of control equivalent to a manual signature.</p> <p>The certificate of analysis should allow traceability to the original manufacturing site(source) and the way to contact the organisation that issues it.</p>	
<b>Chapter 7 – Returns, complaints and recalls</b>			
<b>Returns</b>			
<p><b>7.1</b> Returned active substances should be identified as such and quarantined pending investigation.</p>	<p>Returned APIs should be identified as such and held pending resolution.</p> <p>Procedures for holding, labeling, testing, and any processing of the returned API should be defined.</p>	<p>14.5 Returns</p> <p>10. STORAGE AND DISTRIBUTION 10.1 Warehousing Procedures 10.11</p> <p>17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.8 Handling of Returns 17.80 (APIC)</p> <p>It is a current expectation that system should be in place to evaluate the disposition decision of returned materials. Control of the presence of the proper unique sealing for container integrity and information about storage conditions outside control of the agents, broker... should be available for the decision-making process. If the proper unique seal or storage conditions are not available or known rejecting and destroying the product is advised.</p>	<p>10.1 Goods returned to the supplier should be appropriately identified and handled in accordance with a procedure addressing at least the keeping of the material in quarantine in a dedicated area, and its assessment and disposition by a designated person.</p> <p>Where any doubt arises over the quality of the materials, they should not be considered suitable for reissue or re-use.</p>

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<p><b>7.2</b> Active substances which have left the care of the distributor, should only be returned to approved stock if all of the following conditions are met:</p> <p>(i) the active substance is in the original unopened container(s) with all original security seals present and is in good condition;</p> <p>(ii) it is demonstrated that the active substance has been stored and handled under proper conditions. Written information provided by the customer should be available for this purpose;</p> <p>(iii) the remaining shelf life period is acceptable;</p> <p>(iv) the active substance has been examined and assessed by a person trained and authorised to do so;</p> <p>(v) no loss of information/traceability has occurred.</p> <p>This assessment should take into account the nature of the active substance, any special storage conditions it requires, and the time elapsed since it was supplied. As necessary and if there is any doubt about the quality of the returned active substance, advice should be sought from the manufacturer.</p>	<p>If one of the conditions is not met, the distributor may return the material to the manufacturer who has to perform investigation and verify the status of the material and decide if the material may be returned in the approved stock.</p> <p>In addition to examination, testing of returned product could be considered based on a risk assessment.</p>	--	--
<p><b>7.3</b> Records of returned active substances should be maintained. For each return, documentation should include:</p> <p>(i) name and address of the consignee returning the active substances;</p> <p>(ii) name or designation of active substance, active substance batch number and quantity returned;</p> <p>(iii) reason for return;</p> <p>(iv) use or disposal of the returned active substance and records of the assessment performed.</p>	<p>Self-explanatory</p> <p>Records of returned products should be maintained and should include the name of the APIs and the lot number (or batch number), reason for the return, quantity returned, date of disposition, and ultimate fate of the returned API.</p>	--	--
<p><b>7.4</b> Only appropriately trained and authorised personnel should release active substances for return to stock. Active substances returned to saleable stock should be placed such that the stock rotation system operates effectively.</p>	<p>Self-explanatory</p>	--	--
<b>Complaints and recalls</b>			

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<p><b>7.5</b> All complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure. In the event of a complaint about the quality of an active substance the distributor should review the complaint with the original active substance manufacturer in order to determine whether any further action, either with other customers who may have received this active substance or with the competent authority, or both, should be initiated. The investigation into the cause for the complaint should be conducted and documented by the appropriate party.</p>	<p>Procedures for holding, labeling, testing, and any processing of the returned APIs or API intermediates should be defined.</p> <p>Complaints and information about possible defects during distribution activities should be systematically documented and investigated, based on a written procedure with assigned responsibilities.</p> <p>Investigations should be formally conducted and written up in a timely manner to establish if the complaint is justified, to identify root cause(s), to define any initial and/or follow up action(s), and the method of communication, e.g. to the customer, original manufacturer, authorities etc. Complaint records should be retained and regularly evaluated for trends, frequency and criticality in order to identify possible additional needs for corrective or preventive actions.</p> <p>Investigations should identify whether the reported defect is limited to a single batch of material, or if other batches need to be considered as part of the investigation. Any additional batches implicated should be identified accordingly. The original manufacturer of the API has to be informed about defects with a potential impact on the product quality.</p> <p>For product recalls see section 9.</p>	<p>10. STORAGE AND DISTRIBUTION 10.2 Distribution Procedures 10.24</p> <p>10. STORAGE AND DISTRIBUTION 10.1 Warehousing Procedures 10.11 7. MATERIALS MANAGEMENT 7.4 Storage 7.44</p> <p>15. COMPLAINTS AND RECALLS 15.10 15.13 17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.7 Handling of Complaints and Recalls <b>17.70 APIC:</b> It is a current expectation that any relevant critical complaint or request for recall related to the customer should immediately be informed to the related customers and suppliers.</p>	<p>9.1 There should be a system for recalling promptly and effectively from the market, materials known or suspected to be defective.</p> <p>9.4 All recalled materials should be stored in a secure, segregated area while their fate is decided.</p> <p>8.1 All complaints and other information concerning potentially defective materials must be carefully reviewed according to written procedures that describe the action to be taken, and including the criteria on which a decision to recall a product should be based.</p> <p>8.2 Any complaint concerning a material defect should be recorded and</p>



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		<p><b>17.71 APIC:</b> It is a current expectation that the outcome of any relevant critical investigation and corrective/preventive actions defined related to the customer should be informed promptly to the customer(s). And it is also current expectation that a system should be in place to assure a recall of all products involved can be accomplished in a timely manner. A regular Mock recall audit/exercise, on the most complex distribution system, is advised to be performed and documented. Legal time frames for reporting potential recalls to Health Authorities and customers should be followed.</p> <p>6. DOCUMENTATION AND RECORDS 6.5 Batch Production Records (Batch Production and Control Records) <b>6.53 (APIC):</b> An investigation has to be set up at every critical deviation when the origin of the deviation or when the impact on the product quality isn't known. A SOP on investigations of critical process deviations should define what is to be understood by critical. Compare other (related) batches with the same deviation. Use of the principles in ICH Q9 (Quality risk assessment) is a very useful way to classify critical deviations</p> <p>15. COMPLAINTS AND RECALLS 15.12</p> <p>6. DOCUMENTATION AND RECORDS 6.5 Batch Production Records (Batch Production and Control Records) 6.53 15. COMPLAINTS AND RECALLS 15.13</p>	<p>thoroughly investigated to identify the origin or reason for the complaint (e.g. the repackaging procedure, the original manufacturing process, etc.).</p> <p>8.3 If a defect in a pharmaceutical starting material is discovered or suspected, consideration should be given as to whether other batches should be checked.</p> <p>8.4 Where necessary, appropriate follow-up action, possibly including a recall, should be taken after investigation and evaluation of the complaint.</p>

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		15.14 17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.7 Handling of Complaints and Recalls 17.71	
<p><b>7.6</b> Complaint records should include:</p> <ul style="list-style-type: none"> <li><b>(i)</b> name and address of complainant;</li> <li><b>(ii)</b> name, title, where appropriate, and phone number of person submitting the complaint;</li> <li><b>(iii)</b> complaint nature, including name and batch number of the active substance;</li> <li><b>(iv)</b> date the complaint is received;</li> <li><b>(v)</b> action initially taken, including dates and identity of person taking the action;</li> <li><b>(vi)</b> any follow-up action taken;</li> <li><b>(vii)</b> response provided to the originator of complaint, including date response sent;</li> <li><b>(viii)</b> final decision on active substance batch.</li> </ul>	<p>Self-explanatory</p> <p>Responsibilities on final decision should be specified in the quality agreement.</p>	<p>17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.2 Traceability of Distributed APIs and Inter- mediates 17.20</p>	<p>9.6 All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information on materials supplied to customers (including exported materials).</p>
<p><b>7.7</b> Records of complaints should be retained in order to evaluate trends, product related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action. These should be made available during inspections by competent authorities.</p>	<p>Self-explanatory</p>	<p>Chapter 17.71</p>	
<p><b>7.8</b> Where a complaint is referred to the original active substance manufacturer, the record maintained by the distributor should include any response received from the original active substance manufacturer, including date and information provided.</p>	<p>Self-explanatory</p>	<p>refer to 17.60 ICH Q7 (WHO 8.5)</p>	
<p><b>7.9</b> In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.</p>	<p>Additionally the original manufacturer of the API should be informed about the situation</p>	<p>15. COMPLAINTS AND RECALLS 15.15</p>	<p>9.5 In the event of serious or potentially life-threatening situations all customers and competent authorities in all countries to which a given material may have been distributed should be promptly informed of any intention to recall the material.</p>

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	Confirmed complaints related to distribution with product quality impact should be communicated upstream to the manufacturer and also downstream to the customer(s) in case they may have received product with the same batch number.	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.6 Transfer of Information 17.60	8.5 The manufacturer and customers should be informed if action is needed following possible faulty manufacturing, packaging, deterioration, or any other serious quality problems with a pharmaceutical starting material.
<p><b>7.10</b> There should be a written procedure that defines the circumstances under which a recall of an active substance should be considered.</p>	<p>There should be established written procedures for the organization of any recall activity; implemented system should be frequently tested on functionality (mock recall)</p> <p>The effectiveness of the arrangements for recalls should be evaluated on regular basis via so called Mock recall.</p> <p>Mock recall is to evaluate the traceability system in material distribution and to ensure that the product can be returned in case of any adverse problem.</p> <p>Functions involved in the supply chain should implement written procedures to manage API recall (retrieval) promptly and effectively. The procedure should:</p> <ul style="list-style-type: none"> <li>- describe how the process of recall (retrieval) should be managed, based on the risk involved,</li> <li>- describe a decision-making process with defined responsibilities,</li> <li>- define the functions involved in the process (e.g. Quality Assurance, sales, logistics, competent authorities etc.)</li> <li>- define the communication process and documentation, and</li> <li>- define the steps needed to retrieve the product</li> </ul> <p>Recalled, quarantined, rejected, or returned products should be identified and controlled under a quarantine system designed to prevent</p>	<p>15. COMPLAINTS AND RECALLS 15.13 15.14</p>	<p>9.3 There should be established written procedures for the organization of any recall activity; these should be regularly checked and updated.</p> <p>9.7 The effectiveness of the arrangements for recalls should be evaluated at regular intervals</p>

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	their unauthorized distribution and use in manu- facturing or for sale		
7.11 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated. The designated person (cf. Section 3.1) should be in- volved in recalls.	Self-explanatory In case of a recall in addition agents, brokers, dis- tributors should transfer all quality or regulatory information received from an API or intermedi- ate manufacturer to the customer and from the customer to the API or intermediate manufac- turer.	--	.
<b>Chapter 8 – Self inspections</b>			
8.1 The distributor should conduct and record self-in- spections in order to monitor the implementation of and compliance with these guidelines. Regular self-inspec- tions should be performed in accordance with an ap- proved schedule.	Internal audits should be carried out on a regular basis to determine whether the quality manage- ment system complies with the GDP guidelines and with the aim to have continuous improve- ment. The audit and follow up actions should be carried out in accordance with documented pro- cedures. Different areas and functions need to be audited. Audit results should be documented and discussed with management personnel hav- ing responsibility in the area audited and, if rele- vant, to the firm management. Furthermore, cor- rective action and preventive action should be undertaken on the non-conformities found. Ongoing oversight of the plans and actions should be performed by the firm's Quality de- partment and by the senior management. The Auditor should be independent of the areas subjected to audit and knowledgeable with in- spected subjects and experienced in auditing skills.	<b>2.2 Responsibilities of the Quality Unit(s)</b> 7. Making sure that internal audits (self-inspec- tions) are performed; <b>2.4 Internal Audits (Self Inspection)</b> 2.40 In order to verify compliance with the principles of GMP for APIs, regular internal au- dits should be performed in accordance with an approved schedule. 2.41 Audit findings and corrective actions should be documented and brought to the at- tention of responsible management of the firm. Agreed corrective actions should be com- pleted in a timely and effective manner.	<b>1. Quality management</b> <b>1.9</b> A system should be in place for the performance of regular internal audits with the aim of continuous improve- ment. The findings of the audit and any corrective and preventive actions taken, including verification of their ef- fectiveness, should be documented and brought to the attention of the re- sponsible management.

## Chapter 5 – Glossary of terms

Terms	Definition
Batch	A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.
Batch number	A unique combination of numbers, letters and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.
Brokering of active substances	All activities in relation to the sale or purchase of active substances that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.
Calibration	The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.
Consignee	The person to whom the shipment is to be delivered whether by land, sea or air.
Contamination	The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or active substance during production, sampling, packaging or repackaging, storage or transport.
Distribution of active substances	All activities consisting of procuring, importing, holding, supplying or exporting of active substances, apart from brokering.
Deviation	Departure from an approved instruction or established standard.
Expiry date	The date placed on the container/labels of an active substance designating the time during which the active substance is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.
Falsified active substance	Any active substance with a false representation of: a/ its identity, including its packaging and labelling, its name or its components as regards any of the ingredients and the strength of those ingredients; b/ its source, including its manufacturer, its country of manufacture, its country of origin; or c/ its history, including the records and documents relating to the distribution channels used.
Holding	Storing active substances.
Procedure	A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the distribution of an active substance.
Procuring	Obtaining, acquiring, purchasing or buying active substances from manufacturers, importers or other distributors.
Quality risk management	A systematic process for the assessment, control, communication and review of risks to the quality of an active substance across the product lifecycle.

Quality system	The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met (ICH Q9).
Quarantine	The status of materials isolated physically or by other effective means pending a decision on the subsequent approval or rejection.
Retest date	The date when a material should be re-examined to ensure that it is still suitable for use.
Supplying	All activities of providing, selling, donating active substances to distributors, pharmacists, or manufacturers of medicinal products.
Signed (signature)	The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.
Transport (transportation)	Moving active substances between two locations without storing them for unjustified periods of time.
Validation	A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

## **Chapter 6 References**

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