ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

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 1 – May 2014

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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 recent 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 Guideline partially covering GDP for API. These affect more the handling of APIs at the manufacturing site, but not the distribution outside the site. Only 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 the Principles of GDP for APIs will be 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). However, this work has only been possible by the support of the International Pharmaceutical Excipients Council Europe by providing highly valued ideas for the structure of this document and examples of best practices laid down in The IPEC Good Distribution Practice Guide for Pharmaceutical Excipients, 2006.

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 GUIDELINES ON THE PRINCIPLES OF GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE, draft published by the European Commission DG SANCO on 6 February 2013, based on practical experience. As the guideline describes only the "Principles" of GDP other relevant publications (e.g. ICH Q7, ISO EN 9001:2008, The IPEC Good Distribution Practices Guide for Pharmaceutical Excipients, 2006) were taken into account and references included. This guide provides in particular additional explanatory notes to the WHO "GOOD TRADE AND DISTRIBUTION PRACTICES FOR PHARMACEUTICAL STARTING MATERIALS".

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 in particular WHO.

This document does not intend to provide an exhaustive list of "how to" comply with the above mentioned requirements and recommendations. It does however provide examples of commonly applied solutions and practical assistance 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 un-

less 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 GDP Guideline for APIs. 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

Companies should be aware that 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, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, have to apply the following. 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.
On the other hand 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

n.a.

Chapter 2 Scope

According to the European Falsified Medicines Directive manufacturing authorization holder are responsible to use only active substances which have been distributed in accordance with Good Distribution Practices for active substances. This is one significant new requirement in the EU Falsified Medicines Directive.

In the GUIDELINES ON THE PRINCIPLES OF GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE the scope is defined as follows:

1. For the purpose of these guidelines, the distribution of active substances for medicinal products for human use (hereafter 'active substances') is the procuring, import, holding, supplying or exporting active substances.
2. 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."

For the purpose of this guide "distributors" includes those parties involved in trade and distribution e.g. (re)processors, (re)packagers, transport and warehousing companies, forwarding agents, brokers, traders, and suppliers other than the original manufacturer.

Chapter 3 General Considerations

This document is based on the WHO Good Trade and Distribution Practice for Pharmaceutical Starting Materials (GTDP) guideline, and therefore it follows the same structure.

The WHO GTDP document provides the general principles of good practices in the pharmaceutical starting materials supply chain. This APIC document should provide the practical approach with examples that provide guidance on the application of WHO GTDP principles. In addition, extracts have been taken from IPEC GDP Guide 2006 to clarify certain requirements and maintain consistency.

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.

Concerning the definition of the terms used in this document please refer to the glossary in the ICH Q7-guideline.

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

Since the WHO guideline has been the only guideline taking care of GDP for APIs and is well accepted in industry it was decided to use that as the basis for this How to do document. The different paragraphs of the WHO guideline were transferred into a table. 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 and also with reference to the EU GDP Guide DRAFT 06/02/2013 and ISO 9001:2008.

The following table has to be read from left to right. The requirements of the WHO Guide and the interpretation of APIC have to be read and considered in conjunction. The references in the other columns shall help the user of this document to find the respective paragraphs in the EU GDP Guideline the APIC "How to do" document on ICH Q7 and ISO 9001:2008.

The application of the interpretations in this table shall 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

WHO GTDP	**APIC**	**ICH Q7 / APIC „How to do" Document on ICH Q7**	**EU GDP Guide DRAFT 06/02/2013**	**ISO 9001:2008**
Chapter		**Chapter**		**Chapter**
1. Quality Management				
1.1 Within an organization, quality assurance serves as a management tool. In contractual situations quality assurance also serves to generate confidence in the supplier. There should be a documented quality policy describing the overall intentions and direction of the supplier regarding quality, as formally expressed and authorized by management.	Parties involved in the distribution of APIs should establish a Quality Management System to manage the quality of their products and services, in order to maintain the original quality of the APIs. As an essential prerequisite for any Quality Management System, the top management should elaborate a corporate quality philosophy (Quality Policy).	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.3 Quality Management 17.30	Quality Systems, 3, 4, 5 Personnel 6 Procedures 11 Storage 18 Self-inspections 45	4.1 General Requirements 5.3 Quality Policy 4.2.1 a Documentation requirements general 5.1 b Management Commitment
1.2 Quality management should include: — an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources; — the systematic actions necessary to ensure adequate confidence that a material (or service) and the relevant documentation will satisfy given requirements for quality. (The totality of these actions is termed "quality assurance".); and — a clear procedure for approving suppliers of pharmaceutical starting materials and services (for details see GMP).	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 at a minimum the following elements: - 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 functions. The Quality Management System should also include a procedure to verify that any supplier of APIs, packaging materials or services has the capability to consistently meet previously agreed requirements. This may include periodic audits of the vendor's manufacturing facility if deemed necessary.	2. QUALITY MANAGEMENT 2.1 Principles 2.11, 2.12, 2.15, 2.2 Responsibilities of the Quality Unit(s) 2.20, 2.21		4.1 General requirements 7.4.1 Purchasing Process

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
1.3 The system should cover quality assurance principles.	See 1.2	2. QUALITY MANAGEMENT 2.1 Principles 2.15		2 Process Approach
1.4 All parties involved in the manufacture and supply chain must share responsibility for the quality and safety of the materials and products to ensure that they are fit for their intended use.	Parties involved should share responsibility for assuring that the API provided by the distributor conforms to the mutually agreed specification requirements of the pharmaceutical manufacturer and/or is suitable for the intended use of the API.	2. QUALITY MANAGEMENT 2.1 Principles 2.10		1.1 General
1.5 The responsibilities placed on any one individual should not be so extensive as to present any risk to quality. In the event of a supplier having a limited number of staff, some duties may be delegated or contracted out to designated persons who are appropriately qualified. There should, however, be no gaps or unexplained overlaps related to the application of GTDP.	There should be an adequate number of qualified personnel available either in-house or contractors to carry out all operations in compliance with this guide (refer to 2.2.) The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing e.g. in form of a contract/agreement between the concerned parties.	2. QUALITY MANAGEMENT 2.2 Responsibilities of the Quality Unit(s) 2.22 (1 -15)		6.2 Human Resources
1.6 Where electronic commerce (e-commerce) is used, defined procedures and adequate systems should be in place to ensure traceability and confidence in the quality of the material.	The related computerized system ensuring the required traceability and data integrity should be properly installed, qualified and controlled.	5. PROCESS EQUIPMENT 5.4 Computerized Systems 5.40		7.5.3 Identification and Traceability

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
1.7 Authorized release procedures should be in place to ensure that material of an appropriate quality is sourced from approved suppliers and released for its intended purpose.	If an API is provided only in originally sealed containers from the manufacturer, no additional testing and batch release are required. Inspection of the integrity of the packaging (including labeling) and seals should be carried out. A copy of the manufacturer's quality documents (such as COA or COC) should be provided for each delivery. If material is repacked and/or relabeled the material needs to be released (again) according to authorized procedures. Therefore an appropriate Quality System needs to be in place.	2. QUALITY MANAGEMENT 2.14 2.17 10. STORAGE AND DISTRIBUTION 10.2 Distribution Procedures 10.20		7.4.1 Purchasing Process
1.8 Inspection and certification of compliance with a quality system (such as applicable International Standards Organization (ISO) series and hazard analysis and critical control point (HACCP)) by external bodies is recommended. However, this should not be seen as a substitute for the implementation of these guidelines or for conforming to pharmaceutical GMP requirements, as applicable.	APIs are subject to inspections according to European and/or international regulations. The applied GMP standard is ICH Q7 or equivalent.	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.1 Applicability 17.11		1.1 General
1.9 A system should be in place for the performance of regular internal audits with the aim of continuous improvement. The findings of the audit and any corrective actions taken should be documented and brought to the attention of the responsible management.	Internal audits should be carried out on a regular basis (at least annually) and follow up actions should be carried out in accordance with documented procedures. Different areas and functions need to be audited. Audit results should be documented and discussed with management personnel having responsibility in the area audited. Furthermore, corrective action and preventive action should be undertaken on the non-conformities found.	2. QUALITY MANAGEMENT 2.4 Internal Audits (Self Inspection) 2.40 2.41		8.2.2 Internal Audit

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
2. Organization and Personnel		-		
2.1 There should be an adequate organizational structure and sufficient personnel should be employed to carry out all the tasks for which the supplier is responsible.	There should be a quality unit or function that is independent of the operational functions and ensures quality assurance (QA) responsibilities e.g. documentation and traceability of the API distribution activities. The organization should be documented in an organizational chart. 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.	2. QUALITY MANAGEMENT 2.1 Principles 2.13 2.2 Responsibilities of the Quality Unit(s) 2.12 3. PERSONNEL 3.1 Personnel Qualifications 3.10	Personnel 6, 7, 8 Quality System 4 Returns 38	6.1 Provision of Resources
2.2 Individual responsibilities should be clearly defined, understood by the individuals concerned and recorded in writing (as job descriptions or in a contract). Certain activities, such as the supervision of performance of activities in accordance with local legislation, may require special attention. Personnel should be suitably qualified and authorized to undertake their duties and responsibilities.	Personnel performing work affecting the API quality, including third parties, should have an adequate combination of training, education, and experience to carry out that work. Levels of authorization should be clearly defined in job descriptions. Records should be maintained listing the name, address, and qualifications of any contracted service provider and the type of service they provide.	3. PERSONNEL 3.1 Personnel Qualification 3.11 3.3 Consultants 3.30 3.31		5.5.1 Responsibility and Authority
2.3 All personnel should be aware of the principles of GTDP.	Awareness of the principles includes this APIC GDP Guide. Personnel should be trained on the principles and the chapters relevant for their field of responsibility.			6.2.2 Competence, training and awareness
2.4 Personnel should receive initial and continuing training relevant to their tasks. All personnel should be motivated to support the establishment and maintenance of quality standards.	Quality standards applied should be part of a regular training program provided by qualified individuals and the training should be documented. The extent of training should be dependent upon the company's activities. All personnel should receive initial and regular follow-up training (at least annually) according to the potential impact of the activities on the API.	3. PERSONNEL 3.1 Personnel Qualifications 3.12		6.2.2 Competence, training and awareness

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
2.5 Personnel dealing with hazardous materials (such as highly active, toxic, infectious or sensitizing materials) should be given specific training and should be provided with the necessary protective equipment.	Personnel should be trained in the handling of the material according to requirement of the product safety data sheet. This should also cover hygiene procedures.			6.2.2 Competence, training and awareness
2.6 Personnel who may be exposed to materials from open containers should maintain good hygiene, have no open wounds and be equipped with an appropriate protective outfit, such as gloves, masks and goggles.	To protect APIs from contamination by personnel activities such as handling of unpacked APIs while performing operations like API sampling, bulk handling and repackaging personnel should: - wear clean protective apparel such as head, face, hand, and arm coverings, as necessary; - remove or cover jewelry and other loose items; - store and consume food, drink, tobacco products and similar items only in certain designated areas; - receive an adequate and continued personal hygiene training to practice good sanitation and health habits; - be instructed to report to supervisory personnel any health conditions that may have an adverse effect on APIs.	3. PERSONNEL 3.2 Personnel Hygiene 3.20 3.21 3.22 3.23 3.24		6.4 Work Environment

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
3. Premises				
3.1 Premises 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 cross-contamination, mix-ups, build-up of dust or dirt and, in general, any adverse effect on the quality of materials.	Buildings and facilities used in the distribution of APIs 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 material, such equipment can be located outdoors. There should be defined areas or other control systems for the following activities: receipt, identification, sampling, and quarantine of incoming materials, pending release, rejection or further disposition. Facilities should also be designed to minimize potential contamination. The contamination risk should also be considered in respect to the flow of materials and personnel through the building or facilities.	4. BUILDINGS AND FACILITIES 4.1 Design and Construction 4.10 4.11 4.12 4.13 4.14 4.15 4.16 4.4 Containment 4.43	Premises and Equipment 14 Quality System 4 Procedures 11	6.3 Infrastructure 6.4 Work Environment
3.2 Measures should be in place to prevent unauthorized persons from entering the premises.	Access control of the premises should be ensured. A list of authorized personnel should be maintained.			7.5.5. Preservation of Product 6.3 Infrastructure

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
3.3 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, rodents or other animals.	For premises used for the storage and distribution of APIs a pest control system should be in place. Written procedures should be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment and APIs. Premises should be properly maintained and repaired and kept in a clean condition to ensure maximum protection. The outsourcing of these activities to specialized companies is common practice in industry.	4. BUILDINGS AND FACILITIES 4.7 Sanitation and Maintenance 4.70 4.72		6.3 Infrastructure 6.4 Work Environment
3.4 Suitable supporting facilities and utilities (such as air control, lighting and ventilation) should be in place and appropriate to the activities performed.	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. 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. Particular attention should be given to areas where APIs are exposed to the environment.	4. BUILDINGS AND FACILITIES 4.2 Utilities 4.20 4.21 4.22 4.23 4.24		6.3 Infrastructure 6.4 Work Environment

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
3.5 There should normally be a separate sampling area for pharmaceutical starting materials in a controlled environment. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.	Please refer specifically to chapter 7. MATERIALS MANAGEMENT, 7.3 Sampling and Testing of Incoming Production Materials of the APIC How to do document (interpretation of ICH Q7).	4. BUILDINGS AND FACILITIES 4.1 Design and Construction 4.14 4.4 Containment 4.42 7. MATERIALS MANAGEMENT 7.3 Sampling and Testing of Incoming Production Materials 7.34		7.4.3. Verification of Purchased Product
4. Warehousing and Storage				
GSP (Good Storage Practice) is applicable in all circumstances in which and all areas where materials are stored.	General principles can be found in the GSP – Good Storage Practices for Pharmaceuticals. WHO Technical Report Series, No. 908, 2003, Annex 9 and chapter 10 Warehousing Materials of the APIC How to do document (interpretation of ICH Q7)		Personnel 7 Procedures 11 Receipt 15, 16 Storage 18 – 23 Deliveries to customer 26, 27 Returns 36	6.3 Infrastructure 6.4 Work Environment
4.1 There should be authorized procedures describing the activities relating to the receipt, storage and distribution of materials.	Any warehouse/storage area throughout the distribution chain of the API should have written and approved procedures on how manage receipt, storage and dispatch of the APIs. Preferably procedures should be common throughout the distribution chain and managed by the wholesale distributor.	7. MATERIALS MANAGEMENT 7.1 General Controls 7.10		7.1 Planning of Product Realization

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
4.2 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials.	APIs should be stored in a manner to protect their quality from degradation, contamination, cross-contamination or mix-up. Materials stored in packing materials such as fiber drums, bags or boxes should be stored off the floor. Material should be stored in such a manner that there should be ample space for cleaning and inspection. The storage of different material should be organized in a manner to facilitate selection of the designated materials. APIs should be stored in conformance with safety requirements.	7. MATERIALS MANAGEMENT 7.40 7.41	Storage 18.	6.3 Infrastructure 6.4 Work Environment
4.3 Receipt and dispatch bays should be equipped with the means to protect materials from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned before storage if necessary.	Only materials that are suitable protected in containers and that are not subject to controlled environment (e.g. temperature, light and/or humidity) can be temporarily stored outdoors. Protection from adverse environmental conditions should be considered as a minimum requirement (e.g. roof or shelter) but specified storage conditions should be met when required as specified on packaging/product label and/or transportation documents. Received containers should be considered for cleaning before storage.	7. MATERIALS MANAGEMENT 7.2 Receipt and Quarantine 7.20 7.21 7.4 Storage 7.42 7.43		6.3 Infrastructure 6.4 Work Environment

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
4.4 Segregated areas should be provided for the storage of rejected, recalled and returned materials, including those with damaged packaging.	See 4.2 The storage of different material should be organized in a manner to facilitate selection of the designated materials. And also 4.5	7. MATERIALS MANAGEMENT 7.4 Storage 7.44 10. STORAGE AND DISTRIBUTION 10.1 Warehousing Procedures 10.11		8.3 Control of Non-conforming Product
4.5 Segregated areas and materials should be appropriately identified.	Segregation can be achieved through physical or computer control with appropriate systems in place.			6.3 Infrastructure
4.6 The required storage conditions as specified for the product should be maintained within acceptable limits. The storage areas should be kept clean and dry.	See 4.2; APIs should be stored in a manner to protect their quality from degradation. Material should be stored in such a manner that there should be ample space for cleaning and inspection.	7. MATERIALS MANAGEMENT 7.4 Storage 7.42 10. STORAGE AND DISTRIBUTION 10.1 Warehousing Procedures 10.10 10.2 Distribution Procedures 10.22		6.3 Infrastructure 6.4 Work Environment 7.5.5. Preservation of Product
4.7 Where special storage conditions are required (e.g. particular requirements for temperature or humidity) these should be provided, monitored and recorded.	Material storage conditions should conform to the materials designated conditions. Measurement with calibrated instrument should be performed and controlled and related records should be available to demonstrate on-going conformance to the specified conditions. A recommendation is to set alarm limits on temperature and humidity limits and put in place procedures to manage such situation. In case of temperature excursions during storage tools like e.g. stability studies, cycling studies and the Mean Kinetic Temperature concept could be used in combination with a risk assessment to assess the poten-	7. MATERIALS MANAGEMENT 7.4 Storage 7.42 10. STORAGE AND DISTRIBUTION 10.1 Warehousing Procedures 10.10		6.3 Infrastructure 7.5.5. Preservation of Product

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
	tial impact on the API. Separate air-conditioned areas should be considered where necessary.			
4.8 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 international conventions and national legislation may apply.	Self-explanatory	4. BUILDINGS AND FACILITIES 4.4 Containment 4.41 4.43		6.3 Infrastructure 7.5.5. Preservation of Product
4.9 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.	See also 5.1 The use of non-dedicated storage equipment must be controlled by suitable procedures for cleaning and maintenance to prevent cross-contamination. Records of cleaning and use of storage equipment should be kept and be available. This includes filling and discharge lines, valves etc. Suitable testing procedures should be in place for verification of appropriate cleaning. Certificates of cleaning should be available from suppliers delivering bulk in non-dedicated tankers. The certificate should state the chemical name of the previously transported product.	7. MATERIALS MANAGEMENT 7.2 Receipt and Quarantine 7.22 7.23		7.5.1. Control of Production and Service Provision
4.10 Spillages should be cleaned as soon as possible to prevent possible cross-contamination and hazard.	Self-explanatory	4. BUILDINGS AND FACILITIES 4.7 Sanitation and Maintenance 4.70 4.71		6.4 Work Environment

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
4.11 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, closed containers in enclosed areas, taking into account the relevant national legislation.	See sections 4.2, 4.4, 4.5 and 4.8.	4. BUILDINGS AND FACILITIES 4.6 Sewage and Refuse 4.60		6.3 Infrastructure 8.3 Control of Non-conforming Product
4.12 A system should be in place to ensure that those materials due to expire first are sold or distributed first (earliest expiry/first out (EEFO)). Where no expiry dates are specified for the materials, the first in/first out (FIFO) principle should be applied.	Self-explanatory	7. MATERIALS MANAGEMENT 7.4 Storage 7.42		7.5.1. Control of Production and Service Provision
4.13 Storage areas should be clean and free from accumulated waste and from vermin. A written sanitation program should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas. There should also be a written program for pest control.	Procedures should be available both for cleaning and pest control responsibility and schedules. Regular inspections should be performed and records of the inspections with observations should be available. Suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents should be used so as not to adversely affect the API or its packaging material. (Ref. section 3.3.)	4. BUILDINGS AND FACILITIES 4.7 Sanitation and Maintenance 4.70 4.71 4.72		6.4 Work Environment

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
5. Equipment				
5.1 Equipment must be located, designed, constructed, adapted, used and maintained to suit the operations to be carried out. Defective equipment should not be used, and should either be removed or labeled as defective. Equipment should be disposed of in such a way as to prevent any misuse.	Equipment (including instruments) used in the transport or storage of an API should be designed in such a way as to minimize the possibilities of cross contamination and to facilitate easy cleaning, maintenance and operation. Equipment should be commissioned before use to ensure that it is functioning as intended. Where such equipment is located outdoors there should be suitable control to minimize the risk to API from the environment. Procedures should describe maintenance of equipment used in the holding, transfer or sampling of the API, and how to manage equipment that is not in use. There should be records of equipment use and maintenance.	5. PROCESS EQUIPMENT 5.1 Design and Construction 5.10 5.12 5.13	Quality System 4 Premises and equipment 14	6.3 Infrastructure
5.2 The layout, design and use of equipment must aim to minimize the risk of errors and to permit effective cleaning and maintenance to avoid cross-contamination, build-up of dust or dirt and any adverse effect on the quality of materials.	see respective chapter in the ICH Q7 and APIC "how to do" document	5. PROCESS EQUIPMENT 5.1 Design and Construction 5.10 5.11		6.3 Infrastructure
5.3 Fixed pipe work should be clearly labeled to indicate the contents and, where applicable, the direction of flow.	see respective chapter in the ICH Q7 and APIC "how to do" document	4. BUILDINGS AND FACILITIES 4.2 Utilities 4.23 5.13		6.3 Infrastructure

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
5.4 All services, piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases, liquids and other materials.	see respective chapter in the ICH Q7 and APIC "how to do" document	4. BUILDINGS AND FACILITIES 4.2 Utilities 4.23 5.13		6.3 Infrastructure
5.5 Balances and other measuring equipment of an appropriate range and precision should be available and should be calibrated on a scheduled basis.	There should be procedures in place for calibration and means to verify calibration status of measuring equipment/instruments such as balances, temperature sensors, humidity sensor, pressure differential sensors etc. Records and/or certificates of control and calibration should be maintained. Calibration procedures should at the minimum be available and qualified for quality critical instruments. Documentation of an instruments calibration status should be easily available to operators. Deviations from approved standards of calibration on critical instruments should be investigated and managed.	5. PROCESS EQUIPMENT 5.3 Calibration		7.6 Control of measuring and monitoring Devices
5.6 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.	Procedures should describe operation and maintenance of equipment used in the holding, transfer or sampling of the API. Records of maintenance should be kept. Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should be of appropriate quality to be used in contact with the API.	4. BUILDINGS AND FACILITIES 4.7 Sanitation and Maintenance 4.71 5. PROCESS EQUIPMENT 5.1 Design and Construction 5.14 5.2 Equipment Maintenance and Cleaning 5.20		7.5.1. Control of Production and Service Provision

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5.7 Washing and cleaning equipment should be chosen and used such that it cannot be a source of contamination.	see respective chapter in the ICH Q7 and APIC "how to do" document	5. PROCESS EQUIPMENT 5.2 Equipment Maintenance and Cleaning 5.22 5.25		7.5.1. Control of Production and Service Provision
5.8 Dedicated equipment should be used where possible when handling and/or processing pharmaceutical starting materials. Where non-dedicated equipment is used, cleaning validation should be performed.	Dedicated equipment for handling APIs is always preferable. When non-dedicated equipment coming in direct contact with the product is used for API handling (e.g. repackaging, sieving, milling etc.; see also 7.7), appropriate cleaning procedures and effective cleaning schedules should be maintained and recorded. Cleaning efficiency should be verified by e.g.: − testing the final rinse after cleaning for residues of the previous product or, − checking the equipment after cleaning for residues of the previous product or alternatively, − by testing each batch for residues of the previous product handled with the same equipment in order to avoid contamination and carry-over of previously processed products.	4. BUILDINGS AND FACILITIES 4.4 Containment 4.41 5. PROCESS EQUIPMENT 5.2 Equipment Maintenance and Cleaning 5.20 5.21 5.24 5.26 12. VALIDATION 12.7 Cleaning Validation		7.5.1. Control of Production and Service Provision
6. Documentation				
6.1 Documents, in particular instructions and procedures relating to any activity that might have an impact on the quality of materials, should be designed, completed, reviewed and distributed with care. Documents should be completed, approved, signed and dated by appropriate authorized persons and should not be changed without authorization.	Procedure on document control should be established. A revision history of documents should be readily available. Retention periods of documents should be established.	6. DOCUMENTATION AND RECORDS 6.1 Documentation System and Specifications	Documentation 9 Returns 37	4.2. Documentation Requirements

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6.2 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.	Self-explanatory			4.2. Documentation Requirements
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).	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. The original manufacturing site should be identified by name or unique identifier on the CoA or any other document agreed upon with the customer. Additional data resulting from analyses conducted by the distributor should be provided with clear indication of the source of data. Quality documents should allow traceability back to the manufacturer, along with a contact reference. If any lot mixing is carried out, COAs from manufacturers are no longer valid and the distributor should perform analyses in its own laboratory or at a named and qualified contract laboratory. Otherwise the distributor can supply a certificate of compliance (CoC), provided that all other repackaging and storage activities are carried out according to these guidelines.	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.2 Traceability of Distributed APIs and Intermediates 17.6 Transfer of Information		7.4.1 Purchasing process 8.2.4 Monitoring and Measurement of Product
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.	API should normally be released according their specification for shipment. In case of API pending final release testing, API could be shipped under quarantine in agreement with customer. API should remain in quarantine until full release CoA is obtained by manufacturer.	11. LABORATORY CONTROLS 11.4 Certificates of Analysis		8.2.4 Monitoring and Measurement of Product

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6.5 The original manufacturer and intermediaries handling the material should always be traceable and the information available to authorities and end-users, downstream and upstream.	see respective chapter in the ICH Q7 and APIC "how to do" document	reference to 17.20 (see WHO 6.3)		7.5.3 Identification and Traceability
6.6 Mechanisms should exist to allow for transfer of information including the transfer of quality or regulatory information between a manufacturer and a customer, and of information to the regulatory authority upon request.	The mechanism can be agreed upon between the distributer and the customer within a quality or supply agreement	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.6 Transfer of Information		7.4.1 Purchasing Process 7.2.3. Customer Communication
6.7 Labels applied to containers should be clear, unambiguous, permanently fixed and in the company's agreed format. The information on the label should be indelible.	Self-explanatory	-		7.5.3. Identification and Traceability
6.8 Each container should be identified by labelling bearing at least the following information: — the name of the pharmaceutical starting material, including grade and reference to pharmacopoeias, where relevant; — if applicable, the International Nonproprietary Names (INNs); — the amount (weight or volume); — the batch number assigned by the original manufacturer or the batch number assigned by the re-packer, if the material has been repacked and relabeled; — the retest date or expiry date (where applicable); — any special storage conditions; — handling precautions, where necessary; — identification of the original manufacturing site; and — name and contact details of the supplier.	This is the required minimum of labeling information for the API. In case of relabeling this information should also be transferred to the new label. In addition a controlled label generating systems should be in place. Appropriate verification of label management should be maintained.	9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES 9.4 Packaging and Labeling Operations 9.42 9.43		7.5.3. Identification and Traceability

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6.9 Relevant storage, handling and safety data sheets should be available.	see respective chapter in the ICH Q7 and APIC "how to do" document	10. STORAGE AND DISTRIBUTION 10.2 Distribution Procedures 10.22 10.23		7.2.3. Customer Communication
6.10 Records must be kept and must be readily available upon request in accordance with GSP (2).	Procedure on record management should be established. Retention periods of records should be established. The security and methods of archiving and retrieval of such records should be ensured.	6. DOCUMENTATION AND RECORDS 6.1 Documentation System and Specifications 6.12 6.13 6.14 6.15 10. STORAGE AND DISTRIBUTION 10.2 Distribution Procedures 10.24		4.2.4 Control of Records
7. Repackaging and re-labeling				
7.1 Operations, such as combining into a homogeneous batch, repackaging and/or relabeling, are manufacturing processes and their performance should therefore follow GMP.	Processes where APIs are exposed to the environment such as transferring API from one container to another, e.g. from bulk equipment to storage tanks/silos or from storage tanks/silos into containers, are critical for product quality. Under these conditions APIs could be contaminated with other products, lubricants, cleaners or any other foreign matters. To minimize these risks ICH Q7 GMP principles should be applied.	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.1 Applicability 17.11 8. PRODUCTION AND IN-PROCESS CONTROLS 8.4 Blending Batches of Intermediates or APIs	Scope 2	7.5.1. Control of Production and Service Provision

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7.2 Special attention should be given to the following points: — prevention of contamination, cross-contamination and mix-ups; — security of stocks of labels, line clearance checks, on-line inspections, destruction of excess batch-printed labels; — good sanitation and hygiene practices; — maintaining batch integrity (normally mixing of different batches of the same solid material should not be done); — as part of batch records, all labels that were removed from the original container during operations, and a sample of the new label, should be kept; — if more than one batch of labels is used in one operation, samples of each batch should be kept; and — maintaining product identity and integrity.	Special attention should be given to the following points: - Contamination, cross-contamination and mix-ups should be avoided by using suitable equipment and cleaning procedures according to the recommendations of chapter 5 of this document and with adequate labeling. Environmental conditions and repackaging procedures should be designed to avoid contamination and cross-contamination during repackaging and relabeling operations. Filtered air in the repackaging area should be considered where necessary for the product. Protective clothing for the operators should be clearly defined. - Labels should be printed with a controlled system ensuring that all necessary information is correct (see 6.8). Sufficient cross-checks should be installed to ensure proper data transfer. A procedure should be installed to avoid mislabeling. Therefore printing and usage of labels should be a restricted process. All labeling operations (e.g. generating, printing, storage, usage, destruction) should always be recorded. Labeled containers should be inspected and surplus labels should be destroyed to avoid any misuse. If labels will not be printed just-in–time, security stock should be controlled and limited access should be defined. - Repackaging and relabeling processes should be carried out in an environment clean enough to avoid contamination. It should be clearly defined where and how an APIs will be repackaged and relabeled. Personnel involved in repackaging processes should wear clean protective apparel such as head, face, hand, and arm coverings, if necessary and practice appropriate personnel hygiene (e.g. hand disinfection, following	8. PRODUCTION AND IN-PROCESS CONTROLS 8.5 Contamination Control 8.51 8.52 9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES 9.2 Packaging Materials 9.21 9.22 9.4 Packaging and Labeling Operations 9.40 9.41 9.44 9.45 9.46 17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.4 Repackaging, Relabeling and Holding of APIs and Intermediates 17.40 17.41 19. APIs FOR USE IN CLINICAL TRIALS 19.3 Equipment and Facilities 19.31		6.4 Work Environment 7.5.1. Control of Production and Service Provision 7.5.5. Identification and Traceability

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	health requirements, health monitoring, covering exposed jewelry). Personnel should be trained on special hygiene requirements. Training should be recorded. Repackaging areas should be regularly cleaned and sanitized. - Where new batch numbers are assigned, traceability to original batch numbers should be ensured by proper documentation. Assigning one batch number to containers of different batches complying with the same specification is an unacceptable practice (see also 7.3 and 7.4). - Self explanatory - Self explanatory - All repackaging and relabeling processes should be designed and carried out to avoid commingling and carry-over and to ensure full traceability of the APIs back to the original manufacturer and traceability downstream to the final customer. Every step should be sufficiently recorded by responsible personnel. Name of operator, date and time of every step should also be recorded. This should also be ensured if computerized systems are used. All repackaging and relabeling requirements should be defined in written procedures.			

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7.3 When different batches of a material from the same original manufacturing site are received by a distributor and combined into a homogeneous batch, the conformity of each batch with its specification should be confirmed before it is added.	Before blending of individual batches / lots minimum an identification of individual batches / lots have to be performed. Blending of batches or lots of APIs that individually do not conform to specifications, with other lots that do conform (in an attempt to salvage, or hide adulterated material) is not acceptable. A batch can only be homogenous when conforming material is thoroughly mixed. Mixing to form a homogeneous batch is a manufacturing step following a validated process and should be defined in a written procedure. Mixing should always be controlled and homogeneity should be verified and documented.	8. PRODUCTION AND IN-PROCESS CONTROLS 8.4 Blending Batches of Intermediates or APIs 8.41 8.43		7.4.3 Verification of Purchased Product 7.5.1. Control of Production and Service Provision
7.4 Only materials from the same manufacturing site received by a distributor and conforming to the same specifications can be mixed. If different batches of the same material are mixed to form a homogeneous batch it should be defined as a new batch, tested and supplied with a batch certificate of analysis. In such cases the customer should be informed that the material supplied is a mixture of manufacturers' batches. The supplied material must have a certificate of conformity to a specification at date of supply.	See also 7.1 The blending process should be verified to ensure that it will not impact the quality of the API. The blended API should be tested to ensure conformance to the specification and to provide data for the Certificate of Analysis (COA).	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.2 Traceability of Distributed APIs and Intermediates 17.6 Transfer of Information 1		7.5.1. Control of Production and Service Provision

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7.5 In all cases the original COA of the original manufacturer should be provided. If retesting is done, both the original and the new COA should be provided. The batch referred to on the new COA should be traceable to the original COA.	Quality documents accompanying deliveries should be subject to an agreement between distributor and final customer. In case of retesting, analytical methods of the original manufacturer, and/or an in-house method validated against the pharmacopoeia method and/or pharmacopoeia methods should be applied. See also 7.4	-		7.2 Customer Related Requirements

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7.6 Repackaging of materials should be carried out with primary packaging materials for which the quality and suitability have been established to be equal to or better than those of the original container. The approval of the supplier is necessary for the packaging material used for the repackaging.	Primary packaging material specifications should be established and a written procedure should clearly define primary packaging materials for each individual API based upon the APIs stability. If the same type of packaging material is used for repackaging then it should be equivalent to that used by the original manufacturer. In such cases the re-packager and distributor may rely on the manufacturer's stability evaluation and assign the same shelf life for the API. When primary packaging material differs from the original manufacturer's primary packaging material or if the head space increases significantly, an evaluation of the container and its closure system should demonstrate that it is adequate to protect the API from deterioration and contamination beyond its established specification for the shelf life (re-test or expiration period) defined by the API manufacturer. Otherwise the shelf life defined by the manufacturer cannot be transferred to the repackaged material. The need for stability studies should be confirmed. Storage and handling procedures should be installed which protect containers and closures and minimize the risk of contamination, damage or deterioration, and which will avoid mix-ups (e.g. between containers that have different specifications but are similar in appearance).	9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES 9.1 General 9.2 Packaging Materials 17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.5 Stability		7.5.1. Control of Production and Service Provision

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7.7 The re-use of containers should be discouraged unless they have been cleaned using a validated procedure. Recycled containers should not be used unless there is evidence that the quality of the material packed will not be adversely affected.	The usage of new containers is recommended for APIs. However, if containers are reused, the cleaning procedure should be validated. If returnable API containers are reused, all previous labeling should be removed or defaced.	9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES 9.2 Packaging Materials 9.22 12.7 Cleaning Validation		7.5.1. Control of Production and Service Provision
7.8 Materials should be repackaged only if efficient environmental control exists to ensure that there is no possibility of contamination, cross-contamination, degradation, physicochemical changes and/or mix-ups. The quality of air supplied to the area should be suitable for the activities performed, e.g. efficient filtration.	Environmental controls should ensure that temperature, humidity and cleanliness of air and equipment are appropriate to avoid any contamination or deterioration of the API. It is recommended to define the necessary environmental conditions for the repackaging of each API. See also 3.4 and 7.2			7.5.1. Control of Production and Service Provision
7.9 Suitable procedures should be followed to ensure proper label control.	Procedures should be implemented to ensure that the correct quantity of labels are printed and issued and that labels contain the necessary information. The procedure should also define that labels are reconciled and any excess labels immediately destroyed or returned to controlled storage and appropriately recorded. Repackaging and relabeling facilities should be inspected immediately prior to use, ensuring that all materials that are not required for the next repackaging operation have been removed. See also 7.2 and 7.8	9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES 9.3 Label Issuance and Control 9.30 9.31 9.32 9.33 9.34 9.35 9.36 9.40		7.5.3 Identification and Traceability
7.10 Containers of repackaged material and relabeled containers should bear both the name of the original manufacturing site and the name of the distributor/repacker.	Original manufacturing name and manufacturing site address have to be provided on the label.	9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES 9.4 Packaging and Labeling Operations 9.42		7.5.1. Control of Production and Service Provision

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7.11 Procedures should be in place to ensure maintenance of the identity and quality of the material by appropriate means, both before and after repackaging operations.	Additionally these procedures should include documented traceability downstream and upstream. See also 7.2, 7.8, 7.9	10. STORAGE AND DISTRIBUTION 10.2 Distribution Procedures 10.24		7.5.3 Identification and Traceability
7.12 Batch release procedures should be in place in accordance with GMP.	Appropriate testing of repackaged materials should be performed to demonstrate consistency of API quality. Testing of the complete specification is not necessary in such cases but some defined key quality parameters, which may be affected by the repackaging process, should be tested. Until release testing has been performed, the repackaged materials should be kept under quarantine and identified as such. The materials should comply with the defined specifications before they can be released for distribution. API testing and release should be performed by the Quality Unit and conform to written specifications and analytical test methods. There should be a procedure to ensure that test data are recorded and evaluated prior to release of the repackaged or transferred API.	2. QUALITY MANAGEMENT 2.1 Principles 2.17 6. DOCUMENTATION AND RECORDS 6.7 Batch Production Record Review 6.70		8.2.4. Monitoring and Measurement of Product

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7.13 Only official pharmacopoeia methods or validated analytical test methods should be used for the analysis.	For control of key parameters during re-packaging and or full retesting of APIs, official pharmacopoeia methods or methods validated against the pharmacopoeia methods should be used. Otherwise the original manufacturer's analytical methods are recommended. The methods used should be listed on the Certificate of Analysis accompanying the API or made available to the customer by other documents. These documents should also reference any contract laboratory that is used to perform analyses. The Certificate of Analysis should identify which tests have been performed on the individual batch and which tests have been performed via skip lot testing.	11. LABORATORY CONTROLS 11.2 Testing of Intermediates and APIs 11.20 12. VALIDATION 12.8 Validation of Analytical Methods 12.80		8.2.4. Monitoring and Measurement of Product
7.14 Samples of APIs and excipients of appropriate quantities should be kept for at least 1 year after the expiry or retest date, or for 1 year after distribution is complete.	If APIs are repackaged, processed or packaged from bulk, retained samples representative of the API batch should be kept for one year after the expiration or retest date or for three years after distribution is complete. The sample size should be the amount required to perform two complete analyses. Samples should be stored under the conditions as mentioned on the product label.	11. LABORATORY CONTROLS 11.7 Reserve/Retention Samples		8.2.4. Monitoring and Measurement of Product

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7.15 The repacker and relabeler should ensure that the stability of the material is not adversely affected by the repackaging or relabeling. Stability studies to justify the expiry or retest dates assigned should be conducted if the pharmaceutical starting material is repackaged in a container different from that used by the original manufacturer. It is recognized that some excipients may not need additional stability studies.	Stability and expiration dating of APIs are primarily the responsibility of the API manufacturer. If an API is transferred to another container or repackaged by the distributor, stability and shelf life (retest or expiry period) considerations have to be taken into account. The type of container, primary packaging materials and storage conditions used by the repackaging site has to be taken into account when shelf life (retest or expiry period) is defined for APIs. The recommended expiration date provided by the original manufacturer should be reconfirmed by a stability study according ICH Q1. In such a case the type of container and storage conditions should be clearly defined. If the need for special storage conditions exists (e.g. protection from light, heat, etc.), such restrictions should be indicated on the labeling.	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.5 Stability 17.50 11.6 Expiry and retest dating		8.2.4. Monitoring and Measurement of Product
8. Complaints				
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.	Complaints and information about possible defects should be systematically documented and investigated, based on a written procedure with assigned responsibilities.	15. COMPLAINTS AND RECALLS 15.10 15.13 17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.7 Handling of Complaints and Recalls 17.70 17.71	Complaints and Recalls 39 - 46	7.2.3. Customer Communication

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8.2 Any complaint concerning a material defect should be recorded and thoroughly investigated to identify the origin or reason for the complaint (e.g. the repackaging procedure, the original manufacturing process, etc.).	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.	6. DOCUMENTATION AND RECORDS 6.5 Batch Production Records (Batch Production and Control Records) 6.53 15. COMPLAINTS AND RECALLS 15.12		7.2.3. Customer Communication 8.2.3 Monitoring and Measurement of Processes
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.	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 and labeled (e.g. "under quarantine") accordingly. The original manufacturer of the API has to be informed about the defect.	6. DOCUMENTATION AND RECORDS 6.5 Batch Production Records (Batch Production and Control Records) 6.53		7.2.3. Customer Communication 8.2.3 Monitoring and Measurement of Processes
8.4 Where necessary, appropriate follow-up action, possibly including a recall, should be taken after investigation and evaluation of the complaint.	For product recalls see section 9.	15. COMPLAINTS AND RECALLS 15.13 15.14 17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.7 Handling of Complaints and Recalls 17.71		7.2.3. Customer Communication 8.2.3 Monitoring and Measurement of Processes 8.3 Control of non-conforming process

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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.	Confirmed complaints related to product quality should be communicated upstream to the manufacturer and also downstream to the customer(s) in case they may have received material with the same batch number.	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.6 Transfer of Information 17.60		7.2.3. Customer Communication
9. Recalls				
9.1 There should be a system for recalling promptly and effectively from the market, materials known or suspected to be defective.	Functions involved in the supply chain should implement written procedures to manage API recall (retrieval) promptly and effectively. The procedure should: - describe how the process of recall (retrieval) should be managed, based on the risk involved, - describe a decision making process with defined responsibilities, - define the functions involved in the process (e.g. Quality Assurance, sales, logistics, competent authorities etc.) - define the communication process and documentation, and - define the steps needed to retrieve the material.	10. STORAGE AND DISTRIBUTION 10.2 Distribution Procedures 10.24	Procedures 11 Deliveries to Customers 28 Complaints and Recalls 39 - 46	8.3 Control of non-conforming process
9.2 The original manufacturer should be informed in the event of a recall.	In case of a recall in addition Agents, brokers, distributors, repackers, or relabelers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer and from the customer to the API or intermediate manufacturer.	refer to 17.60 ICH Q7 (WHO 8.5)		7.4.1 Purchasing process 8.3 Control of non-conforming process

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9.3 There should be established written procedures for the organization of any recall activity; these should be regularly checked and updated.	There should be established written procedures for the organization of any recall activity; implemented system should be frequently tested on functionality (mock recall)	15. COMPLAINTS AND RECALLS 15.13 15.14		8.3 Control of non-conforming process
9.4 All recalled materials should be stored in a secure, segregated area while their fate is decided.	Recalled, quarantined, rejected, or returned materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing. Procedures for holding, labeling, testing, and any processing of the returned APIs or API intermediates should be in accordance with written procedures.	10. STORAGE AND DISTRIBUTION 10.1 Warehousing Procedures 10.11 7. MATERIALS MANAGEMENT 7.4 Storage 7.44		8.3 Control of non-conforming process
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.	Additionally the original manufacturer of the API has to be informed about the situation.	15. COMPLAINTS AND RECALLS 15.15		7.2.3. Customer Communication
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).	Self-explanatory	17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.2 Traceability of Distributed APIs and Intermediates 17.20		4.2.4 Control of Records
9.7 The effectiveness of the arrangements for recalls should be evaluated at regular intervals.	The effectiveness of the arrangements for recalls should be evaluated on regular basis via so called Mock recall. 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.	17.71		8.2.2. Internal Audit

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10. Returned goods				
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. Where any doubt arises over the quality of the materials, they should not be considered suitable for reissue or reuse.	Returned APIs should be identified as such and held pending resolution. Procedures for holding, labeling, testing, and any processing of the returned API should be in accordance with written procedures. 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.		Procedures 11 Returns 33 - 38	8.3 Control of non-conforming process
11. Handling of non-conforming materials				
11.1 Non-conforming materials should be handled in accordance with a procedure that will prevent their introduction or reintroduction into the market. Records covering all activities, including destruction, disposal, return and reclassification, should be maintained.	Additionally the original manufacturer of the API has to be informed about the situation.	14. REJECTION AND RE-USE OF MATERIALS 14.1 Rejection 14.10	?	8.3 Control of non-conforming process
11.2 An investigation should be performed to establish whether any other batches are also affected. Corrective measures should be taken where necessary.	The investigation should be documented as well as actions taken to prevent recurrence of the problem. In addition the original manufacturer of the API has to be informed about the situation.	8. PRODUCTION AND IN-PROCESS CONTROLS 8.1 Production Operations 8.15 11. LABORATORY CONTROLS 11.1 General Controls 11.15		8.3 Control of non-conforming process
11.3 The disposition of the material, including downgrading to other suitable purposes should be documented.	The manufacturer takes the decision of the fate of the out of specification material (API). The decision needs to be documented.	14.10		8.3 Control of non-conforming process

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Chapter		**Chapter**		**Chapter**
11.4 Non-conforming materials should never be blended with materials that do comply with specifications.	Self-explanatory	8. PRODUCTION AND IN-PROCESS CONTROLS 8.4 Blending Batches of Intermediates or APIs 8.41		8.3 Control of non-conforming process
12. Dispatch and transport				
12.1 Materials should be transported in a manner that will ensure the maintenance of controlled conditions where applicable (e.g. temperature, protection from the environment). The transport process should not adversely affect the materials.	Transport conditions and the equipment to be used should be defined according to the characteristics of the products. Any special transport conditions should be monitored and recorded. In case of temperature excursions during transportation tools like e.g. stability studies, cycling studies, shipping studies, Mean Kinetic Temperature concept could be used in combination with a risk assessment to assess the potential impact on the API.	10. STORAGE AND DISTRIBUTION 10.2 Distribution Procedures 10.21	Records 13 Deliveries to customers 25, 26, 27	7.5.1 Control of Production and Service Provision 7.5.5 Preservation of Product
12.2 Requirements for special transport and/or storage conditions should be stated on the label. If the pharmaceutical starting material is intended to be transferred outside the control of the manufacturer's materials management system, the name and address of the manufacturer, quality of contents, special transport conditions and any special legal requirements should also be included on the label.	Documents accompanying a delivery should also list any special requirements for storage and transportation.	10. STORAGE AND DISTRIBUTION 10.2 Distribution Procedures 10.22		7.5.3. Identification and Traceability
12.3 The supplier of the materials should ensure that the contract acceptor for transportation of the materials is aware of and provides the appropriate storage and transport conditions.	The supplier should provide the contract acceptor with information about any special requirements for appropriate transport and storage conditions. The ability of the contract acceptor to comply with these requirements should be evaluated (e.g. audit).	10. STORAGE AND DISTRIBUTION 10.2 Distribution Procedures 10.23		7.5.1 Control of Production and Service Provision 7.5.5 Preservation of Product

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
12.4 Procedures should be in place to ensure proper cleaning and prevention of cross-contamination when liquids (tanks) and bulk or packed materials are transported.	Best practice for bulk transport is to use dedicated equipment and defined handling processes. If this is not possible, the type of transport equipment and suitable supplies (e.g. seals, fittings, hoses, pumps) should be specified. The materials used should be compatible with the transported APIs. Possible incompatibilities between sealing materials or hoses and the product transported should be taken into account especially for solvents. Cleaning procedures with documented evidence of their efficiency should be used between loadings of different materials. Consideration has to be given to previous cargoes. A list of restricted or acceptable previous cargoes should be communicated to and agreed upon with the transport companies. Changes to bulk transport equipment and supplies should be well controlled, evaluated and finally approved by the contract giver.	9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES 9.2 Packaging Materials 9.20 9.21 9.22		7.5.1 Control of Production and Service Provision 7.5.5 Preservation of Product
12.5 The bulk transport of pharmaceutical starting materials requires numerous precautions to avoid contamination and cross contamination. The best practice is to use dedicated equipment, tanks or containers.	See section 12.4	9.21 9.22		7.5.1 Control of Production and Service Provision 7.5.5 Preservation of Product
12.6 Packaging materials and transportation containers should be suitable to prevent damage to the pharmaceutical starting materials during transport.	Self-explanatory	9.20		7.5.5 Preservation of Product
12.7 For bulk transport, validated cleaning procedures should be used between loadings, and a list of restricted previous cargoes must be supplied to the transport companies.	See section 12.4			7.5.1 Control of Production and Service Provision 7.5.5 Preservation of Product

WHO GTDP	**APIC**	**ICH Q7 / APIC „How to do" Document on ICH Q7**	**EU GDP Guide DRAFT 06/02/2013**	**ISO 9001:2008**
Chapter		**Chapter**		**Chapter**
12.8 Steps should be taken to prevent unauthorized access to the materials being transported.	Consideration should be given to security aspects. For example, transportation of bulk APIs should have a sealing system in place. Containers should bear tamper evident seals.	9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES 9.4 Packaging and Labeling Operations 9.46		7.5.1 Control of Production and Service Provision 7.5.5 Preservation of Product
12.9 General international requirements regarding safety aspects (e.g. prevention of explosion and of contamination of the environment, etc.) should be observed.	Proper HSE regulations should be followed according to local requirements and/or agreements with the customer.			7.2.3. Customer Communication 7.5.5 Preservation of Product
13. Contract activities				
13.1 Any activity performed, as referenced in the GMP and GTDP guidelines, delegated to another party, should be agreed upon in a written contract.	There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GDP responsibilities, including the quality measures, of each party; as described in this guideline.	16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) 16.12	Deliveries to customers 26	4.1 General Requirements
13.2 The contract giver should evaluate the proposed contract acceptor's compliance with GTDP before entering into an agreement.	The evaluation should include an audit of the contract acceptor's premises and quality system. Based on a risk assessment this could also be done by a questionnaire.	16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) 16.11		4.1 General Requirements

WHO GTDP	APIC	ICH Q7 / APIC „How to do" Document on ICH Q7	EU GDP Guide DRAFT 06/02/2013	ISO 9001:2008
Chapter		**Chapter**		**Chapter**
13.3 All contract acceptors should comply with the requirements in these guidelines. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.	All agents, brokers, traders, distributors, repackers, and relabelers should comply with GDP as defined in this Guide.	16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) 16.10 17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS 17.1 Applicability 17.11 17.4 Repackaging, Relabeling and Holding of APIs and Intermediates 17.41		4.1 General Requirements
13.4 There should be a written and approved contract or formal agreement between the contract giver and contract acceptor that addresses and defines in detail the responsibilities, GTDP and which party is responsible for which quality measures.	Self-explanatory	refer to 16.12 ICH Q7 (WHO 13.1)		4.1 General Requirements
13.5 Subcontracting may be permissible under certain conditions, subject to approval by the contract giver, especially for activities such as sampling, analysis, repacking and relabeling.	Self-explanatory	16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) 16.14		4.1 General Requirements

Chapter 5 Appendix

5.1 References

"GOOD TRADE AND DISTRIBUTION PRACTICES FOR PHARMACEUTICAL STARTING MATERIALS"
World Health Organization, WHO Technical Report Series, No. 917, 2003

"GUIDELINES ON THE PRINCIPLES OF GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE"
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The IPEC Good Distribution Practice Guide for Pharmaceutical Excipients
The International Pharmaceutical Excipients Council, 2006

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GMPs for APIs: "How to do" document, Interpretation of the ICH Q7 Guide,
ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE, Version 7, update August 2012

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A: IN THE PRODUCT INFORMATION OF MEDICINAL PRODUCTS
B: FOR ACTIVE SUBSTANCES
ANNEX TO NOTE FOR GUIDANCE ON STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS
ANNEX TO NOTE FOR GUIDANCE ON STABILITY TESTING OF
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USP 36, The United States Pharmacopeial Convention August 2013