

Good Storage and Distribution practices for Pharmaceuticals in European Union

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Abstract:

Distribution is an important activity in the integrated supply-chain management of pharmaceutical products. Good Pharmaceutical Storage Practices are often accompanied by the concept of Good Distribution Practice (GDP). In this regard just like GDPs, GSPs is also a part of the Quality Management System. To maintain the original quality of pharmaceutical products, every party active in the distribution chain has to comply with the applicable legislation and regulations. Good Storage Practices (GSPs) also play an integral role in various Pharmaceutical and Pharmacovigilance-oriented companies, organizations and institutions. Every individual in the pharmaceutical industry is responsible to maintain drug substance or drug product for its identity, strength, quality and purity. Every activity in the distribution of pharmaceutical products should be carried out according to the principles of GMP, good storage practice (GSP) and good distribution practice (GDP) as applicable. All drugs should be stored at stipulated temperature areas, protected from excessive light, dust, and humidity. The loss of potency during the storage may lead to decrease in the efficacy of the drug product. In this particular article, the Good Distribution and storage practices with respect to European Union are discussed and specific storage conditions from the proposed EU Guidelines were highlighted.

Key Words: Distribution, Quality Management system, Warehouse, Wholesale

INTRODUCTION:

Good storage and distribution practices may apply to all organizations and individuals involved in any aspect of the storage and distribution of all the drug products. Storage and distribution may involve the complex movement of products around the world, differences in documents and handling requirements and communication among various entities in the supply chain. The good storage and distribution practices would facilitate the movement of the drug product throughout the supply chain that is controlled, measured and analyzed for continuous improvements and should maintain the integrity of the drug product in its packaging during storage and distribution. [1]

The commission has published the EU Guidelines on Good Distribution Practice (GDP) in 1994. Revised guidelines were published in March 2013[2] 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. [3]

- EU Commission has revised the Guideline on Good Distribution Practices.
- The new GDP was published in November 2013.
- GDP guidance was in place from 1994.
- Amendment of GDP was essential in line with amendment of EC Dir. 2001/83/EC, since there was an alarming level of falsified medicinal products entering entering in EU for past few years.
- The EC Directorate for public health and risk assessment issued Dir. 2011/62/EU dated 8th June, 2011; amending Dir. 2001/83/EC [4]

The wholesale distribution of medicinal products is an important activity in integrated supply chain management.

Today's distribution network for medicinal products is increasingly complex and involves many players. These Guidelines lay down appropriate tools to assist wholesale distributors in conducting their activities and to prevent falsified medicines from entering the legal supply chain.

- According to Article 1 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.
- Any person acting as a wholesale distributor has to hold a wholesale distribution authorization.
- Possession of a manufacturing authorization includes authorization to distribute the medicinal products covered by the authorization.
- 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 actors such as brokers may also play a role in the distribution channel for medicinal products. According to Article 85b of Directive 2001/83/EC, persons brokering medicinal products must be subject to certain provisions applicable to wholesale distributors, as well as specific provisions on brokering.

Chapter 1: Quality Management [5]

- Wholesale distributors must maintain a quality system setting out responsibilities, processes and risk management principles in relation to their activities.
- All distribution activities should be clearly defined and systematically reviewed. All critical steps of distribution processes and significant changes should be justified and where relevant validated.

- The quality system is the responsibility of the organization's management and requires their leadership and active participation and should be supported by staff commitment.
- The quality system should be fully documented and its effectiveness monitored
- All quality-system-related activities should be defined and documented
- A quality manual or equivalent documentation approach should be established
- The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the product delivered maintains its quality and integrity and remains within the legal supply chain during storage and/or transportation
- A change control system should be in place

1.1 Principle

1.2 Quality System

1.3 Management of outsourced activities

1.4 Management review and monitoring

1.5 Quality risk management

Chapter 2: Personnel

- The correct distribution of medicinal products relies upon people. For this reason, there must be sufficient competent personnel to carry out all the tasks for which the whole sale distributor is responsible. Individual responsibility should be clearly understood by the staff and be recorded.
- Clarifies role of Responsible Person, approved organogram, laid down job descriptions and expectations on staff training and hygiene.

2.1 Principle

2.2 Responsible person

2.3 Other personnel

2.4 Training

2.5 Hygiene

Chapter 3: Premises and Equipment

- Wholesale distributors must have suitable and adequate premises, installations and equipment, so as to ensure proper storage and distribution of medicinal products. In particular, they should be Clean, Dry & Maintained within specified Temperature conditions and limits.
- Expectation on details of Premises, Temperature mapping, Electronic system to segregate stock & qualification & validation of equipment. Key new areas.

3.1 Principle

3.2 Premises

3.2.1 Temperature and environment control

3.3 Equipment

3.3.1 Computerized Systems

Appropriate validation or verification studies, that the system is capable of achieving the

- A written detailed description of the system should be available.

- The document should describe the principles, objectives, security measures & the way it interacts with other systems.

- Authorized to do so accidental or un-authorized modifications.

- Stored data should be checked periodically back up data should be retained for the period stated in national legislation but

- Procedures to be followed if the system fails or breaks down should be To use the computerized system, it has to be demonstrated that it provides solution consistently & with required reproducibility. (including diagrams where appropriate). Its functionality, security and risk assessment should be done as per EU GMP annex 11 requirements. Any manual intervention for the computerized system would lead to the appropriate investigation technical justification and assessment of risk associated with the deviation...

3.3.2 Qualification and validation

Wholesale distributors should identify what key equipment qualification and/or key process. Validation is necessary to ensure correct installation and operation. The scope and extent of such qualification and/or validation activities (such as storage, pick and pack processes) should be determined using a documented risk assessment approach.

Chapter 4: Documentation

- Good documentation constitutes an essential part of the quality system. Written documentation should prevent errors from spoken communication and permits the tracking of relevant operations during the distribution of medicinal products.

Key New Areas:

- The documentation should be in language understood by the users and operator's version control for procedures and emphasis on ensuring documentation is up to date

4.1 Principle

4.2 General

Chapter 5: Operations

- All actions taken by wholesale distributors should ensure that the identity of the medicinal product is not lost and that the wholesale distribution of medicinal products is performed according to the information on the outer packaging.
- The wholesale distributor should use all means available to minimize the risk of falsified medicinal products entering the legal supply chain.
- This requirement is laying down significant delaying of service providers / suppliers / warehouse etc. Main areas covered but not limited to...
 - Verifying the supplier that it is GDP compliant...
 - Due diligence checks on the supplier
 - stock statements review to identify any stock statements reviews to identify any misuse or diversion of medicines
 - Requirement for a control report when sourcing goods from EEA States

- Requirement for First Expiry First out – FEFO, rather than FIFO
- Stock inventories should be performed regularly
- Exporting medicines out of the EEA requires a wholesale authorizations and ion and GDP has to be has to be applied

5.1 Principle

5.2 Qualification of suppliers

5.3 Qualification of customers

5.4 Receipt of medicinal products

5.5 Storage

5.6 Destruction of obsolete goods

5.7 Picking

5.8 Supply

5.9 Export to third countries

Chapter 6: Complaints, Returns, Suspected Falsified Medicinal Products and Medicinal Product Recalls

- All complaints, returns, suspected falsified medicinal products and recalls must be recorded and handled carefully according to written procedures. Records should be made available to the competent authorities. An assessment of returned medicinal product should be performed before any approval for resale. A consistent approach amongst all partners within the supply chain is required in order to be successful in the fight against falsified medicinal products.”
- No significant changes to current requirement
- The new guide suggests 10 days may be an acceptable time limit to return medicines that have been outside the licensed chain.

Stolen medicines that are recovered cannot be returned to saleable stock

6.1 Principle

6.2 Complaints

6.3 Returned medicinal products

6.4 Falsified medicinal products

Chapter 7: Outsourced Activities

- Any activity covered by the GDP Guide that is outsourced should be correctly Defined, Agreed & Controlled in order to avoid misunderstandings which could affect the integrity of the product. There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party.”
- Requirements for contracts between parties where GDP has been outsourced are set very clear. Outsourced activities should be audited as a part of management review. Audits by independent external experts may be useful but should not be substituted for self-inspection!

7.1 Principle

7.2 Contract giver

7.3 Contract acceptor

Chapter 8: Self-Inspections

- Self-inspections should be conducted in order to monitor the implementation and compliance with

GDP principles and to propose necessary corrective measures.

Expectations:

Self-inspections can be carried out by staff other than RP.

An independent external audit is recommended.

The reports should be subject to CAPA principles.

8.1 Principle

8.2 Self-inspections

Chapter 9: Transportation

- It is the responsibility of the supplying wholesale distributor to protect medicinal products against breakage, adulteration and theft, and to ensure that temperature conditions are maintained within acceptable limits during transport. Regardless of the mode of transport, it should be possible to demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity. A risk-based approach should be utilized when planning transportation.
- A significant expansion on the requirements to control distribution channel. It is expected that products should be shipped according to the labelled conditions and that excursions are reported. There are detailed requirements for shipping shipping temperature sensitive items. Contracted transporters should be informed of storage conditions.

Key new areas:

- Medicines to be shipped within label conditions
- Temperature excursions should be reported and investigated
- Risk assessments of delivery routes to identify when temperature control is needed.
- Dedicated vehicles to be used where possible. 1 Procedures to cover use of non-dedicated vehicles
- A contract to be in place with transporters as required by Chapter 7
- The required storage conditions for medicinal products should be maintained during transportation within the defined limits as described by the manufacturers or on the outer packaging
- If a deviation such as temperature excursion or product damage has occurred during transportation, this should be reported to the distributor and the recipient of the affected medicinal products. A procedure should also be in place for investigating g and handling temperature excursions.
- Risk assessment of delivery routes should be used to determine where temperature controls are required. Equipment used for temperature monitoring during transport within vehicles and/or containers, should be maintained and calibrated at regular intervals at least once a year.
- Dedicated vehicles and equipment should be used, where possible, when handling medicinal products. Where non-dedicated vehicles and equipment are used procedures should be in place to ensure that the quality of the medicinal product will not be compromised.

- Where transportation is performed by a third party, the contract in place should encompass the requirements of Chapter 7.

Transporters should be made aware by the wholesale distributor of the relevant transport conditions applicable to the consignment. Where the transportation route includes unloading and reloading or transit storage at a transportation hub, particular attention should be paid to temperature monitoring, cleanliness and the security of any intermediate storage facilities.

- Provision should be made to minimize the duration of temporary storage while awaiting the next stage of the transportation route
- Containers should bear labels providing sufficient information on handling and storage requirements & precautions to ensure that the products are properly handled and secured at all times. The containers should enable identification of the contents of the containers and the source

9.1 Principle

9.2 Transportation

9.3 Containers, packaging and labelling

9.4 Products requiring special conditions

Chapter 10: Specific Provisions for Brokers

- “A "Broker" is a person involved in activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consists of negotiating independently and on behalf of another legal or natural person. Brokers are subject to a registration requirement. They must have a permanent address and contact details in the Member State where they are registered. They shall notify the competent authority of any changes thereof without unnecessary delay. By definition, brokers do not procure, supply or hold medicines. Therefore, requirements for premises, installations and equipment as set out in Directive 2001/83/EC do not apply. However, all other rules in Directive 2001/83/EC that apply to wholesale distributors also apply to brokers.
- Sets out the requirements for records and procedures required for brokers. This is a new area not previously required.

10.1 Principle

10.2 Quality system

10.3 Personnel

10.4 Documentation

Chapter 11: Final Provisions

Principles of Wholesaling in EU:

Falsified Medicines Directive, 2011/62/EU

The aim of this Directive is to control the falsified medicines through various measures at different stages:

Addition of safety features for Prescription Medicines and for Non-prescription products at risk of falsification.

Supply Chain & Good Distribution Practices for wholesale distribution of medicinal products in the Union extending Regulation to brokers.

Also includes import from 3rd country for re-export of medicinal products to 3rd country (products ‘introduced’ introduced in EU)

DIRECTIVE 2001/83/EC with amendment Dir. 2011/62/EC

According to Article 85b of Directive 2001/83/EC, persons brokering medicinal products must be subject to certain provisions applicable to wholesale distributors, as well as specific provisions on brokering.

Art.76 - Distribution of medicinal products only with Marketing Authorization (MA)

Art 77- Need of a wholesale authorization issued by competent authority (CA)

Art 78 – Timeline for decision of CA to grant the authorization: 90 Days

DIRECTIVE 2001/83/ E 2001/83/EC with amendment Dir 2011/62/EC

Art.79 - Minimum Requirements for obtaining the authorization:

- Suitable premises, Systems or procedures and installations, equipment’s, Trained and competent Staff
- Responsible Person
- Fulfilling obligations as defined in Art. 80

DIRECTIVE 2001/83/EC with amendment Dir. 2011/62/EC

Art. 80 - Minimum requirements (running the business) Suitable premises, installations and equipment accessible to the persons responsible for inspection

Supply chain only from and to the partners with wholesale authorization

Emergency plan for recall– Mock recall for verification

DIRECTIVE 2001/83/ E 2001/83/EC with amendment Dir. 2011/62/EC

- Art.81 - Mutual acceptance of Wholesale authorizations within the member states of the EU. Any obligations imposed on wholesaler of another EU country exceeding the national requirements forbidden.
- Art 82 Minimum requirements of information on the delivery slip to persons entitled to supply the public (i.e. pharmacies)
- Art 83 Special National requirements concerning Narcotic/ psychotropic substances within their territory, Medicinal products derived from blood, Immunological medicinal products, Radiopharmaceuticals

Management Review and monitoring:

“The management should have a formal process for reviewing the quality system on a periodic basis.

The review should include:

Evaluation and assurance of quality system objectives; Assessment indicators that can be used to monitor the effectiveness of processes within the Quality System, such as complaints, deviations, CAPA, changes to processes; feedback on outsourced activities; self-assessment processes including risk assessments & audits;

GOOD STORAGE PRACTICES:

The storage plays an important role in order to

- Ensure the potency of the drug product is maintained
- To prevent the deterioration, spoilage and degradation
- To maintain physical integrity
- To ascertain that the quality and safety is maintained throughout their shelf life.

WHO Annex 9 is intended for those involved in the storage, transportation and distribution of pharmaceuticals. It is closely linked to other existing guides recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, such as: [6]

- Good trade and distribution practice (GTDP) of pharmaceutical starting materials;
 - The stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms (information given in connection with regulation for marketing authorization);
 - Good manufacturing practices (GMP)
1. Personnel
 2. Premises and facilities
 - a. Storage areas
 - b. Storage conditions
 - c. Monitoring of storage conditions
 3. Storage requirements
 - a. Documentation: written instructions and records
 - b. Labelling and containers
 - c. Receipt of incoming materials and pharmaceutical products
 - d. Stock rotation and control

- e. Control of obsolete and outdated materials and pharmaceutical products
4. Returned goods
5. Dispatch and transport
6. Product recall

CHMP has proposed guideline on Declaration of Storage Conditions which has given the following specifications:

Core Storage Statements: [7]

The storage conditions must be possible for the user to follow and it is therefore necessary to restrict the statements to those achievable in practice Results from stability studies, presented at the time of submission, should serve as guidance and there should be a direct linkage between the label statements and the demonstrated stability characteristics of the finished product. However, a storage statement cannot be used to compensate for insufficient stability data, e.g. omission of stability studies at accelerated or intermediate testing conditions. The use of terms such as ‘room temperature’ or ‘ambient conditions’ is unacceptable.

The exact wording of the statements given in the table below will be applied throughout the Community taking into consideration that because of national linguistic and cultural differences, two alternatives are presented for storage below 25°C and below 30°C, respectively, and it is the decision of the competent authority which of these should be used. Any other statements are only acceptable if unavoidable and, in particular, where the core storage statements are documented to be inappropriate. The alternative proposal is to be supported by relevant data and must be realistically achievable in practice.

Testing conditions where the product is stable	Required labelling statement	Additional labelling statement*, where relevant
25°C/60%RH(long-term) 40°C/75%RH(accelerated)or 30°C/65%RH(long-term) 40°C/75%RH (accelerated)	None***	Do not refrigerate or freeze
25°C/60%RH (long term) 30°/60or65°% RH (intermediate) or 30°C/65%RH (long term)	Do not store above 30°C or Store below 30°C	Do not refrigerate or freeze
25°C/60%RH (long term)	Do not store above 25°C or Store below 25°C	Do not refrigerate or freeze
5°C ± 3°C (long term)	Store in a refrigerator or Store and transport refrigerated *****	Do not freeze
Below zero	Store in a freezer or Store and transport frozen *****	

* Depending on the pharmaceutical form and the properties of the product, there may be a risk of deterioration due to physical changes if subjected to low temperatures. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

** The SPC and Package Leaflet (PL) should include a reference to the temperature range e.g. (2°C to 8°C)

*** The following SPC and PL statements are required:

This medicinal product does not require any special storage conditions.

**** The stability data generated at 25°C/60%RH (acc) should be taken into account when deciding whether or not transport under refrigeration is necessary. The statement should only be used in exceptional cases.

***** The statement should only be used when critical.

OTHER SPECIFIC STORAGE STATEMENTS

In principle, medicinal products should be packaged in containers that ensure stability and protect the finished product from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Nevertheless, the following statements may be used to emphasize the need for precautions to the patient.

Sl. No	Storage problem	Additional labelling statements* depending on the packaging
1	Sensitivity to moisture	Keep the container*** tightly closed
2	Sensitivity to moisture	Store in the original package
3	Sensitivity to light**	Store in the original package
4	Sensitivity to light**	Keep container*** in the outer carton

* When such a standard statement is used, an explanation specifying whether the product is sensitive to light and/or moisture should be added.

** Details of evaluation are included in the CPMP/ICH Guideline on photostability testing.

*** The actual name of the container should be used, e.g. bottle, blister.

Where a supplementary warning, e.g. "Store in the original package" is required, the SPC statement "This product does not require any special storage conditions" (see footnote to the table in 4.) should be revised to read "This medicinal product does not require any special temperature storage conditions" as necessary.

The exact wording of the above texts will be uniformly applied throughout the Community.

The storage conditions for active substances should be based on evaluation of the stability studies undertaken on the active substance. The principles elaborated above in relation to standard storage declarations for finished medicinal products should also form the basis for storage declarations of active substances. For substances to be stored/transported refrigerated or frozen, the temperature range should be included in the labelling.

CONCLUSION:

The Good Distribution practices and Good Storage Practices ensure that the distributed products are authorized in accordance with the relevant legislation; appropriate storage conditions are maintained at all times, including movement of goods between various parts of the distribution network; contamination by other products is avoided; an appropriate turnover of stock takes place; and that products throughout the distribution chain are stored in safe and secure areas. In addition, to help combat counterfeiting, there should be a system(s) to enable faulty products to be rapidly found and recalled and proper legislative systems and the guidelines proposed by the Regulatory Authority plays a vital role to monitor the distribution and storage practices. Storage also forms an important activity of the integrated supply chain management of the pharmaceutical products (Medicine).

The guidelines laid by the CHMP EMEA are being discussed in the current article.

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