Good Distribution Practices and Medicinal products

a trip to the Excellence

EU regulations and Implementation

Which Regulation Do I need to follow for Health Care products ?

Medicinal products

Active Pharmaceutical Ingredients (API)

Veterinary products

Medical Devices

Blood & plasma products

…etc

Cosmetic products & Nutraceuticals

HEALTH CARE- "The act of taking **preventative** or necessary **medical procedures to improve a person's well-being**. This may be done with surgery, the administering of medicine, or other alterations in a person's lifestyle. These services are typically offered through a **health care system** made up of hospitals and physicians."

Specific regulation for Distribution/ Transport arrangement

Medical Devices

Veterinary products

Cosmetic products & Nutraceuticals

Blood & plasma products

No legal regulation !!

but

TRUE for all products kind of

Customer requirements → Customer contract agreement

Product (Quality, Safety, Traceability, Integrity) requirements (Dir. 93/42/CE, 90/385/CE, 98/79/CE for MD, …) during **Manufacturing** (and storage, as part of the manufacturing !) → Product Label requirements

3PL own requirements → 3PL Quality Manual

Specific regulation for Distribution/ Transport arrangement

Active Pharmaceutical Ingredients (API)

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

Medicinal products

Our center of interest today !

Dir. 2001/83/CE, relating to Medicinal products of Human Use/ Title VII- Wholesale Distribution of Medicinal products

Art.84

Guidelines of 19 march 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use (2015/C 95/01)

Dir. 2011/62/EU amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of falsified medicinal products,

+ **special storage conditions** (and special authorizations) may be required for particular products (e.g. narcotics and psychotropic substances).

Medicinal product ?

Article 1 of Directive 2001/83/EC establishes the following **definition of medicinal product:**

Medicinal products

(a) Any substance or combination of substances **presented as having properties** for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either **with a view to restoring, correcting or modifying physiological functions** by exerting a **pharmacological, immunological or metabolic action**, or to making a medical diagnosis.

borderline products (food products/food supplements, medical devices, biocides or cosmetics)

when there is uncertainty over the classification of a product, the stricter regime of medicinal products applies !!!

Why do we need to consider Medicinal products as different from others ?

+++ stricter regime +

Medicinal products

- Based on the principle that medicinal products may be placed on the market only following a marketing authorization granted by the competent authorities.
- Community procedures (centralized, mutual recognition, inspection) are in place since the mid-90s
- A pharmacological, immunological or metabolic action (proof of)

Medical Devices

Intended to be use for

- diagnosis, prevention, monitoring, treatment or alleviation of disease/ of or compensation for an injury
- investigation, replacement, modification, or support of the anatomy or of a physiological process
- Disinfection

Cosmetic products & Nutraceuticals

(or make-up)

- substances or products used to enhance or alter the appearance or fragrance of the body

How to do business here ?

Loss of product Traceability

No marketing authorization

No pharmacological, immunological, metabolic action

Loss of product Integrity

Loss of product Quality

Loss of product Efficacy

Loss of product Identity

License and legal authorizations

1

Specific Risks to be take into consideration within our supply-chain….

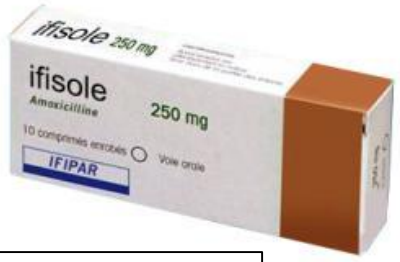
2

GDP requirements and Objectives

No business !

The GDP's Objectives- focus on product

The PRODUCT quality and **the integrity** of the medicinal products have to be **maintained** (proof)



Medicinal product

No harms to the patient

SECURITY

No contamination

QUALITY

Lead to the desired efficacy

EFFICACY

Like the GMP !

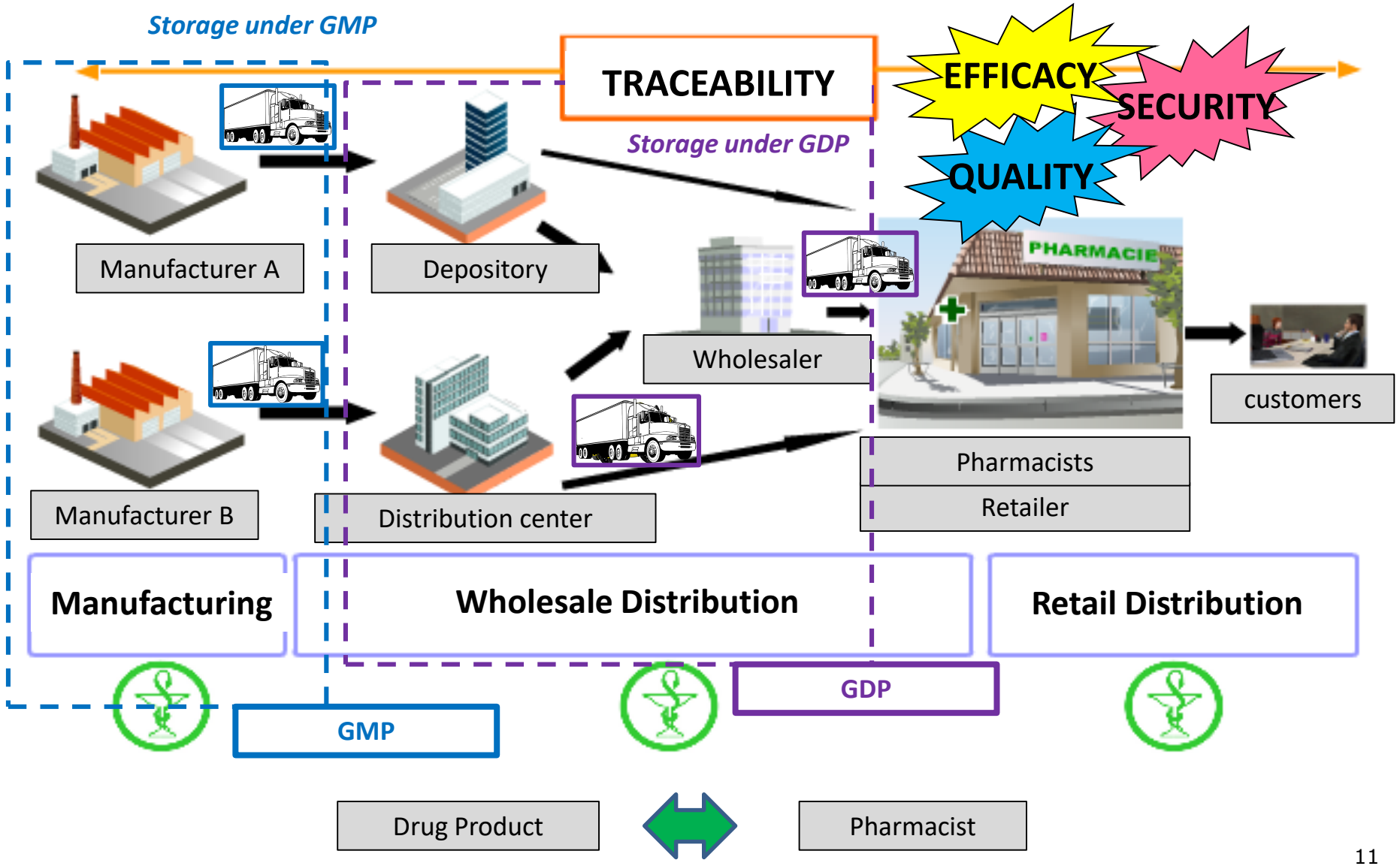
The GDP's Objectives- a management system

GDP is "that **part of Quality Assurance that ensures that the quality of medicinal products is maintained throughout all stages of the supply chain from the site of manufacture to the pharmacy or person authorized or entitled to supply medicinal products to the public**".

Supply chain flows

It is of key importance that **the quality** and **the integrity** of the medicinal products are **maintained during the entire supply chain** from the manufacturer to the patient.

To maintain the entire supply-chain ?



License and Legal Authorizations

The GDP applies to all medicinal products under any of the following **licensed pharmaceutical establishments:**

- ***Manufacturer*** (make, assemble or import human medicines)

⇔ (site) Manufacturer authorization (in addition to the marketing product authorization !)

- ***Wholesaler dealer / Wholesale distributor*** (To sell or supply medicines to anyone other than the patient using the medicine, you need a wholesaler license) *Our center of interest today !*

⇔ a wholesale dealer license or a wholesale distribution authorisation

List of authorized EU Authorized holders

http://eudragmdp.ema.europa.eu/inspections/mia/searchMIA.do

Transport arrangement and Pharmaceutical products legal requirements

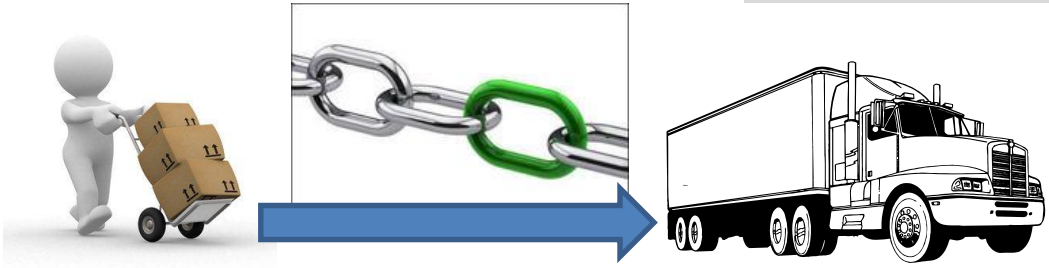
⇔ Therefore the **transportation** arrangements from one location to another should be regarded as an **extension of the storage activities** and

distributors are expected to treat each journey as unique, with the length and complexity, as well as any seasonal variations, being considered when choosing the packing method and mode of distribution.

The Good Distribution Practices (GDP)

⇔ The Good Storage Practices (GSP)

⇔ The Good Transport Practices (GTP)



Storage is okay but where is the Transport arrangement taking into consideration ?

Medicinal products

Chapter 9 of the **EU GDP Guidelines** is dedicated to this subject (Transport)

One specific chapter above 11 in total

(but still)

Pharmaceutical license

It is the **responsibility of the supplying wholesale distributor** to ensure that, “the required storage conditions should be maintained during transportation within the defined limits as described by the manufacturer or on the outer packaging”… (of the product).

Medicinal products GDP and Liability

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

Wholesale distributor activities + medicinal products = **to follow the 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**. All obligations related to wholesale distribution activities (such as exporting, holding or supplying) also apply to these distributors."
(GDP guidelines- Introduction)

“Wholesale distribution” of medicinal products ?

- Depository
- Wholesaler
- Distribution center

By DEFINITION

“**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** (upstream process) or with pharmacists and persons authorized or entitled to supply medicinal products to the public (downstream process) in the Member State concerned.”

Directive 2001/83/CE, **Art.1 ¤17**

http://eurlex.europa.eu/search.html?qid=1491732662975&text=Directive%202001/83/EC&scope=EURLEX&type=quick&lang=en

“All activities” ?

Many different (potential) activities under the same license !

- **Procuring** : obtaining, acquiring, purchasing or buying medicinal products from manufacturers, importers or other wholesale distributors

Brokers

- **Holding** : storing medicinal products
- **Supplying** : all activities of proving, selling, donating medicinal products to wholesalers, pharmacists, or persons authorized or entitled to supply medicinal products to the public
- **Exporting** : allow goods to leave the customs territory of the European Union (supplying of medicines from EU Member State to a contracting State of the European Economic Area is not considered as export)

Wholesale distributor activities + medicinal products = **to follow the GDP** !

« GDP » of medicinal products?

DIRECTIVE 2001/83/CE and **GUIDELINES** 2013/C 343/01 → To all EEC State Members !

GDP

Directive 2001/83/CE, relating to Medicinal products of Human Use/ Title VII- Wholesale Distribution of Medicinal products

The law

Art.84

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

A choice !

Directive 2011/62/EU amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of falsified medicinal products,

The law

+ **product labeling** and **special storage conditions** (and special authorizations) may be required for particular products (e.g. narcotics and psychotropic substances).

The law

GDP Guidelines, to take « as is » ?

Regulatory status of the EU GDP Guidelines

- Medicinal products distribution **must follow the EU GDP directives.**

- **CEN /ISO standards** (and other certifications-types) **do not have** (here) **any legitimacy**. However, CEN/ISO standards norms can be taken into account, but are not sufficient.

- It is known (and agreed) that **the EU GDP Guidelines methods/means can be substituted by other methodologies/means of control** (other standards), as long as they provide (at leas)t the same level of confidence and that they are validated and followed.

The easy way is then to follow the EU GDP Guidelines, but maybe not (always) the most efficient !

EU GDP Guidelines- The Philosophy behind

- Those Guidelines give **objectives to be reach**
- Those Guidelines **do not give the pathway** of ensuring the objectives will be met
- It is **up to the different actors to define the means** and ways to reach the goal
- Ways and means will **be firm- specific, product-specific and risk-specific**

Again, GDP is about to maintain the Quality

From here

To here

Production

Distribution

⇔The product Distribution is an <u>added-value to the product Manufacturing</u>

GMP

Therefore, any GMP-GDP links ?

GDP

GDP/GMP interfaces ?

YES !!

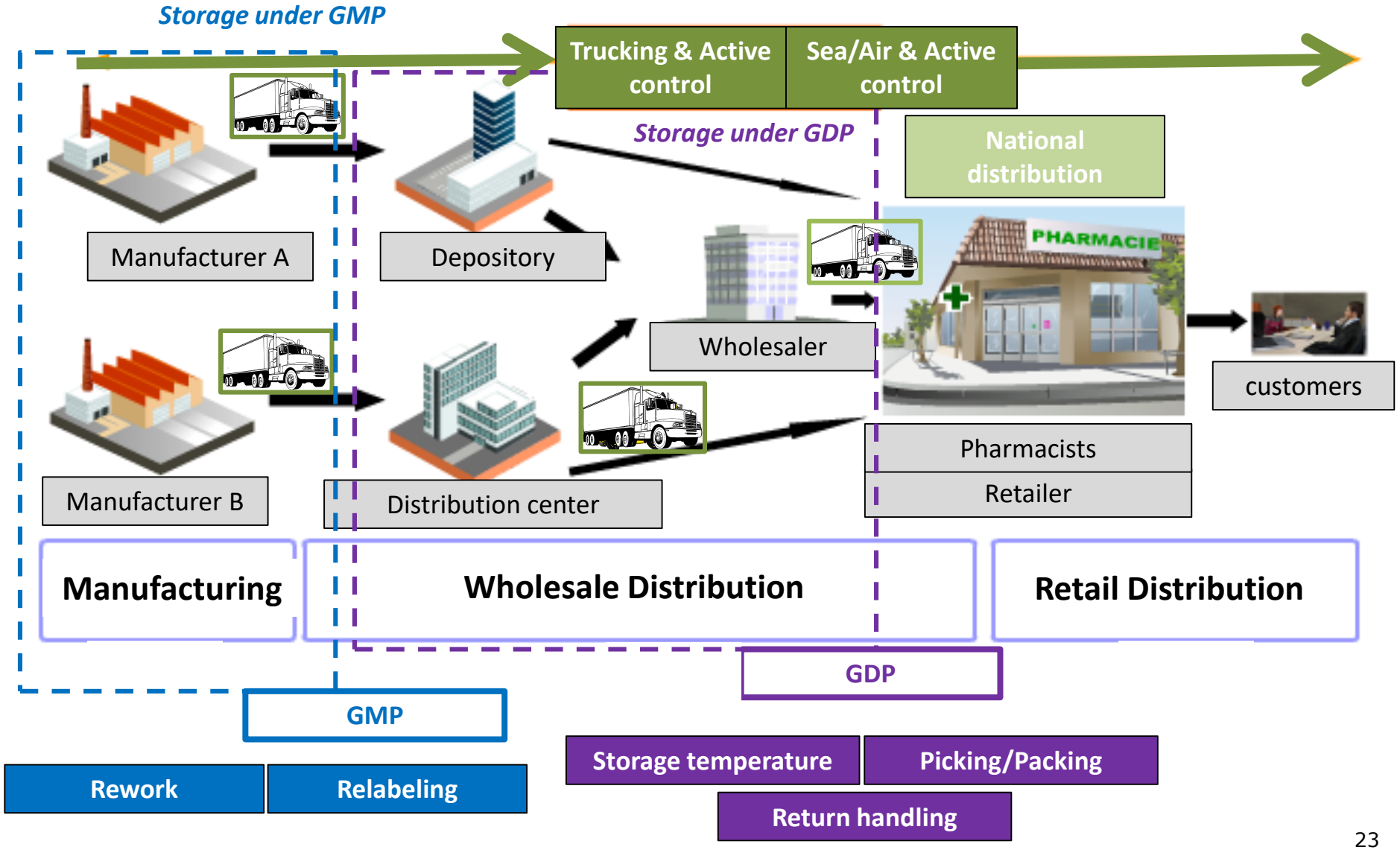
Good distribution practice is laid down in Directive 2001/83/EC and specified in periodically updated Commission guidelines based on **Article 84 and Article 85b**:

- The guidelines on **GDP contain similar criteria to those on GMP, but additionally cover measures to avoid suspected falsified medicinal products from entering the EU supply chain.**

- "**Possession of a manufacturing authorisation includes authorisation to distribute the medicinal products covered by the authorisation"**.
  ⇔Manufacturers performing any distribution activities with their own products must therefore comply with GDP. "

However wholesale distribution license does not authorize GMP activities !!!

GDP/GMP interfaces – understand the differences



GDP/GMP interfaces – understand the differences

Activities (legally) !

GMP

- Rework
- Relabeling

GDP

- Storage temperature
- Picking/Packing
- Return handling

License Authorizations !

GMP Authorization ⇢ **Wholesale Distributor license** → **GMP Authorization**

“Falsified medicines” ?

Falsified medicinal products are “fake” medicines **as regards their identity, history or use**.

They usually contain sub-standard or falsified active substances and pose a major threat to public health.

The term “**falsified**” is used to distinguish them from “**counterfeit**” medicines, which violate intellectual property rights.)

Illegal medicinal products

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

Protection against falsified medicines

The legal basis for preventing falsified medicinal products from entering the EU supply chain is **Directive 2001/83/EC as amended by Directive 2011/62/EU**, which adds relevant provisions. The **new legislation** introduces/ reinforces stricter rules to ensure that medicines are safe and that the trade in medicines is rigorously controlled:

- A common, EU-wide logo to identify legal online pharmacies, which has to be clearly displayed on every page of the website offering the medicine
- An obligation to ensure that manufacturers
  - Comply with GMP for active substances, including stricter controls and inspections and EU-wide rules on the import of active substances
  - An obligatory safety feature (unique identifier such as a barcode) on the outer packaging of medicines to verify the authenticity of a medicinal product ⇔ Manufacturing authorisation holders who repackage medicinal products should be liable for damages in the cases !

- Increase reliability in the supply chain, wholesale distributors should verify that their supplying wholesale distributors are holders of a wholesale distribution authorisation and comply with other applicable Union legislation

Protection against falsified medicines

Example of safety feature (unique identifier such as a barcode) on the outer packaging of medicines to verify the authenticity of a medicinal product :

flash code

INTERACTION PATIENT

Services d'interaction pour le patient via une application smartphone

Anti-counterfeit

ANTI-CONTREFACON

Solutions d'authentification:
- Packaging: Empreinte matière
- Étiquette: Étiquette de sécurité
- Marquage: Marqueurs secrets

serialization

SERIALISATION TRACABILITE

Solution modulable (génération de codes, système de Track & Trace)

TEMOIN D'EFFRACTION

Solutions de scellage spécifiques et adaptées

Seal evidence feature

Under the Manufacturer

Falsified medicines and Logistic requirements ?

Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use (2013/C 343/01) (as amended by Directive2001/83/EC -Art.84):

6.4. **Falsified medicinal products**

"Wholesale distributors **must immediately inform the competent authority and the marketing authorisation holder** of any medicinal products they identify as falsified or suspect to be falsified. **A procedure should be in place** to this effect. It should be recorded with all the original details and investigated.

Any falsified medicinal products found in the supply chain should **immediately be physically segregated** and stored in a dedicated area away from all other medicinal products. All relevant activities in relation to such products should be documented and **records retained**. "

A specific process !

Product serialization

Pharmaceutical serialization is the **tracking and tracing of the passage of prescription drugs (only)** through the supply chain from manufacturing to dispensing.
This is accomplished through automated, electronic means, and is legally required in Europe (due **February 2019**). It involves such company practices as recording, authenticating, maintaining and sharing accurate records of items prior to dispatching, within an authentication process, based on serial numbers on individual pharma packages.

Part of the EU 2016/161, supplement to Directive 2001/83/EC- Falsified medicines:

"Medicine authenticity should be guaranteed by an end-to-end verification system supplemented **by risk-based verifications by wholesalers**. Medicines should be systematically verified at the point of supply to the public (e.g. at pharmacy level). Medicines at higher risk of falsification (returned medicines or medicines not being distributed directly by manufacturers, marketing authorisation holders or people acting on their behalf) should additionally **be checked at wholesaler level.**"

Will impact Storage and Transport

Logistic and Risk management

EU GDP Guidelines- The Philosophy behind

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- Those Guidelines **do not give the pathway** of ensuring the objectives will be met
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- Ways and means will **be firm- specific, product-specific and risk-specific**

Risks?

- **Risk** is defined by the **"chance of injury or loss as defined as a measure of the combination of the probability and severity of an adverse effect (harm) to health, property, the environment, or other things of value »**

- "The evaluation of the risk to quality **should ultimately link back to the protection of the patient**"

- Will require at least, **Risk Identification** and **Risk Scenario** (defined sequences of events, from hazard to risk, with an associated frequency and consequences).

- (ICH Q9) "**The level of effort**, formality and documentation of the quality risk management process **should be commensurate with the level of risk** and based on scientific knowledge"

Is that enough to Manage risk or are there other steps to consider ?

Risk Assessment- Key points

Need to define first the scope of investigation

- **Risk Identification**: "The systematic **use of information** to **identify potential sources of harm (hazards)** referring to the **risk question or problem description**"

⇔Risk identification addresses the "***What might go wrong?"*** question, including identifying the possible consequences. This provides the basis for further steps like :

- **Risk Analysis** (the qualitative or quantitative process of **linking the likelihood of occurrence and severity of harms**. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk)

⇔ "***What is the likelihood (probability) it will go wrong***?" and "***What are the consequences (severity)?***"

- And the **Risk Evaluation** (which compares the identified and analyzed risk **against given risk criteria**). Risk evaluations ***consider the strength of evidence for all three of the fundamental questions.***

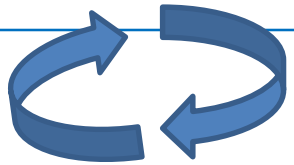
Risk Control- Key points

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

RISK Reduction	Act to mitigate the severity and/or probability of harm
RISK Acceptance	Accept as is (and accept the consequences)
RISK Resilience	A third option-change the situation

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?



GDP processes and key points

1 Quality system Management & Review

- Define process maps of their critical activities, define the critical control points and describe the areas of responsibilities
- Procedures should be developed and verified by systematic reviews to ensure that they appropriately control processes to ensure consistency and address potential risks
- The implementation of the Quality Management System shall be led by the organization's management
- it is important that this effectiveness is monitored and actions taken to
- Management Review practices is in place

- **QRM** introduces the opportunity to understand those risks and to put into place measures to reduce the risks and/or to control risks that cannot be removed
- To ensure **products delivered and ultimately administered to patients will still retain their quality attributes**
- A **change control system** should ensure that all relevant personnel are made aware of the changes in advance of the change and that the change is subject to a post implementation review to ensure its satisfactory implementation and absence of unintended consequence
- A **good CAPA system** not only addresses correction of issues identified as having occurred, but, using quality risk management principles, actively seeks to anticipate risks and mitigate them through appropriate preventive actions
- To **minimizes risk of counterfeit product** entering the supply chain and maintained product quality by ensuring the specified conditions for storage and transportation of the product are respected
- A key requirement of a QMS is that **all records are made at the time actions are completed** and never retrospectively to ensure accuracy (“data integrity”). This is a fundamental requirement of a GDP QMS. Personnel should be trained on the importance of this requirement

2 Personnel & Training

- It is important that one person be identified to take responsibility for ensuring that the quality system is implemented and kept up to date and reflective of current practice, best practice and regulatory and legislative expectations
- Organisation chart together with clear and comprehensive job descriptions
- Recruitment practices should ensure that appropriately educated and, where appropriate, experienced personnel are recruited
- Appropriate resources should be provided i.o to fulfil duties and GDP responsibilities
- Jobs descriptions should be subject to continual review to ensure they reflect the current expectations
- To ensure that the initial and continuous training of personnel is implemented.
- Training frequency and results of competency tests be captured along with prompts for retraining
- Complete training records to enable management tracking training needs of individuals and the company as a whole and therefore address any knowledge or experience gaps as required

Personnel & Training

2

- **RP** must **be contactable** for two mains reasons; firstly to seek advice in case of unexpected incidents to ensure any actions taken to resolve will still meet GDP requirements, and secondly to keep the RP informed of all activities being undertaken, so constant review of risks can take place

- In order for a wholesale distributor to demonstrate compliance with GDP, **all activities performed must be documented and recorded.**

- Personnel to be aware that activities must be done in accordance with defined processes (SOP's) to ensure that records are made consistently. Records must be completed at the time of performing activities, including signature and date ("**good documentation practices**")

- To **understand the wholesale dealer RP's responsibilities** and have defined contact names in front of

- Personnel should be given training in **understanding the complexities of supply chains with emphasis on how these may be exploited by counterfeiters**

- When handling of **hazardous products/ temperature-sensitive product**, personnel should be given training in understanding the risk, the complexities of supply chains with emphasis on how these may be exploited by counterfeiters.

3 Premise & Equipment

- Companies need to determine what is ‘proper’, ‘adequate’ or ‘suitable’ for the activities they undertake. The organization should identify all equipment that may have an impact on product quality

- In the event that gaps are identified, potential risks to the organisation can be used to influence colleagues and management to support appropriate corrective or preventive actions (CAPA)

- The (preventive) maintenance required and its frequency should be defined for each piece equipment/ type of equipment based on risk assessment. Guidance on preventive maintenance requirements can typically be obtained from the equipment manufacturer.

- For equipment deemed critical to operational continuity (e.g., Temperature controls), consider also the need for:
    - o Alarms
    - o Critical Spares
    - o Service agreements, including emergency/out of hours cover

- A procedure should define the communication and actions to be taken in case of alarm, e.g., quarantine the product, notification to the customer. To improve reliability and speed of response, consideration should be given to using automated systems to send alarm messages to personnel through SMS or mobile calls, etc.

- A list should define (at serial number level) the requirements for maintaining and calibrating the status of each piece of equipment. Software packages for managing equipment maintenance are frequently used to provide this equipment list and maintenance programme.
- Completion of preventive and corrective maintenance should be documented (maintenance certificates). These records should make reference to the equipment (individual identification) and the maintenance activities carried out on the equipment. Calibration and tests of alarms should be included in the maintenance plan.

- All systems and records should be subject to regular self-inspection.

3 Premise & Equipment

(**Computerized systems) 3.3.1**

- The approach to computerized system management, including validation should be defined in a **procedure**
- All computerized systems with a potential to impact product quality within the facility should be identified by **risk assessment** and documented.
- A controlled document describing each system will **help to ensure that all changes** on the system are agreed with the organization and also will support the use of the system for example for new employees. All changes should be subject to a formal change control process.
- Steps in the validation process include:
  - o URS (User Requirement Specification) to document what is expected from the system.
  - o DQ (Design Qualification),
  - o IQ (Installation Qualification),
  - o OQ (Operational Qualification)
  - o PQ (Performance Qualification)
- **Controls and access rights** should be defined and implemented.
- **Regular backups of IT systems** should be performed
- A **Business Continuity Management Plan** should exist to cover the event of IT system failure
- Reference to **EU Annex 11**

3 Premise & Equipment

(**Qualification & Validation) 3.3.2**

- All processed and equipment with a potential to impact product quality within the facility should be identified by risk assessment and documented

- For each process / equipment protocols should be prepared. The protocols document the risk (failure modes) associated with the processes / equipment. Based on the severity, probability and capability for detection, verifications / inspections should be defined to test the equipment.

- Protocols should be executed and results documented. If the acceptance criteria are met according to the protocol, the process / equipment can be considered qualified. Otherwise, corrective / preventive actions should be implemented and documented.

- Protocols and associated reports should be **approved by the Responsible Person or delegate within the quality organisation.**

- Further useful information on Qualification and Validation may be found in **EU GMP Annex 15**.

4 Documentation

- **Good documentation practice (GDP)** needs to be a fundamental part of the quality system and includes consideration of matters such as:

  - Appointing a person to manage the documentation system
  - **Making active decisions regarding the documentation required and the format in which it will be created, used and archived**
  - **Where electronic systems** are used, these should be appropriately specified and validated to ensure data integrity (3.3.1)
  - Defining responsibilities for review and approval of each type of document.
  - Training all staff to ensure they understand the principles behind the required documentation practices – staff are more likely to be compliant with a requirement that they appreciate the reason for than one that is required 'because it says so'
  - Recording data directly into official records, not on scraps of paper, and to do so at the time the operation is performed – this **reduces the risk of errors arising from lapses of memory or transcription.**
  - For paper records, information should be recorded in pen with permanent ink, not using a pencil or some other means of recording that might not endure.
  - For paper records, consideration of the manner in which the document will be archived might drive requirements for use of particular ink colors and decisions regarding single or double-sided printing.
  - Whenever records are made, care should be taken to ensure that they are legible, accurate and unambiguous so that they can be easily read and understood by someone else at a future date without recourse to the person who made them

- To ensure that **activities are undertaken correctly and recorded accurately,** instructions and templates for recording need to be both clear and free from errors. Signing and dating documents ensures that there is clarity regarding who performed the activity and when. Note that signing and dating may be by electronic means as well as 'pen on paper'. By making records at the time each operation is undertaken, the risk of errors is reduced as there is no need to rely on memory or the transcription of data from unofficial records made in personal notebooks or on pieces of paper. Contemporaneous data capture is one of the key principles helping to assure data integrity.

4 Documentation

(Documentation Design)

- Instructional documents and templates for data recording are expected to be typed, not hand-written, **to help avoid any errors** that might be caused by difficulties with reading another person's handwriting. But it is recognised that some records will need to be made by hand

- **Procedures and work instructions need to be followed at all times**; therefore they need to be located in the workplace, with enough copies and/or terminals available in larger facilities

- It enables operators to refer to procedures and access other required **documents without having to search for them**. Failure to have instructional documents in place and readily available/retrievable may result in staff undertaking activities without recourse to the instructions, thus increasing the risk of error

- It enables **operators to make contemporaneous records** – entering information directly into the computer system or onto the formal paper record at the time an activity takes place, not writing information onto pieces of paper for later transcription which increases the risk of data being lost or errors being made.

- Given that **procedures will change over time**, they should be version controlled. This enables clarity regarding which procedure was current at the time a given activity was performed.

- To enable **historical procedures** to be referred to in the event of an investigation or to support an audit, they should be archived for a defined period of time

4 Documentation

- Documentation, **whether as paper or electronic file**, is both the foundation of the quality system and a key output from the activities undertaken (paper files = electronic files)

- It is important that **data integrity** is maintained and that it is possible to trace back and understand any changes made. Signing and dating identifies who made the change and when. Making the alteration in a way that permits the reading of the original information and recording a reason for the alteration provide clarity on the history of the change – what was originally entered, what it was changed to and why this change was made. It is essential that they are readily available/retrievable, either for reference or in order to make records contemporaneously. Documents also need to be readily available/retrievable for self-inspections and audits by third parties or regulatory authorities to provide answers/evidence in response to auditor questions in a timely manner

- Some of the data required to be held and processed as part of distribution activities will fall within the **scope of European Union legislation designed to protect individuals' right to privacy and there are penalties for infringements**

- All staff should **be trained** in the principles of good documentation practice, including the requirements associated with any alterations made

- The intent of this requirement is to ensure that complete records are available for each batch for the full duration of time that it remains available for use. The minimum duration of five years aligns with the maximum shelf life accepted by the European Medicines Agency for a marketed medicinal product for human use (document retention SOP)

- **Specific minimum requirements for records associated with transactions in medicinal products**, be these receipts, supplies or brokering arrangements. They are intended to ensure traceability of data giving the history of each batch of product, underpinning the security of the supply chain, facilitating investigation into complaints and enabling prompt and comprehensive recall if required

5.2 Qualification of suppliers

- To ensure that these activities happen, and evidence is documented and maintained the process of selection, and approval should be controlled by a written procedure

- Appropriate technical/quality agreements and should include:
  - Arrangements to allow for audits
  - The communication of outcomes of regulatory inspections
  - Arrangements for the communication and handling of complaints and recalls
  - Any quality critical aspects specific to the products to be supplied
  - Suitable Key Performance Indicators (KPIs) to enable performance to be monitored

- To ensure that **suppliers are authorised and appropriate to act as suppliers** it is important that an initial 'qualification' and further ongoing qualification and approval of the selected suppliers

- **Where products are sourced from outside the European Union (EU),** there is a requirement for a Qualified Person (QP) to certify that they have been manufactured and checked in accordance with EU Good Manufacturing Practice (GMP) legislation and so a manufacturing authorisation (on which the QP is named) must be held

- Complying with these requirements will also safeguard **against risks that might be associated with goods handling**:
  - Without appropriate documentation
  - Prior to QP certification
  - With incomplete audit trail
  - Not having the requisite marketing authorisation
  - Labelled in the wrong language for the intended customer
  - Subject to recall
  - With inadequate shelf life remaining to enable onward supply to customers

- A mechanism should be in place to promptly **detect any loss of authorisation by suppliers**. EU based wholesale dealers should work to a single standard of GDP which meets EU requirements, irrespective of where products are going to be supplied. A robust process should be in place to ensure that products are only supplied to markets where they are authorised, or to other wholesale dealers. Include market details within the inventory description.

5.3 Qualification of Customers

- N/A

- By ensuring that they **only supply to appropriately authorised persons**, wholesale dealers help to maintain a reliable 'chain of custody' to the patient and **reduce the risk of products being misdirected and/or misused**
- It is important that there are **periodic rechecks because authorizations may change over time**
- Wholesalers may be in a position **to detect unusual sales patterns that might indicate illegal activities** which would not otherwise be identified

5.8 5.9 Supply & Export to 3rd countries

- N/A

- To ensure that the driver **knows where to deliver** the ordered product(s) & **to whom**
- So that the recipient can **check the delivery against the order**
- So that the recipient is aware of and able to **confirm the transport and storage conditions**
- To provide a '**chain of custody' in the event of a recall or other issue**
- The **delivery note** should be used by the recipient to check:
  - That the goods received are those that have been ordered
  - That products have been transported under appropriate conditions
- EU based wholesale dealers should work to a single standard of GDP which meets EU requirements, irrespective of where products are going to be supplied
- A robust process should be in place to ensure that products are **only supplied to markets where they are authorised**, or to other wholesale dealers. **Include market details within the inventory description**

6.1 Post-delivery activities

The minimum requirements must be in place:
- Robust, clear procedures on actions to take when any complaint, return, suspected falsified medicinal product or recall occurs
- Personnel identified who are authorised to assess returned product and clear instructions available for this purpose.
- Clear, detailed job descriptions stating responsibilities of each person.
- Clear, comprehensive record keeping so any emerging trends can be easily identified.
- Regular review of records and appropriate CAPAs initiated
- Regular training and learning sessions held, using real examples where possible to reinforce messages.
- Procedures reviewed critically and thoroughly after any incident to check whether they are robust, complete and effective

The minimum requirements must be in place:
- Any approval for sale of **returned goods** made by the Responsible Person (RP).
- **Appropriate segregation of each category of product during storage/transport to avoid any mix up**
- Sufficient well trained resource available at all times that understands the potentially serious implications of **any defective product entering the supply chain**
- **Mock recall** completed annually to ensure process is robust and will work in the case of an actual recall
- To ensure that everyone understands the importance of careful management of complaints, returns, suspected falsified medicinal products and recalls according to formal procedures and within agreed timelines

- The **minimum requirements** must be in place:
  - Robust, clear procedures on actions to take when any complaint, return, suspected falsified medicinal product or recall occurs
  - Personnel identified who are authorised to assess returned product and clear instructions available for this purpose.
  - Any approval for sale of returned goods made by the Responsible Person (RP).
  - Appropriate segregation of each category of product during storage to avoid any mix up.
  - Mock recall completed annually to ensure process is robust and will work in the case of an actual recall.

6.2 Customer(s) Complaints

The minimum requirements must be in place:

- Sufficient well trained resource available at all times that understands the potentially serious implic ctive product entering the supply chain.
- Clear, detailed job descriptions stating responsibilities of each person.
- Clear, comprehensive record keeping so any emerging trends can be easily identified.
- Regular review of records and appropriate CAPAs initiated
- Regular training and learning sessions held, using real examples where possible to reinforce messages.
- Procedures reviewed critically and thoroughly after any incident to check whether they are robust, complete and effective.

- Complaints are important inputs for detecting problems in the processes and/or quality of the product and are a useful tool for quality improvements**.** Complaints may arise from a failure of the quality of the product or the service (for distribution). Depending on each case the corrective / preventive actions can be very different

- It is important that correct actions are taken, including contacting the authorities where required. The organisation needs to correct then learn from the issue to minimize the risk to patients and minimize the chance of the same issue arising again in the future

- Complaints related to product quality issues **could affect patient safety**.

- All product related complaints **must involve the manufacturer and therefore be passed on quickly to the Marketing Authorisation Holder (MAH)**. Service complaints are typically the responsibility of the Wholesale Dealer Authorisation (WDA) Holder

- **Timelines** for the completion of identified actions should be defined and status discussed periodically at management review meetings

- The procedure should also define complaints that require **communication with the MAH or health authorities**

6.3 Returned Products

- A risk-based assessment will facilitate decision making regarding whether or not to return product to saleable stock. To assist wholesalers in this risk assessment, the regulators have provided significant detail in this section. Appropriate procedures for handling returns will ensure compliance with national laws and contractual arrangements, thus safeguarding business.

- If the returned products have been approved to re-enter the supply chain FEFO principles need to also apply to these products. Any doubts about the authenticity or quality of the product should mean it is not approved for resale

- **Returns can only be accepted under certain circumstances** and must always be assessed thoroughly before any approval for resale. This is to safeguard patients against product which may not have been stored or transported correctly and/or has been substituted. Products are returned for a variety of reasons including wrong product or quantity delivered (supplier error) or the customer no longer wants it / has over ordered. Depending on how the product was handled and stored after dispatch, this could result in physical damage, product degradation or contamination

- **Ensuring that these products are stored in a separate segregated and secure area** at the labelled storage conditions, so they do not enter the supply chain prior to proper assessment and decision on disposition

- The final disposition decision for a returned product should **be made by the Responsible Person**, in conjunction with the MAH where required in the Technical Agreement

- The **following factors should be considered as part of the assessment:**
  - Returned product should be received in the unopened, undamaged state.
  - There must be reasonable evidence that the product was supplied to that customer originally (via copies of the original delivery note or by referencing invoice number etc.) and the batch numbers are those that were originally supplied. This will provide some confidence that it is not a falsified product.
  - Is there recorded evidence that the product has been stored at the appropriate conditions for the whole period since its original supply?
  - How long has the product been with the customer? Some regulators have published expectations for the maximum length of time between a supply and return for it to be acceptable, e.g., the UK MHRA suggest 24 hours for refrigerated products and a maximum of 5 days for other products returned from unlicensed sites.

6.4 Falsified Products

- N/A

- **Falsified medicines present a serious risk to public health** (multiple deaths have occurred), and wholesale dealers are a potential source of entry for such products into the supply chain

- Extended (international) supply chains are especially vulnerable to such criminal activity. **Ensuring that falsified medicines are kept out of the legitimate supply chain is an ongoing challenge**. It is therefore imperative that wholesalers are vigilant to help ensure they identify any falsified medicines they receive and prevent them from being supplied to patients

The following needs to be in place as a minimum:

- Ensure purchase of medicinal products is always from a legitimate source. This should be checked and monitored the first time an order is due to be placed, then at regular intervals afterwards by relevant personnel through appropriate licence checks (Bona Fides), Quality Agreements, Audits and any other suitable means. Refer to 5.2 for further guidance.
- Have evidence on receipt that the correct transport route has been followed to the storage site
- Thereafter ensure products are only supplied to a bona fide customer; i.e. check authorisations when orders are received from new customers and at regular intervals afterwards. Refer to 5.3 for further guidance.
- Staff should be trained to look out for warning signs of falsified products, such as quality of packaging / printing of components, differences/changes to packaging materials, and to compare suspect packs with known originals. Training using real examples, where possible, will reinforce understanding.
- A procedure should define how the suspect / falsified medicine could be identified and actions to be taken. These should include how and where the falsified product is segregated and stored from other products and communication process to the authorities and MAH

6.5 Products Recalls

- N/A

- Recalls **are instigated by the Marketing Authorisation Holder or Regulatory Authority**. They are triggered when a serious quality defect has been identified so it is important that instructions are followed carefully and actions taken quickly to prevent continued presence in the market and any further affected product entering the supply chain.

- The purpose is to ensure that **each party in the supply chain understands and takes responsibility for their role** should a product recall be initiated, so that prompt and effective action can be taken, including 'out of hours'

- **Periodic evaluations enable assessment of the effectiveness of recall procedure**s and provide confidence in the personnel involved

- Distributors must have **procedures** in place which describe how they will act following receipt of a recall communication from MAH/CA. Distributors must have resources enabling them to communicate directly with appropriate individuals at customer organizations, e.g., other wholesalers, hospitals, clinics, surgeries and retail pharmacies

- Depending on the size of company the recall process must **be managed and coordinated by an individual**, who may be, for example, the Head of Quality, or the Responsible Person

- Evidence of communications should be retained **providing records** that customers have been contacted. Where named patient supplies have been made, these should also be contacted and records retained

1.3 7 Outsourced activities

- When an activity is outsourced it remains the responsibility of the contract giver to ensure it is carried out correctly, but it is outside of their direct operational control

- To avoid any misunderstanding or uncertainty regarding requirements and responsibilities, there needs to be a written agreement between the parties and on-going communication processes. The contract acceptor needs to exercise appropriate oversight to ensure the ongoing suitability of the contractor's performance and act to address matters if this is not the case

- The Contract Giver is ultimately responsible for the product in the marketplace even where certain activities are contracted out. They are therefore responsible for defining appropriate controls in a clear written Contract and monitor to ensure that the Contract Acceptor performs the outsourced activity as required

- The assessment of the suitability of the Contract Acceptor goes beyond initial selection and approval and should be a feature of the on-going relationship between the parties for the lifetime of the contract, so repeat audits should be undertaken at a frequency determined by the Contract Giver's risk assessment

- Where there has been a change to the scope of the contracted activities, a formal review in the form of an audit should be carried out to ensure that the contracted party remains suitable to carry out the contracted activity

- To ensure that where a Contract Acceptor sub-contracts work to another third party that the arrangements agreed with the Contract Giver are fully maintained

- The Contract Acceptor should have a process to manage sub-contracting

- Where the Contract Giver does not have the expertise to assess the information provided, they should forward the information and seek advice as appropriate

1.3 | 7 Outsourced activities

- To ensure that the Contract Giver maintains a **full knowledge of the supply chain** and is in a position to evaluate any changes and assess their impact

- The Contract should specify that the Contract Giver can perform an inspection of the Contract Acceptor's site at any time with an appropriate notice period and that if required a representative of a Regulatory Authority can enter the premises of the Contract Acceptor for **the purpose of auditing in relation to GDP activities** carried out on behalf of the Contract Giver

- It should be obvious that the Contract Giver needs to provide the Contract Acceptor with all the information necessary for them to ensure that they do as expected. This could include **specific product requirements,** such as:
  - storage conditions
  - other relevant requirements
  - particular documentation requirements for certain countries

The ultimate expertise on the product and parameters which may impact its quality will lie with the Marketing Authorisation Holder.

- Although it is primarily the responsibility of the Contract Giver to ensure that the Contract Acceptor is suitable, **the Contract Acceptor should identify any challenges to the Contract Giver prior to accepting work**. For example, if they do not have sufficient capacity of the stipulated storage facility/transport for the anticipated volume of work over a full year

- To **ensure that product quality is not adversely affected in the supply chain**. This requirement can be met by:
  - Complying with general GDP requirements (and any additional specific requirements in the Contract
  - Complying with any product specific requirements detailed in the Contract
  - Taking account of any additional information provided by the Contract Giver
  - Being mindful of limitations in knowledge and if in doubt asking the Contract Giver for advice

8.1 8.2 Self-inspection

- The implementation of a self-inspection programme is a crucial element of all Quality Management Systems, be they pharmaceutical or ISO 9000

- Self-inspections reinforce the importance of company staff and management taking responsibility for quality. They:
  - Increase management awareness and staff awareness of potential risks
  - Provide input to continuous improvement

- Self-inspection programme (and SOP):
  - Ensures full coverage with appropriate prioritisation based on risk assessment
  - Drives the conduct of inspections and provides a basis for checking progress
  - Provides a basis for assessment and management of resources – for auditors and auditees

- Self-inspections reinforce the importance of company staff and management taking responsibility for quality and **check compliance with GDP requirements**, helping to prepare for customer and regulatory audits

9.1 9.2 Transportation

- The licensed supplier of the medicinal products (e.g. a wholesaler or manufacturer) must ensure that products are transported so that they are received by the intended recipient 'fit for use'

- The IATA label is recommended for time and temperature sensitive products (see link below for more information)

- A temperature excursion is a deviation from the labelled storage conditions of a product for any duration of time whether during storage or transportation. All excursions should be successfully managed under a Quality Management System and as per the detailed specifications in your Technical Agreements. Corrective actions should be identified and implemented following the investigation of any deviation in order to prevent recurrence

- Temperature-sensitive product: Having a robust approach to qualification will provide the proof of suitability to both the regulator and the client. Completing properly documented mapping and qualification exercises shows suitability of use for a chosen purpose and provides the best possible chance of product being transported in the correct conditions

- Equipment critical to assuring the quality of product should be calibrated according to written procedures and an established schedule.

- (for temperature-sensitive products) Vehicle mapping should be carried out in Summer & Winter conditions (worst case) and repeated according to the results of a documented risk assessment or whenever significant modifications are made to the temperature controlling equipment or vehicle

9.1 9.2 Transportation

- The supply chain must have adequate security **to prevent theft of product and minimize the risk of falsified products entering the supply chain**

- **The chosen route of transportation** must ensure that the products are maintained within their required temperature parameters at all times (Risk assessment is required)

- **Documented evidence must be kept and be available**, showing the supply chain route that the products were distributed through **and the conditions that they were exposed to during transportation**. This could be demonstrated with temperature monitoring in vehicles, data loggers included in the shipment or previous qualification of the transportation route (taking into account seasonal variations). All distribution of medicinal products must be based on risk and documented accordingly, for example, taking into account the type of product and required storage conditions, journey time, method of travel (road, sea, air), time of year and expected external conditions

- Normally, the manufacturer has responsibility to the Distribution/Wholesaler and the Distribution/Wholesaler then takes over responsibility to final delivery point (Transporter is subcontractor of either one or the other one!)

- Precautions when use of **non-dedicated vehicle** (carry medicinal product as well as non-medicinal product /materials on the same vehicle)
  - Risks associated with non-dedicated vehicles: medicinal products could be loaded with other medicinal products or indeed any other types of product, e.g. Agricultural, chemicals, food, flowers etc. These other products may be packed on pallets or loose cartons/drums, destined for multiple delivery locations. Untrained and/or unapproved transport contractors and sub-contractors might be used.
  - Non-dedicated vehicles used for collections (and deliveries) will require procedural controls and processes that can demonstrate distribution compliance based on risk. These should be supported by very good contracts with responsibilities/accountability clearly defined

- **Delivery note requirements**: the document containing, but not limited to, full delivery address (including consignee details and telephone number); customer name; protocol name; carrier details; description and quantity of the product; shipping and storage conditions for the product (⇔ packing list; airway bill; manual order form; Proforma invoice….)

9.1 9.2 Transportation

- All deliveries should be accounted for and have a POD (**proof of delivery** - usually retained by a carrier) available. Date, time, consignee name and signature should be documented upon each delivery. Deliveries of medical products considered hand-to-hand service specific to the consignee indicated on the delivery note, therefore at no time should medical products be left on alternative premises

- For **emergency deliveries outside normal business hours**, persons should be designated and written procedures should be available (⇔ emergency delivery versus premium service provider)

- To **map your supply chain** to understand all touch points including the use of air, sea, road and a mixture of unloading and reloading hubs, warehouses/touch points (to identify stop over and hand over locations and **risks assessed** and documented). The 'owner' (title holder) of the product should be responsible for mapping the shipment route to the next party in the supply chain

- **Storage conditions on product labels** are based on stability data submitted as part of the Marketing Authorisation Application (MAA). Shipping studies are useful in documenting temperatures from the outside of packages to the chosen destinations

- Products such as **narcotics, radioactive or psychotropic substances** must be managed under procedures that will ensure national and international safety measures are in accordance with best practice as you source, store, transport and deliver these products
- (**Temperature-sensitive products**) Active or passive packaging solutions can be considered as well as temperature controlled vehicles. On-going monitoring programmes (data logger position and placement density) should be based upon the mapping exercise or qualification of the shipment method. Temperature monitoring data should be assessed for each shipment and regularly reviewed for any trends in location/route failures

- The packaging is the **carton or box that the product is placed in for transportation**. It could be a cardboard carton, validated insulated shipper, tote box etc. Labelling is referring to the shipment labels and not the actual product labelling. All shipments of medicinal products should bear labels showing the type of product, the required temperature conditions and any special handling requirements