WORKSHOP Quality and Regulatory: new frontiers in API manufacture
Pavia, 26th September 2014

How GDP guidelines impact on APIs manufacturers

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INTRODUCTION

The manufacture and supply of medicines has changed enormously in recent times. This change is principally in the use of outsourced manufacture and in many cases includes very lengthy and complex supply chains which span several countries outside the EU. Such supply chains, while providing many advantages, have also led to further opportunities for counterfeiters to introduce falsified constituents and finished products along the product lifecycle.

The Falsified Medicines Directive provides new EU regulatory control measures to address this changed global supply landscape and promotes closer cooperation between international regulatory authorities.

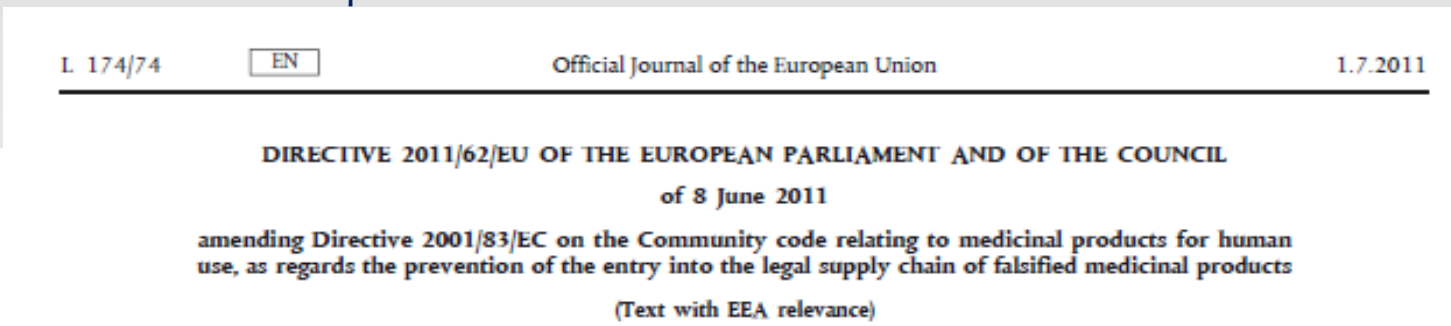
In December 2008, the European Commission issued a "pharmaceutical package" of three legislative proposals to strengthen the EU's human medicines regulatory framework for public health protection. They covered:

- Access to reliable information **(patient information access)**
- The safety monitoring of medicines **(pharmacovigilance)**
- The better protection of EU citizens from the serious threats posed by fake medicines **(falsified medicines).**

The pharmaceutical package was an amendment to EU Directive 2001/83/EC and was subject to the usual EU legislative procedures. The pharmacovigilance provisions were agreed first and were implemented in July 2012. The falsified medicines provisions (Falsified Medicines Directive (FMD)) were adopted next and published in the Official Journal on 1 July 2011, with phased implementation.

The new falsified medicines legislation added additional requirements to four main areas; active substances, supply chain and **good distribution practices (GDP),** safety features and internet supply .

It also defined for the first time in EU medicines legislation what is meant by "falsified medicinal product".



L 174/74 EN Official Journal of the European Union 1.7.2011

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

(Text with EEA relevance)

Importers, distributors and manufacturers of active substances based in the EU must be registered with the relevant national competent authority and the details entered onto EudraGMDP, the Community database on manufacturing, import and wholesale distribution authorizations, and GMP and GDP certificates.

Each batch of active substance imported from third countries must be accompanied by a written confirmation from the competent authority of the exporting country to confirm that GMP at the source plant is at least equivalent to that laid down in the EU for active substances. This confirmation may be waived if the third country is listed by the European Commission (the "white list") as having systems and standards equivalent to EU GMP for active substances. Exceptionally, and to maintain supply, active substances may be imported from manufacturing sites that hold a valid GMP Certificate issued by an EU national competent authority.

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

In Italy the recent Italian Legislative Decree of 19 February 2014 n. 17 has transposed Directive 2011/62 /EC amending Directive 2001/83 / EC on the Community code relating to medicinal products for human use, in order to prevent the entry of counterfeit medicines in Europe.

The decree then makes several changes to the legislative decree of 24 April 2006 no. 219 also about the counterfeiting

The main measures introduced can be summarized as [...]

With regard to the production of active substances used in the composition of the drugs must be followed good manufacturing practices, whether these substances come from EU countries whether products imported from third countries.

In the manufacture of active substances in third countries for export to the European Union, the competent authority of the exporting country must certify that the establishments concerned have been subjected to periodic inspections stringent and transparent, even willing to guarantee a level of public health protection at least equal to the required standards at European level.

In order to strengthen the legal protection of the supply chain, importers, manufacturers and distributors of active substances must be registered with the competent authority. In addition, the authorization holders should verify through direct controls that manufacturers and distributors of drugs comply with the best practices. They are required also to verify that the excipients used in the manufacture of medicinal products are fit for purpose, also wholesale distributors of medicinal products should ensure that their suppliers are in possession of the necessary authorizations.

In case of suspicion about the authenticity of medicinal products, manufacturers are obliged to inform the competent authorities (Ministry of Health and AIFA), is also envisaged the creation of an information network in order to prevent the drugs reported as suspected may be placed in circulation.

It is expected that the AIFA can perform periodic inspections (without notice) in places of production and storage of substances used for medicinal use. Given that the competent authorities referred to above are responsible for putting in place a system of controls in order to prevent the introduction into commerce of drugs of dubious origin, thus enabling the withdrawal of the same, is also provided for the implementation a system that allows, in case of serious risks to public health, to extend the warning to the authorities of the other Member States and to proceed immediately to the withdrawal of dangerous drugs [...]. "

GDP DEFINITION

"GDP is that part of quality assurance which ensures that the quality of medicinal products is maintained throughout all stages of the supply chain from the site of manufacturer to the pharmacy or person authorized or entitled to supply medicinal products to the public."

(***GDP Guidelines*** *2013/C 343/01)*

MORE ABOUT GDP GUIDELINES: Major developments

PHARMACEUTICAL PRODUCTS

- GDP Guidelines are based on Article 84 and Article 85b(3) of Directive 2001/83/EC
- The Commission has published EU Guidelines on Good Distribution Practice (GDP) in 1994
- Revised guidelines were published in March 2013 in order to take into account recent advances in practices for appropriate storage and distribution of medicinal products in the European Union, as well as new requirements introduced by Directive 2011/62/EU

A new version of the Guidelines on good distribution practice (GDP) of medicinal products was published on Novembre 2013 (2013/C 343/01)

OTHER GENERAL INFORMATION

➢According to Article 1(17) of Directive 2001/83/EC, **wholesale distribution of medicinal products** is all activities **consisting of procuring, holding, supplying or exporting medicinal products,** apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned.

➢Any person acting as a wholesale distributor has to hold a wholesale distribution authorization. Article 80(g) of Directive 2001/83/EC provides that distributors must comply with the principles of and guidelines for GDP.

➢Possession of a manufacturing authorization includes authorization to distribute the medicinal products covered by the authorization. Manufacturers performing any distribution activities with their own products must therefore comply with GDP.

The definition of wholesale distribution does not depend on whether that distributor is established or operating in specific customs areas, such as in free zones or in free warehouses.

OTHER GENERAL INFORMATION

GDP guideline introduce the application of a **GMP–like** system to the Pharmaceuticals Products distribution focused on :

- the maintenance of a quality system setting out responsibilities, processes and risk management principles in relation to wholesale activities;

- suitable documentation which prevents errors from spoken communication; sufficient competent personnel to carry out all the tasks for which the wholesale distributor is responsible;

- adequate premises, installations and equipment so as to ensure proper storage and distribution of medicinal products;

OTHER GENERAL INFORMATION

- appropriate management of complaints, returns, suspected falsified medicinal products and recalls;

- outsourced activities correctly defined to avoid misunderstandings;

- rules for transport in particular to protect medicinal products against breakage, adulteration and theft, and to ensure that temperature conditions are maintained within acceptable limits during transport;

- Specific rules for brokers (person involved in activities in relation to the sale or purchase of medicinal products).

WHAT ABOUT GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE

It is logical to consider the regulations recent changes in the order in which they affect a product's lifecycle, starting with **active substance manufacture.**

The active substance must be manufactured in accordance with good manufacturing practice (GMP) for active substances (ICH Q7 as adopted by the EU). All active substances are in the scope of the legislation, including atypical active substances. For medicines made in the EU it is the responsibility of the dosage form manufacturer to ensure this by performing on-site audits.

The active substance must also be distributed in accordance with GDP for active substances

NORMATIVES BACKGROUND ABOUT GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE

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.

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.

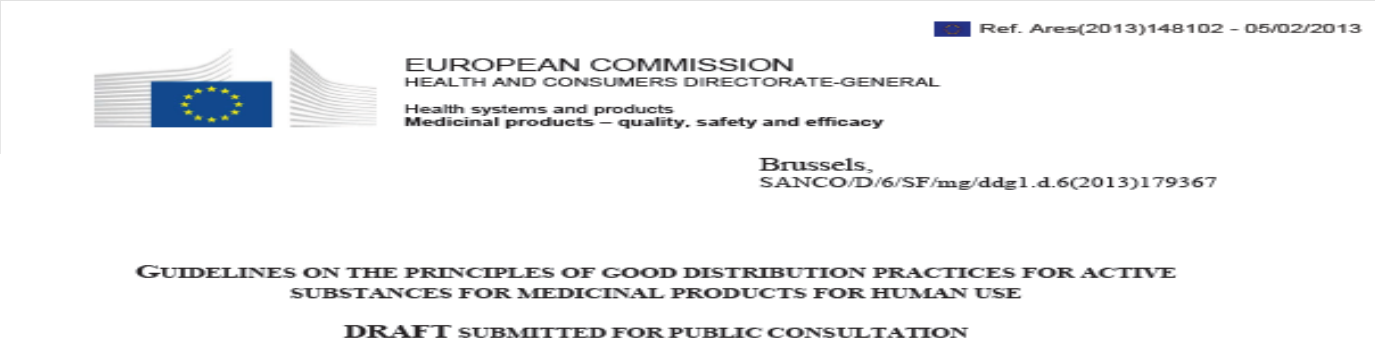
The EU Commissions **Guideline on the Principles of GDP for APIs** has been the first regulatory binding document specifically for distribution activities of APIs.

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,

1- The guideline describes only the "Principles" of GDP

2- 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.**

3- Activities consisting of re-packaging, relabelling or dividing up of active substances are manufacturing activities and as such are subject to the guidelines on Good Manufacturing Practice of active substances.



Ref. Ares(2013)148102 - 05/02/2013

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – quality, safety and efficacy

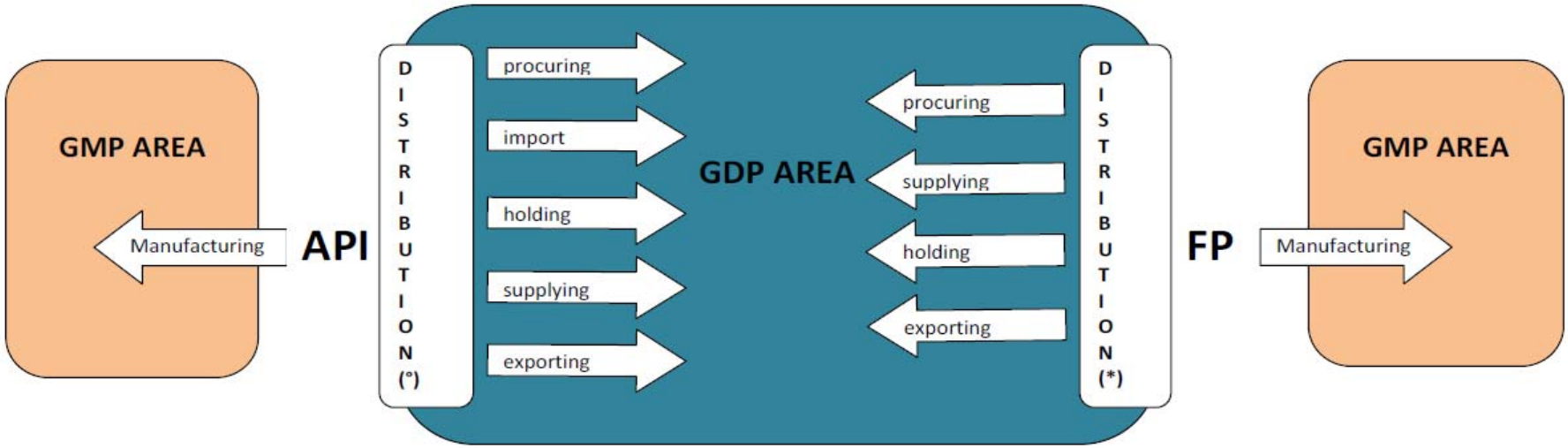
Brussels,
SANCO/D/6/SF/mg/ddg1.d.6(2013)179367

GUIDELINES ON THE PRINCIPLES OF GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE

DRAFT SUBMITTED FOR PUBLIC CONSULTATION

GDP GUIDELINES IMPACT ON APIs MANUFACTURERS

All manufacturers of active substances that also act as **procuring , import, holding, supplying or exporting** active substances shall comply with the requirements of GDP



(°) GUIDELINES ON THE PRINCIPLES OF GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE SANCO/D/6/SF/mg/ddg1.d.6(2013)179367

(*) Guidelines of 5 November 2013 on Good Distribution Practice of medicinal for human use (2013/C 343/01)

Glossary of terms

Procuring : Obtaining, acquiring, purchasing or buying drug substance from manufacturers, importers or other wholesale distributors

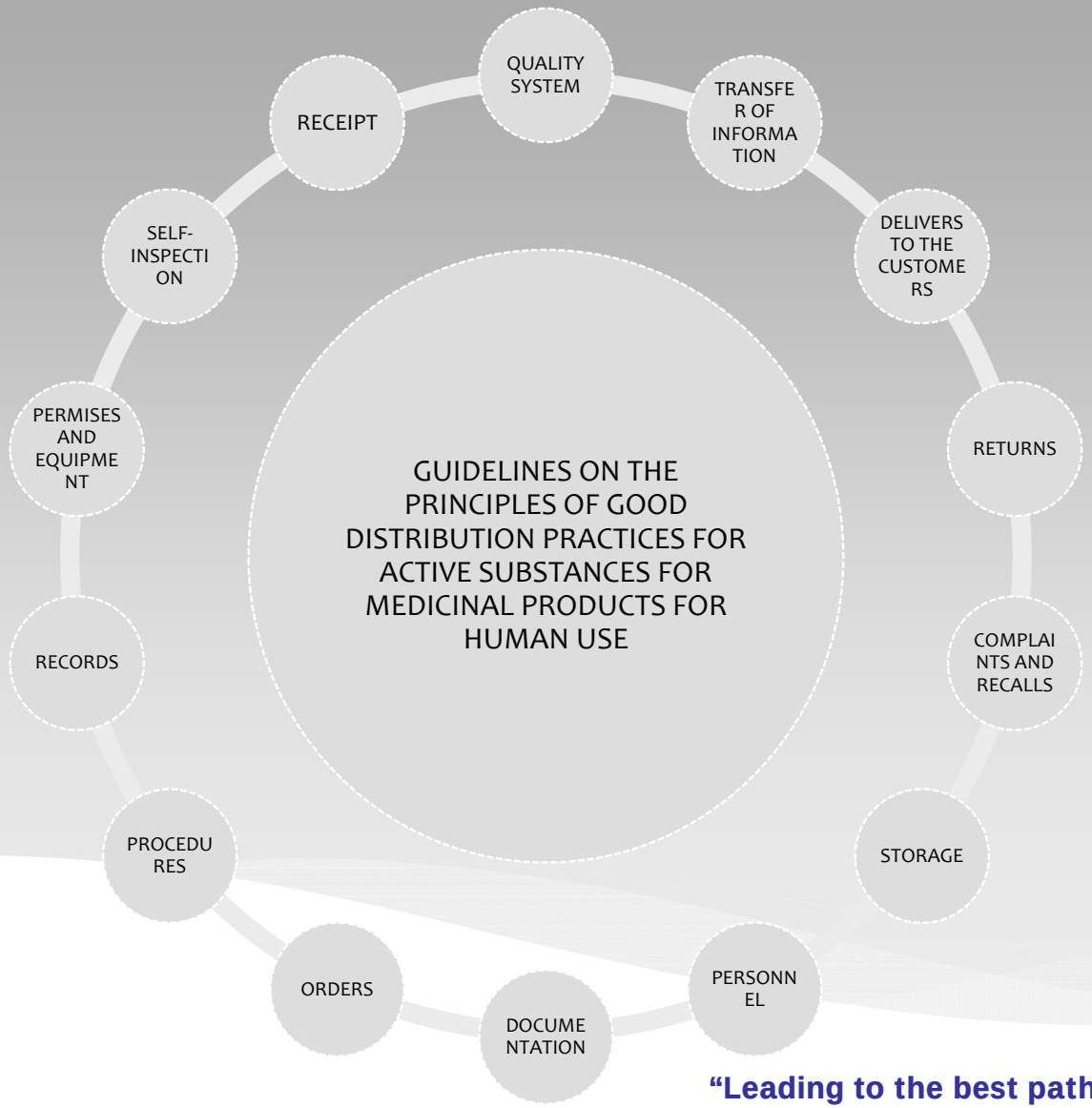
Import procedure : Allow goods to enter in the EU conutry from a not EU country

Holding : storing drug substance

Supplying : All activities of providing, selling, donating drug substance to wholesalers, pharmacists, or persons authorized or entitled to supply medicinal products to the public

Export procedure: Allow Community goods to leave the customs territory of the Union.

GUIDELINES ON THE PRINCIPLES OF GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE



"Leading to the best pathway"

EUTICALS

GDP How to Do doc_May 2014.

This document was developed and written 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

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".

GDP guideline for drug substance main areas general principles and impact on the on APIs manufacturers

1. Quality 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).

❑ **IMPACT : no impact because a quality system is in place for all the API manufacturers , under surveillance of AIFA , FDA and other Regulatory Authorities.**

2. Organization and Personnel

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.

❑ **IMPACT : no impact because an organization and adequate personnel are in place and in force for all the API manufacturers , under surveillance of AIFA , FDA and other Regulatory Authorities .**

3. Premises

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.

❑ **IMPACT : no impact because AIFA with the ministerial decree N° 219/2006 and subsequent updates required a dedicated authorization for active ingredients manufacture and for distribution with handling if not included in the manufacturing license.**

4. Warehousing and Storage

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 Ware-housing Materials of the APIC How to do document (interpretation of ICH Q7)

❑ **IMPACT : no impact because a warehouse and storage areas for all the API manufacturers are requested to be in place according to GMP rules.**

5. Equipment

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 intend-ed. 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.

❑**IMPACT : no impact because equipments for all the API manufacturers are requested working according to GMP rules.**

6. Documentation

Procedure on document control should be established. A revision history of documents should be readily available.

Retention periods of documents should be established.

❑**IMPACT : no impact because documentation as batch record , log book , validations , cleaning procedures and standard SOP for API manufacturers are requested according to GMP rules.**

7. Repackaging and relabeling

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.

❑**IMPACT : yes, so API manufacturers also involved in the distribution of active substance ,as intended in the GDP guideline ,must be in compliance with the above requirements .**

8. Complaints

Complaints and information about possible defects should be systematically documented and investigated, based on a written procedure with assigned responsibilities.

❑**IMPACT : yes, so API manufacturers also involved in the distribution of active substance ,as intended in the GDP guideline ,must be in compliance with the above requirements .**

9. Recalls

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

❑**IMPACT : yes, so API manufacturers also involved in the distribution of active substance ,as intended in the GDP guideline ,must be in compliance with the above requirements .**

10. Returned goods

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.

❑**IMPACT : yes , so API manufacturers also involved in the distribution of active substance ,as intended in the GDP guideline ,must be in compliance with the above requirements .**

11. Handling of non-conforming materials

Additionally the original manufacturer of the API has to be informed about the situation.

- **IMPACT : yes, so API manufacturers also involved in the distribution of active substance ,as intended in the GDP guideline ,must be in compliance with the above requirements .**

12. Dispatch and transport

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.

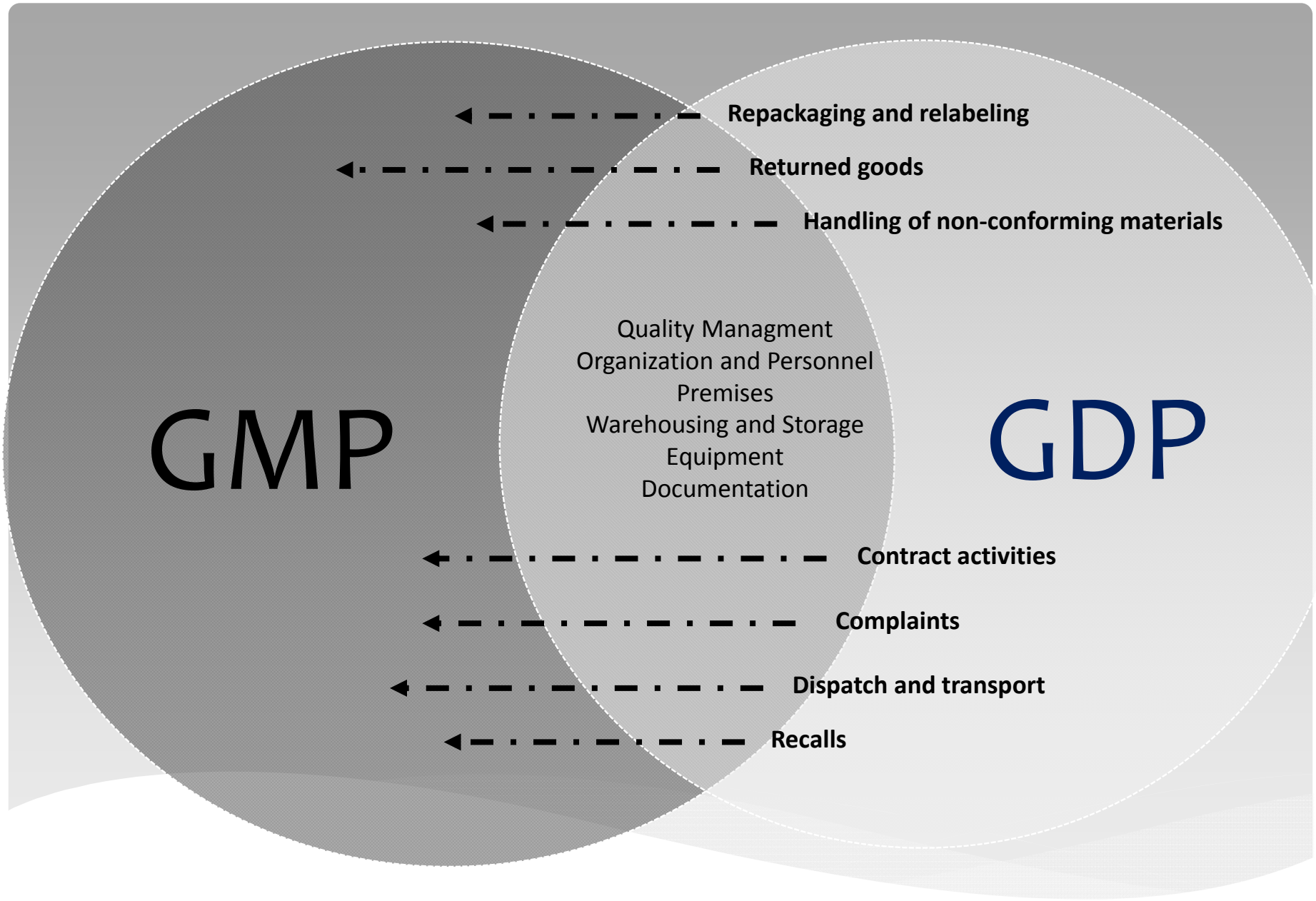
In case of temperature excursions during transportation tools like e.g. stability studies, cycling studies, shipping studies, Mean Kinetic Temperature concept could be used in combination with a risk assessment to assess the potential impact on the API.

❑**IMPACT : yes , so API manufacturers also involved in the distribution of active substance ,as intended in the GDP guideline ,must be in compliance with the above requirements (selection of correct transporters , qualification , quality agreement , certifications risk analysis , monitoring of temperature , declaration for use of second transporter in the chain , cleaning of truck).**

13. Contract activities

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.

❑**IMPACT : yes, so API manufacturers also involved in the distribution of active substance ,as intended in the GDP guideline ,must be in compliance with the above requirements as part of correct GMP approach.**


Repackaging and relabeling
Returned goods
Handling of non-conforming materials
Quality Managment
Organization and Personnel
Premises
Warehousing and Storage
Equipment
Documentation
GMP
GDP
Contract activities
Complaints
Dispatch and transport
Recalls

THANK YOU FOR THE ATTENTION !

“Leading to the best pathway”