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HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Public Health and Risk Assessment
Pharmaceuticals

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Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use

Legal basis for publishing the guidelines: Article 84 of Directive 2001/83/EC on the Community code relating to medicinal products for human use. The proposed guidelines will replace the Guidelines on Good Distribution Practice of Medicinal Products for Human Use published in 1994 in the Official Journal of the European Communities[1].

Status of the document: revision for **public consultation**

Deadline for public consultation: 31 December 2011

Reasons for change: The content of the Guidelines on Good Distribution Practice published in 1994 is no longer adequate. It needs to be reviewed to take into account advancements of practices for an appropriate storage and distribution of medicinal products in the European Union. Moreover, it should take into account the amendments to the Community Code which have been introduced with Directive 2011/62/EU of the European Parliament and of the Council 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[2].
Deadline for coming into operation: 6 months after publication

[1] OJ 1994, C63, p. 3.
[2] OJ 01.07.2011, L174, p. 74-87

Table of Contents

Introduction

The present guidelines are based on Articles 84 and 85a(3) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[3] ("Directive 2001/83/EC').

The wholesale distribution of medicinal products is an important activity in the integrated supply chain management. Today's distribution network for medicinal products is increasingly complex and involves many players. The quality and the integrity of medicinal products can be affected by a lack of adequate control over the numerous activities, which occur during distribution and it is also necessary to address the threat that falsified medicinal products pose to the distribution channel. It is necessary to exercise control over the entire chain of distribution objectives by observing good manufacturing practice of medicinal products. This policy ensures that products manufactured in, or imported into the European Union are of the appropriate quality. This level of quality should be maintained throughout the distribution network without any alteration.

According to Article 1(17) of Directive 2001/83/EC, wholesale distribution is "all activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public".

Commento [L1]: Important to specify the difference and the related responsibilities between depots (pharma products owned by AIC owners) and wholesalers (grossisti) who have the property of Pharma products

Any person engaging in the activity of a wholesale distributor has to be holder of a wholesale distribution authorisation.

Possession of a manufacturing authorisation shall include authorisation to distribute the medicinal products covered by the authorisation.

The definition of wholesale distribution is independent as to 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 storing) also apply to these actors.

Other actors, such as brokers, also may play a role in the distribution channel of medicinal products.

Article 80(g) of Directive 2001/83/EC provides that distributors must comply with the principles and guidelines of good distribution practice (GDP). Manufacturers distributing their own products should also comply with GDP. According to Article 85b, persons brokering medicinal products shall be subject to certain provision applicable to wholesale distributors, as well as specific provisions for brokering.

The relevant sections of these guidelines should also be considered for implementation by, among others, governments, regulatory bodies, international procurement organisations and donor agencies, as well as all parties involved in any aspect of distribution of medicinal products.

This Guideline is presented as a set of basic requirements in different Chapters providing details about specific areas of activity.

[3] OJ L 311, 28.11.2001, p. 67

Chapter 1 Quality Management

Principle

Wholesale distributors must maintain a quality system setting out responsibilities, processes and risk management measures in relation to their activities[4]. They should ensure that the quality of medicinal products and the integrity of the distribution chain is maintained throughout the distribution process.

All distribution activities should be clearly defined and systematically reviewed and all critical steps of distribution processes and significant changes should be validated.

The quality system should incorporate quality risk management principles. The attainment of this quality objective is the responsibility of the organisation's senior management and requires their leadership and active participation and should be supported by the commitment of staff.

Quality System

1.1 The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the product delivered is not adulterated during storage and/or transportation.

1.2 A responsible person should be appointed by the management for each distribution site, who should have defined authority and responsibility for ensuring that a quality system is implemented and maintained.

1.3 Senior management of the distributor should ensure that all parts of the quality system are adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities.

1.4 The size and complexity of distributor's activities should be taken into consideration when developing the quality management system or modifying an existing one.

1.5 The quality system should be fully documented and its effectiveness monitored. All quality related activities should be defined and documented. A quality manual or equivalent documentation approach should be established.

1.6 The quality system should be organised in a way, that it reflects the size and structure of the organisation.

1.7 A change control system should be in place for management of changes to critical processes. This system should incorporate quality risk management principles.

1.8 The quality system should ensure that:

i) medicinal products are procured, held, supplied or exported in a way that is compliant with the requirements of GDP;
ii) management responsibilities are clearly specified;
iii) products are delivered to the right recipients within a satisfactory time period;
iv) quality related activities are recorded at the time they are performed;
v) deviations from established procedures are documented and investigated;
vi) appropriate corrective and preventive actions (CAPA) are taken to correct deviations and prevent them in line with the principles of quality risk management.

[4] Article 80 point h of Directive 2001/83/EC

Management of Outsourced Activities

1.9 The quality management system should extend to the control and review of any outsourced activities. These processes should incorporate quality risk management and include:

i) Assessing prior to outsourcing operations, the suitability and competence of the other party to carry out the activity and checking authorisation status, if required;
ii) Defining the responsibilities and communication processes for quality related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor;
iii) Monitoring and reviewing of the performance of the contract acceptor, and the identification and implementation of any needed improvements on a regular basis.

Management Review and Monitoring

1.10 Senior management should have a formal process for reviewing the quality management system on a periodic basis. The review should include:

i) Measurement of achievement of quality management system objectives;
ii) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the quality management system, such as complaints, deviations, CAPA, changes to processes; feedback on outsourced activities; self assessment processes including risk assessments, and audits; external assessments such as regulatory inspections and findings and customer audits.
iii) Emerging regulations, guidance and quality issues that can impact the quality management system;
iv) Innovations that might enhance the quality management system;
v) Changes in business environment and objectives.

Commento [L2]: Important to specify for Italy the splitted responsabilites between AIFA, that looks at GMP and Manufacturing sites, and Ministero della Salute that is responsible for Distribution and GDP.

1.11 The outcome of this management review of the quality management system should be timely and effectively communicated.

Quality Risk Management

1.12 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of medicinal products. It can be applied both proactively and retrospectively.

1.13 Quality risk management should ensure that the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient. The level of effort, formality and documentation of the process should be commensurate with the level of risk. Examples of the processes and applications of quality risk management can be found inter alia in the EU Guidelines to Good Manufacturing Practice[5] or publications of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ('ICH').

[5] http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Chapter 2 Personnel

Principle

The establishment and maintenance of a satisfactory quality management system and the correct distribution of medicinal products relies upon people. For this reason, there must be sufficient competent personnel to carry out all the tasks, which are the responsibility of the wholesale distributor. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of GDP that affect them and should receive initial and continuing training relevant to their responsibilities.

Responsible Person

2.1 The wholesale distributor must designate a person as Responsible Person[6]. The Responsible Person should fulfil his/her responsibilities personally and should be permanently available. The Responsible Person should meet the conditions provided for by the legislation of the Member State concerned.

2.2 The written job description of the Responsible Person should define his/her authorisation to take the decisions with regard to his/her responsibilities. The wholesale distributor should give the Responsible Person defined authority, resources and responsibility needed to fulfil his/her duties.

2.3 The qualifications of the Responsible Person should meet the conditions provided by the legislation of the Member State concerned and should be appropriate to fulfil the assigned duties. A degree in Pharmacy is desirable. He/she should have appropriate competence and experience as well as knowledge and training on GDP.

2.4 The Responsible Person should carry out his/her activities personally in order to ensure the wholesale distributor can demonstrate GDP compliance and that public service obligations are met.

2.5 His/her responsibilities include, but are not limited to:

i) ensuring that a quality management system is implemented and maintained;
ii) focussing on the management of authorised activities and the accuracy and quality of records;
iii) approving the initial and continuous training programme for all personnel involved in distribution activities;
iv) coordinating and performing promptly any recall operations of medicinal products;
v) ensuring that relevant customer complaints are dealt with effectively;
vi) performing the qualification and approval of suppliers and customers;
vii) authorising the return to saleable stock of any returned medicines;
viii)viii)approving any contract between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to wholesale distribution and/or transportation of medicinal products;
ix) ensuring that self inspections are performed at appropriate regular intervals following a prearranged programme and necessary corrective measures are put in place;
x) delegating his/her duties when absent and keeping appropriate records relating to any delegation;
xi) being involved in any decision to quarantine or dispose of returned, rejected, recalled or falsified products;
xii) ensuring that any additional requirements imposed on certain products by national law are adhered to, as foreseen in Article 83 of Directive 2001/83/EC.

Commento [L3]: Important to highlight that the PR's role and responsabilities are different in the case of depot or grossista

Commento [L4]: Need to foresee a possible delegate, as for QP in GMP regualations

Commento [L5]: The definition is misleading; does it mean 24 x 7 ? In tis case we feel necessary to foresee the formalisation of one or more deputies

Commento [L6]: A guideline should focus on requested competencies and previous experiences to be appointed as PR, more than specify the kind of preferred degree

Commento [L7]: Should be changed in "....guaranteee that...."

Commento [L8]: Need to clarify what we mean for "qualification" is it as for chapter 4 GMP ??

Commento [L9]: Need to clarify who do we mean as "customer": for depots the customers are the AIC owners who utilize the depot, for the grossisti the customers are the entities (hospitals, pharmacies) who buy the drugs

Commento [L10]: Contraddicti on with previous 2.1; need to define the role of deputy PR

[6] Article 79 of Directive 2001/83/EC

Other Personnel

2.6 There should be an adequate number, in respect of the scope of its activities, of competent personnel, involved in all stages of the wholesale distribution activities of medicinal products in order to ensure that the quality of the product is maintained.

2.7 The organisational structure of the distributor should be defined in an organizational chart. The responsibility, role and interrelationships of all personnel should be clearly indicated.

2.8 The responsibilities and roles of employees working in key positions to medicinal products quality should be defined in written job descriptions, in which the deputyship arrangements of employees are also laid out.

2.9 The duties placed on any individual should not be so extensive as to present unacceptable risk to product quality.

Training

2.10 All personnel involved in wholesale distribution activities should be qualified in GDP requirements by training and should have the appropriate competence and experience prior to commencing their tasks.

2.11 In addition, training should include aspects of product identification and avoidance of falsified medicines entering the supply chain.

2.12 Personnel dealing with medicinal products requiring more stringent handling such as hazardous products, radioactive materials as well as products presenting special risks of abuse, narcotics or psychotropic substances, or temperature sensitive products should be given specific training.

2.13 Personnel should receive initial and continuing training relevant to their tasks, based on written standard operating procedures (SOPs) and in accordance with a written training programme. The Responsible Person should also maintain his/her competence in GDP through regular training.

2.14 A record of all training should be kept, and the practical effectiveness of training should be periodically assessed and documented.

Hygiene

2.15 Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established and observed. Such procedures should cover health, hygiene and clothing.

2.16 The storage of food, drink, smoking materials or medication for personal use in the storage areas should be prohibited.

Chapter 3 Premises and Equipment

Principle

Wholesale distributors must have suitable and adequate premises, installations and equipment[7], so as to ensure proper conservation and distribution of the medicinal products.

Premises

3.1 The premises should be designed or adapted to ensure that good storage conditions are maintained. They should be suitably secure, structurally sound and of sufficient capacity to allow for the safe storage and handling of the medicinal products. Storage areas should be provided with adequate lighting to enable all operations to be carried out accurately and safely.

3.2 Where premises are not directly operated by the wholesale distributor, a contract should be in place and the premises should be covered by a wholesale distribution authorisation.

3.3 There should be segregated areas designated for the storage of products awaiting further decisions as to their fate. These include any product suspected of falsification, returned products, rejected product, product awaiting disposal and recalled product. The appropriate degree of security should be applied in these areas to ensure that such items remain separate from saleable stock.

Commento [L11]: Need to specify better: phisical segregation should be foreste for the following kind of drugs: narcotics, obsolete, to be destroyed.
The products returned from the customers should be stored in a well identified area, waiting for a decision (destroy or deliver to the market).
They should be stored in a "logical quarantine" if a validated computerised system is in place

3.4 Medicinal products not intended for the Union market should be kept in segregated areas.

3.5 Where specific storage conditions are required, control should be adequate to maintain all parts of the relevant storage area within defined temperature, humidity or light parameters.

3.6 Special attention should be paid to the storage of products with specific handling instructions as specified in national law. Special storage conditions (and special authorisations) may be required for such products (e.g. narcotics).

3.7 Radioactive materials and other hazardous products, as well as products presenting special risks of fire or explosion (e.g. pressurized gases, combustibles, flammable liquids and solids) should be stored in a dedicated area(s) subject to appropriate safety and security measures.

3.8 Receiving and dispatch bays should protect products from prevailing weather conditions. There should be adequate separation between the receipt and dispatch areas and storage areas. Reception areas where deliveries are examined at receipt should be designated and suitably equipped.

3.9 Unauthorised access to all areas of the authorised premises should be prevented. Prevention measures would usually include, but not be limited to, a monitored intruder alarm system and appropriate access control.

3.10 Premises and storage facilities should be clean and free from litter and dust. Cleaning instructions and records should be in place. Cleaning equipment should be chosen and used in order not to be a source of contamination.

3.11 Facilities should be designed and equipped so as to afford protection against the entry of insects, rodents or other animals. A preventive pest control programme should be in place.

[7] Article 79(a) of Directive 2001/83/EC

3.12 Rest, wash and refreshment rooms for employees should be adequately separated from the storage areas.

Temperature and Environment Control

3.13 Suitable equipment and procedures should be in place to ensure adequate control of the environment of medicinal products during storage. Environmental factors to be considered include, but are not limited to, temperature, humidity, and cleanliness of the premises.

3.14 Storage areas should be temperature mapped under representative conditions and should take into account seasonal variations. An initial mapping should be carried out prior to the commencement of use. The mapping exercise should be repeated according to the results of a risk assessment exercise or whenever significant modifications are made to the facility or the temperature controlling equipment. Temperature monitoring equipment should be located according to the results of the mapping exercise.

Equipment

3.15 All equipment used for storage and distribution of medicinal products should be designed, located and maintained to a standard which suits its intended purpose. Planned preventive maintenance should be in place for key equipment vital to the functionality of the operation.

3.16 Equipment used to control or to monitor the environment of the medicinal product, should be calibrated and their correct operation and suitability for purpose verified at defined intervals by the appropriate methodology.

3.17 Calibration of equipment should be traceable to a primary standard. Appropriate alarm systems should be in place to provide alerts when there are deviations from pre-defined storage conditions. Alarm levels should be appropriately set and alarms should be regularly tested to ensure adequate functionality.

3.18 Repair, maintenance, and calibration operations of equipment should be carried out in such a way that the integrity of the medicinal products is not compromised.

3.19 Adequate records of repair, maintenance and calibration activities for key equipment should be made and the results should be retained. Relevant pieces of equipment would include (but not be limited to) cold stores, refrigerators, thermo hygrometers, or other temperature and humidity recording devices, air handling units and any equipment utilised in conjunction within the onward supply chain.

Computerised Systems

3.20 Before a computerised system is brought into use, it should be confirmed as being capable of achieving the desired results.

3.21 A written detailed description of the system should be available (including diagrams where appropriate). This should be kept up-to-date. The document should describe the principles, objectives, security measures and scope of the system and the main features, how the computerised system is used and the way it interacts with other systems.

3.22 Data should only be entered into the computerised system or amended by persons authorised to do so.

3.23 Data should be secured by physical or electronic means against wilful or accidental damage. Stored data should be checked for accessibility, durability and accuracy.

3.24 Data should be protected by backing up at regular intervals. Back up data should be stored for a period stated in national legislation but at least 5 years at a separate, secure location.

3.25 Procedures to be followed if the system fails or breaks down should be defined. This should include systems for the restoration of data.

Qualification and Validation

3.26 Wholesale distributors should identify what qualification and/or validation work is necessary to demonstrate control of key aspects of their activities. The scope and extent of such validations should be determined by a documented risk assessment approach. Validation activities should be planned and documented. The plan should specify acceptance criteria.

3.27 Prior to implementation and after any significant changes or upgrades, systems should be validated to ensure correct installation and operation.

3.28 A validation report should be prepared summarising the results obtained and commenting on any observed deviations. The principles of corrective and preventive actions (CAPA) should be applied where necessary. Evidence of satisfactory validation and acceptance of a process or piece of equipment should be produced and approved by appropriate personnel.

3.29 Re-qualification of equipment following repair or maintenance should be considered dependant on the scope of the changes made. Such decisions should be justified utilising a risk based approach.

Chapter 4 Documentation

Principle

Good documentation constitutes an essential part of the quality management system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Instructions, procedures, and records should be free from errors and each employee should have access to such instructions and procedures concerning his or her activities at any time.

General

4.1 Documentation comprises all written procedures, instructions, contracts, records and data, in paper or in electronic form.

4.2 Documentation should be sufficiently comprehensive with respect to the scope of the distributor's activities and in a language understood by personnel. It should be written in clear and unambiguous language.

4.3 Documentation should be approved, signed and dated by appropriate authorized persons, as required. It should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.

4.4 Any alteration made in the documentation should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.5 Documents should be retained for a period stated in national legislation but not shorter than 5 years.

4.6 All documentation should be readily available.

4.7 Attention should be paid to maintaining the SOP system so as to ensure the use of valid and approved procedures. Documents should have unambiguous contents; title, nature and purpose should be clearly stated. Documents should be reviewed regularly and kept up-to-date. Version control should be applied to SOPs and superseded versions should be archived. After revision of documents a system should exist to prevent inadvertent use of the superseded versions. Superseded or obsolete SOP documents should be removed from workstations.

4.8 Records

Commento [L12]: Eliminate

4.9 Records must be kept either in the form of purchase/sales invoices, delivery slips, or on computer or in any other form, for any transaction in medicinal products received, supplied or brokered.

Commento [L13]: Becomes 4.8

4.10 Records should include the following information: date; name of the medicinal product; quantity received, supplied or brokered; name and address of the supplier, broker or consignee, as appropriate; and batch number where required.

Commento [L14]: Becomes 4.9

4.11 Records should be made at the time each operation is taken and in such a way that all significant activities or events are traceable.

Commento [L15]: Becomes 4.10

Chapter 5 Operations

Principle

All actions taken by the distributor should ensure that the identity of the medicinal product is not lost and that wholesale distribution of medicinal products is handled according to the specifications given on the packaging information. The wholesale distributor should use all means available to ensure that the source of all arriving products is known to minimise the risk of falsified medicinal products entering the legal supply chain.

All medicinal products distributed in the EU by a wholesale distributor have to have a marketing authorisation granted by the EU or by a Member State[8]. If the product is intended to be exported see below.

Any distributor, not being the marketing authorisation holder, who imports a medicinal product from another Member State shall notify the marketing authorisation holder and the competent authority in the Member State to which the medicinal product will be imported of his intention to import that product0[9],[10].All key operations should be fully described in the quality management system in appropriate standard operating procedures.

Qualification of Suppliers

5.1 Wholesale distributors must obtain their supplies of medicinal products only from persons who are themselves in possession of a wholesale distribution authorisation, or who are in possession of a manufacturing authorisation which covers the product in question[11].

Commento [L16]: Should be better a clear definition of the different actors with relevant roles and responsibilities:
Depots, grossista, AIC owner, final customer

5.2 Where the medicinal product is obtained from another wholesale distributor, wholesale distributors must verify compliance with the principles and guidelines of good distribution practices by the supplying wholesale distributor. This includes verifying whether the supplying wholesale distributor holds a wholesale distribution authorisation.[12]

5.3 Where the medicinal product is obtained from the manufacturer or importer, wholesale distributors must verify that the manufacturer or importer holds a manufacturing authorisation.[13]

5.4 Purchase of medicinal products should be controlled by written procedures. The supply chain of medicinal products should be known and documented.

5.5 Appropriate qualification should be performed prior to any procurement. The selection, including qualification and approval of suppliers is an important operation. This operation should be controlled by a standard operating procedure and the results documented and periodically rechecked.

5.6 If the medicinal product is obtained through brokering, the wholesale distributor must verify that the broker is registered and complies with the requirements in Chapter 10[14].

[8] Article 76(1), (2) of Directive 2001/83/EC
[9] Article 76 paragraph 3 of Directive 2001/83/EC
[10] Article 76, paragraph 3 of Directive 2001/83/EC
[11] Article 80 point b of Directive 2001/83/EC
[12] Article 80, 2nd paragraph of Directive 2001/83/EC
[13] Article 80, 3rd paragraph of Directive 2001/83/EC
[14] Article 80 of Directive 2001/83/EC

5.7 Due-diligence should be carried out by the distributor when entering a new contract with new suppliers in order to assess the suitability, competence and the reliability of the other party to supply medicinal products. A risk based approach should be used for this purpose considering:

i) searches for the new supplier's reputation or reliability and its authorised activities;
ii) certain medicinal products are more likely to be target of falsification;
iii) large offers of medicinal product which are generally only available in limited quantities;
iv) out of range prices.

Qualification of Customers

Commento [L17]: Need to clarify who do we mean as "customer": for depots the customers are the AIC owners who utilize the depot, for the grossisti the customers are the entities (hospitals, pharmacies) who buy the drugs

5.8 Wholesale distributors must ensure they must supply medicinal products only to persons who are themselves in possession of the distribution authorisation or who are authorized or entitled to supply medicinal products to the public in the Member State concerned.[15] Qualification of customers should be appropriately documented.

5.9 Checks and periodic re-checks may include (but are not limited to): requesting copies of customer's authorisations according to national law, verifying status on an authority website, requesting evidence of qualifications or entitlement according to national legislation.

5.10 Wholesale distributors should monitor their transactions and investigate any irregularity in sale patterns to avoid diversion of medicinal products at risks of being misused and to ensure fulfilling any public service obligation imposed upon them.

Marketing authorisation

Commento [L18]: In this case a "documental" qualification should be requie, in order to guarantee on the correct origin of drugs

5.11 Wholesale distributors wishing to distribute or distributing medicinal products in Member State(s) other than the Member State in which the marketing authorisation was granted should, on request, make available a copy of the marketing authorisation to the national competent authority. Where appropriate, the competent authorities will inform the wholesale distributor of any public service obligation imposed on wholesale distributors operating on their territory.

Receipt of Goods

5.12 The purpose of the receiving function is to ensure that the arriving consignment is correct, the medicinal products originate from approved suppliers and that they have not been damaged or altered during transportation.

5.13 Where medicinal products require special storage or security measures, they should be transferred to appropriate storage facilities immediately after appropriate checks have been conducted.

5.14 In the event of any suspicion of falsified medicinal product, the batch should immediately be segregated and reported to the national competent authority and, where applicable to the marketing authorisation holder[16].

5.15 Batches of medicinal products intended for the Union market should not be transferred to saleable stock before assurance has been obtained in accordance with written procedures, that they are authorised and released for sale for the market in question. For batches coming from another Member State, prior to their transfer to saleable stock, the control report referred to in Art 51(1) of Directive 2001/83/EC or another proof

[15] Article 80 (c) of Directive 2001/83/EC
[16] Article 80 point i of Directive 2001/83/EC

of release to the market in question based on an equivalent system should be carefully checked by appropriately trained personnel.

5.16 Distributors receiving medicinal products from third countries for the purpose of importation, i.e. for the purpose of placing these products on the EU market, must hold a manufacturing/import authorisation[17].

Storage

5.17 Medicinal products should be stored separately from other products and protected from harmful effects of light, temperature, moisture or other external factors. Particular attention should be paid to products where specific storage conditions are required.

5.18 Incoming containers of medicinal products should be cleaned, if necessary, before storage.

5.19 Warehousing operations should ensure appropriate and good storage conditions and allow the orderly storage of the various categories of medicinal products, products in quarantine, and released, rejected, returned or recalled products as well as those suspected to be falsified.

5.20 Steps should be taken to ensure stock rotation according to the expiry dates of batches of medicinal products.

5.21 Medicinal products should be handled and stored in such a manner as to prevent spillage, breakage, contamination and mix-ups. Medicinal products should not be stored directly on the floor.

5.22 Medicinal products beyond their expiry date or shelf life should be withdrawn immediately from saleable stock either physically or through other equivalent electronic segregation. Physical removal of unsuitable stock should be performed regularly.

5.23 Stock inventories should be performed regularly. Timings should be defined using a risk based approach. Irregularities should be investigated and documented.

Segregation of Goods

5.24 If required, medicinal products should be stored in segregated areas, which are clearly marked and their access restricted to authorised personnel. Any system replacing physical segregation such as electronic segregation based on a computerised system shall provide equivalent security and should be validated.

5.25 Segregation should be provided for the storage of rejected, expired, recalled or returned products and suspected falsified medicinal products. The products and the areas concerned shall be appropriately identified.

Commento [L19]: See previous 3.3: Need to specify better: phisical segregation should be foreste for the following kind of drugs: narcotics, obsolete, to be destroyed.
The products returned from the customers should be stored in a well identified area, waiting for a decision (destroy or deliver to the market).
They should be stored in a "logical quarantine" if a validated computerised system is in place

Destruction of obsolete Goods

5.26 Medicinal products intended to be destroyed should be appropriately identified, kept separately and handled in accordance with a written procedure.

5.27 Destruction of medicinal products should be in accordance with national or international requirements for disposal of such products, and with due consideration to the protection of the environment.

[17] Article 40, paragraph 3 of Directive 2001/83/EC

5.28 Records of all destroyed medicinal products should be maintained.

Picking

5.29 Controls should be in place to ensure the correct product is picked. The product should have an appropriate remaining shelf life when it is picked. It should be picked on a "first expired first out" (FEFO) basis. The batch number should be recorded, where required.

Packing

5.30 Products should be packed in a way to avoid breakage, contamination and theft. The packing should be adequate to maintain the storage conditions of the product during transport. The containers in which medicinal products are shipped should be sealed.

Delivery

5.31 Deliveries should be made only to customers appropriately authorised or entitled to receive medicinal products.

5.32 For all supplies to a person authorised or entitled to supply medicinal product to the public, a document must be enclosed to ascertain the date; name and pharmaceutical form of the medicinal product, batch number at least for products bearing the safety features, where required; quantity supplied; name and address of the supplier, name and delivery address of the consignee (actual physical storage premises, if different) and applicable transport and storage conditions. Records should be kept so that the actual physical journey undertaken by the product can be tracked.

Commento [L20]: Refer to what already stated inside Directive CEE 62/2011., art.1

Commento [L21]: Actually, in Italy the traceability is guaranteed only up to delivery to grossista. The grossista doesn't track the lot when deliver goods to final customers

Export

5.33 The export of medicinal products falls within the definition of "wholesale distribution"[18]. A person exporting medicinal products must thus hold a wholesale distribution authorisation or a manufacturing authorisation. This is also the case if the exporting wholesale distributor is operation from a free zone.

5.34 The rules for wholesale distribution[19] apply in their entirety in the case of export of medicinal products, with the following exceptions[20]:

a. The medicinal product does not have to be covered by a marketing authorisation of the EU or a Member State;
b. The customer does not have to be holder of a distribution authorisation;
c. Moreover, where the medicinal product intended for exportation has been obtained directly from another third country, without the product being prior to that placed on the market (ie without prior import), the supplier does not have to bear a wholesale distribution authorisation.

5.35 If the medicinal product is supplied to a person in a third country authorized or entitled to supply medicinal products to the public, the rules for document enclosure apply as for supply of the medicinal product established in the EU.[21]

[18] Article 2(17) of Directive 2001/83/EC
[19] Article 85a of Directive 2001/83/EC
[20] Article 85a of Directive 2001/83/EC
[21] Article 85a of Directive 2001/83/EC

Chapter 6 Complaints, Returns, suspected falsified Medicinal Products and Medicinal Product Recalls

Principle

All complaints and other information concerning potentially defective medicinal products must be collected and reviewed carefully according to written procedures. A special 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. A system should be designed to recall products known or suspected to be defective from the market in a prompt and effective manner. Any return, rejection or recall operation should be recorded and records should be made available to the competent authorities.

Standard Operating Procedures for handling product recalls and other similar situations should be prepared, maintained, and implemented.

Complaints

Commento [L22]: Shuld be intended as just the complaints relevant to distribution issues

6.1 There should be a written procedure in place for the handling of complaints. A distinction should be made between complaints about the quality of a medicinal product and those relating to distribution. In the case of a complaint about the quality of a medicinal product, the manufacturer and/or marketing authorisation holder should be informed without delay.

6.2 A person should be appointed for handling the complaints with sufficient supporting personnel to assist him/her.

6.3 Any complaint concerning a potential product defect or a potential falsified product should be recorded with all the original details and investigated. The national competent authority should be notified without delay.

Commento [L23]: Need to clarify better this point.
It is not easy for a person in the Distribution channel to distinguish counter fight drugs; In any case should be specified the requirement to inform immediately the AIC owner

6.4 Any product distribution complaint should be thoroughly investigated.

6.5 If necessary, appropriate follow-up actions should be taken after investigation and evaluation of the complaint.

Returned Medicinal Products

6.6 There should be written procedures for the handling and acceptance of returned medicinal products.

6.7 A risk assessment should be performed taking into account the product concerned, any specific storage requirements and the time elapsed since the medicinal product was originally dispatched.

6.8 Returned medicinal products should be kept segregated from saleable stock until a decision is taken regarding their disposition.

Commento [L24]: At present difficult to identify due to the lack of tamper proof evidence

6.9 Medicinal products which have left the premises of the distributor should only be returned to saleable stock if:

i) the medicinal products are in their unopened and undamaged secondary packaging and in good condition;
ii) medicinal products returns from a customer not holding a wholesale distribution authorisation should only be returned to saleable stock if they were returned within five days of original dispatch;

Commento [L25]: Which are the criteria to establish 5 days ? It seems more reasonable to say, in the quickest possible time, that should be dependent from the kind of product, the typology of distribution....

iii) it is demonstrated that the medicinal products have been transported, stored and handled under proper specified/predefined conditions;
iv) they have been examined and assessed by a sufficiently trained and competent person authorised to do so;
v) the distributor has reasonable evidence that th the product was upplied to that customer and the batch number of the dispatched product is known, that a copy of the original delivery note is attached and that there is no reason to believe that the product has been falsified.

Commento [L26]: Mistake, remove

6.10 Medicinal products requiring low temperature storage conditions can be returned to saleable stock only if the batch number of the dispatched product is known and there is evidence that the product has been stored within the authorised storage conditions throughout the entire time. This evidence should include but is not limited to the following:

- delivery to customer
- opening of the packaging
- examination of the product
- returning of the product to the packaging and sealing of the packaging
- collection and return to the distributor
- return to the distribution site refrigerator

6.11 All handling of returned medicinal products including their return to saleable stock or disposal should be approved by the Responsible Person and recorded.

6.12 Products returned to saleable stock should be placed such that the "first expired first out" (FEFO) system operates effectively.

Suspected falsified Medicinal Products

Commento [L27]: This seems difficult for a depot, more easy for a grossista. See previous 6.3

6.13 There should be documentation in place that describes how the distributor increases their staff's awareness of the risks of falsified medicinal products entering the supply chain.

6.14 Distributors must immediately inform the competent authority and, where applicable, the marketing authorisation holder of the medicinal products they identify as falsified or suspect to be falsified[22]. A procedure should be in place to this effect.

6.15 Any suspected falsified medicinal products found in the supply chain should be immediately physically and securely segregated from legitimate medicinal products. All products and relevant activities should be recorded.

Medicinal Product Recalls

6.16 There should be a written procedure for the management of recalls. The procedure should be periodically tested.

6.17 Recall operations should be capable of being initiated promptly and at any time.

6.18 The distributor must follow the instructions of a recall message, which should be approved, if required, by the competent authorities.

[22] Article 80 point i of Directive 2001/83/EC

6.19 Any recall operation should be recorded at the time it is carried out and records should be made available to the competent authorities.

6.20 The distribution records should be readily available to the person(s) responsible for the recall, and should contain sufficient information on distributors and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and quantities delivered), including those for exported products and medicinal product samples.

6.21 Recalled medicinal products should be identified and stored separately in a secure area while awaiting a decision on their disposition.

6.22 The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the medicinal products.

6.23 The effectiveness of the arrangements for recalls should be evaluated regularly.

Chapter 7 Contract Operations

Principle

When outsourcing activities a written contract should be drawn up. Both the contract giver and the contract acceptor must hold a distribution authorisation. The written and signed contract should cover all wholesale distribution activities and clearly establish the duties and responsibilities of each party. Written contracts should be established for any activity likely to impact on GDP related activities.

Contract Giver

7.1 The Contract Giver is responsible for the activities contracted out.

7.2 The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract and through audits that the principles and guidelines of GDP are followed. An audit of the Contract Acceptor should be performed before the beginning of the outsourced activities and afterwards audits should be done periodically.

7.3 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations in accordance with the specific product requirements and any other relevant requirements.

Contract Acceptor

7.4 The Contract Acceptor should have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver.

7.5 The Contract Acceptor carrying out activities falling under the definition of wholesale distribution of medicinal products is a wholesale distributor. As such, he is subject to all obligations for wholesale distribution of medicinal products.

7.6 The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements and an audit of the third party. Arrangements made between the Contract Acceptor and any third party should ensure that the wholesale distribution information is made available in the same way as between the original Contract Giver and Contract Acceptor.

7.7 The Contract Acceptor should refrain from any activity, which may adversely affect the quality of the product handled for the Contract Giver.

7.8 The Contract Acceptor must forward any information that can influence the quality of the products to the Contract Giver in accordance with the requirement of the contract.

Contract

7.9 A written contract should be drawn up between the Contract Giver and the Contract Acceptor, which specifies their respective responsibilities relating to the wholesale distribution activities. Written contracts should be drawn up for any other outsourced activity (e.g. cleaning, pest control etc).

7.10 The contracts should permit the Contract Giver to audit the Contract Acceptor at any time.

Chapter 8 Self-Inspections

Principle

Self-inspections should be conducted in order to monitor the implementation and compliance with GDP principles and to propose necessary corrective measures.

Self-Inspections

8.1 A self-inspection programme should be implemented to cover all aspects of GDP and compliance with regulations, guidelines and operating procedures within a defined time frame, whilst individual self inspections may be limited in scope.

8.2 Self-inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Audits by independent external experts may also be useful but should not be relied upon as sole means of self inspection to confirm compliance with GDP.

8.3 Audit of subcontracted activities should be a part of the self-inspection programme.

8.4 All self-inspections should be recorded. Reports should contain all the observations made during inspections. A copy of the report should be provided to the senior management and other relevant persons. In the event that irregularities and/or deficiencies are observed, their causes should be determined and the CAPA should be documented and followed-up.

Chapter 9 Transportation

Principle

It is the responsibility of the wholesale distributor that, during the supply of medicinal products, the transport conditions are such as to maintain the quality of the product, to protect against breakage, adulteration and theft, and to ensure appropriate environmental conditions are maintained during transport.

Adequate precautions should be taken to this effect.

Medicinal products should be transported in accordance with the storage conditions indicated on the packaging information.

Appropriate transport methods should be employed which may include transport by air, road, sea, rail or a combination of the above. Regardless of the chosen mode, it should be possible to demonstrate that the medicines have not been subjected to conditions during transportation that may compromise their quality. A risk based approach should be utilized when planning transportation routes.

Commento [L28]: Should be added also a note relevant to the different kind of pallets utilized, to the specific manufacture processes utilized for the production of the pallets itself, and to the products utilised for pallets cleaning

Transportation

9.1 The required storage conditions for medicinal products should be maintained during transportation within the defined limits as described on the packaging information.

9.2 If a deviation has occurred during transportation, this should be reported to the distributor and recipient of the affected medicinal products.

9.3 In cases where the recipient notices the deviation, it should be reported to the distributor. Where necessary, the manufacturer of the medicinal product should be contacted for information about appropriate steps to be taken.

Commento [L29]: Change with …in any case……

Commento [L30]: Change with …the AIC owner……

9.4 It is the responsibility of the distributor to ensure that vehicles and equipment used to distribute, store or handle medicinal products are suitable for their use and appropriately equipped to prevent exposure of the products to conditions that could affect their quality and packaging integrity, and to prevent contamination of any kind.

9.5 Delivery drivers (including contract drivers) should be trained in the relevant areas of GDP.

9.6 There should be procedures in place for the operation and maintenance of all vehicles and equipment involved in the distribution process, including cleaning and safety precautions. Particular attention should be paid to the fact that cleaning agents should not have an adverse effect on product quality.

9.7 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.

Commento [L31]: It is not clear what is meant for "container" better to specify the "glossary of terms" what do we mean for container

9.8 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.

9.9 Deliveries should be made directly to the address stated on the delivery note and must be handed into the care of the consignee. Medicinal products should not be left on alternative premises.

9.10 In case of emergency deliveries outside normal business hours persons should be designated and written procedures should be available.

9.11 If transportation is sub-contracted to a third party then the contract should encompass the requirements contained within Chapter 7. In addition the contractors should be fully aware of all relevant conditions applicable to the storage and transportation of medicinal products.

9.12 Where transportation hubs are utilised in the supply chain, a maximum time limit of normally 24 hours should be set to await the next stage of the transportation route. Where medicinal products are held on the premises for longer than this defined time limit, the hub will be deemed to be acting as a storage site and required to obtain a wholesale distribution authorisation. For refrigerated product any storage at a transportation hub for any period of time would require that premises to hold a wholesalers distribution authorisation.

9.13 In the event that the transportation of medicinal products requires unloading and reloading e.g. at terminals and hubs, these premises should be audited and approved prior to deployment. Whenever any changes are made to the approved premises or functions, attention should be paid to the continued suitability of the changed premises or functions for their intended use. Particular attention should be paid to temperature monitoring, cleanliness and the security of unguarded intermediate storage facilities.

Containers, packaging and labelling

9.14 Medicinal products should be transported in containers that have no adverse effect on the quality of the products, and that offer adequate protection from external influences, including contamination.

9.15 Selection of a container and packaging should be based on the storage and transportation requirements of the medicinal products; the space required for the amount of medicines; the anticipated external temperature extremes; the estimated maximum time for transportation including transit storage at customs and the validation status of the packaging and shipment containers.

9.16 Containers should bear labels providing sufficient information on handling and storage requirements and 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.

Transportation of Products requiring special Conditions

9.17 In relation to deliveries containing medicinal products requiring special conditions such as narcotics or psychotropic substances, the distributor should maintain a safe and secure supply chain for these products in accordance with requirements laid down by the concerned Member States. There should be additional control systems in place for delivery of these products. There should be a protocol to address the event of theft occurring.

9.18 Transportation of medicinal products comprising highly active and radioactive materials should be transported in safe, dedicated and secure containers and vehicles. In addition, these safety measures should be in accordance with international agreements and national legislation.

Temperature Control during Transport

9.19 Validated temperature-control systems (e.g. thermal packaging, temperature-controlled containers, and refrigerated vehicles) should be used to ensure correct transport conditions are maintained between the

Commento [L32]: We agree on the requirement for a specific authorization to tansport drugs, but don't feel necessary to have the autrhorisation for drug stortage linked to transport authorization. We feel important to specify the meaning of technical stop of the vehicoles (length and implications for t°)

Commento [L33]: We feel it is not the case to specify a lenght of time, ie. 24 hours We feel as specific cases the week ends, the holidays, and return drugs management

Commento [L34]: In Italy this point is covered by D leg 219/2006 which foresees the presence of a Responsible Person in the storage point; however actually the transit points are not considered as "storage points", therefore it is not required at present the presence of an autorisation .

Commento [L35]: . It is not clear what is meant for "container" see previous 9.7. In this case it seems that container refers to a different thing

distributor and customer. Customers should be provided with a temperature data to demonstrate that products remained within the required temperature storage conditions during transit, if requested.

Commento [L36]: Add: …by them.

Commento [L37]: Actually it is very difficult for the grossista

9.20 If refrigerated vehicles are used, the temperature monitoring equipment used during transport should be maintained and calibrated at regular intervals or at a minimum of once a year. This includes temperature mapping under representative conditions and should take into account seasonal variations. Customers should be provided with data to demonstrate that products remained within the required temperature storage conditions during transportation, if requested.

9.21 If cool-packs are used in insulated boxes, they need to be located such that the product does not come in direct contact with the cool-pack. Staff must be trained on the procedures for assembly of the insulated boxes (seasonal configurations) and on the reuse of cool-packs.

9.22 There should be a system in place to control the reuse of cool-packs to ensure that incompletely cooled packs are not used in error. There should be adequate physical distinction between frozen and chilled ice packs.

Commento [L38]: Need to better specify what it is meant for cool-packs May be in the "glossary terms" ?

9.23 The process for delivery of sensitive products and control of seasonal temperature variations should be described in a written procedure. This procedure should also cover unexpected occurrences such as vehicle breakdown or non-delivery. A procedure should also be in place for investigating and handling temperature excursions.

Chapter 10 Specific Provisions for Brokers[23]

Principle

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 consist of negotiating independently and on behalf of another legal or natural person[24].

Thus a person that procures, holds, supplies or exports medicinal products is never a broker. This is independent of whether that person physically handles or stores the medicinal product.

Rather, a broker is a person who negotiates independently (not as employee) and on behalf of another person the sale or purchase of medicinal products.

Brokers are subject to a registration requirement. They must have a permanent address and contact details in the Union under which they are registered. They shall notify the competent authority of any changes thereof without unnecessary delay[25].

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. In particular, brokers must maintain a quality management system that ensures applicable records are kept, efficient emergency plans for supporting recalls are in place and that competent authorities are immediately informed of any suspected falsified medicines offered in the supply chain[26].

Quality System

10.1 The quality system of a broker should be defined in writing, approved and kept up-todate. It should set out the responsibilities, processes and risk management in relation to their activities.

Personnel

10.2 Any member of personnel involved in the brokering activities should be trained in the applicable EU and national legislation and in the issues concerning falsified medicinal products.

Documentation

10.3 The general provisions on documentation in Chapter 4 apply.

10.4 In addition, at least the following procedures and instructions should be in place:

- Procedure for complaints handling;
- Procedure for informing competent authorities and marketing authorization holders of suspected falsified medicinal products;
- Procedure for supporting recalls
- Procedure for ensuring that medicinal products brokered have a marketing authorisation

[23] Article 85b point 3 of Directive 2001/83/EC
[24] Article 1, point 17a of Directive 2001/83/EC
[25] Article 85b of Directive 2001/83/EC
[26] Article 85b paragraph 1 of Directive 2001/83/EC

- Procedure for verifying that their supplying wholesale distributors hold a distribution authorisation, their supplying manufacturers or importers hold a manufacturing authorisation and their customers are authorised to supply medicinal products in the Member State concerned.

10.5 Records should be kept for any transaction in medicinal products brokered at least the following information:

- date;
- name of the medicinal product;
- quantity brokered;
- name and address of the supplier and the customer;
- batch numbers of the medicinal product, where required.

Annex

Glossary of Terms

[Industry is invited to provide list of terms to be included in the Glossary]

Commento [L39]: Need to review the annex, clarifying better the definitions and adding the definitions as i.e. medical product, customers, conteiners, cool packs……

Terms	Definition
Brokering	All activities in relation to the sale or purchase of medicinal products, except for wholesale distribution as defined in point 17 of this article, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person. (Defined in Article 1 of Directive 2001/83/EC, as amended)
Exporting	All activities relating to the supply of a medicinal product to a state other than a EU Member State or a Contracting State of the European Economic Area.
Falsified medicinal product[27]	Any medicinal product with a false representation of: (a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients; (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorization holder; or (c) its history, including the records and documents relating to the distribution channels used.
Free zones and free warehouses[28]	Free zones and free warehouses shall be parts of the customs territory of the Community or premises situated in that territory and separated from the rest of it in which: (a) Community goods are considered, for the purpose of import duties and commercial policy import measures, as not being on Community customs territory, provided they are not released for free circulation or placed under another customs procedure or used or consumed under conditions other than those provided for in customs regulations; (b) Community goods for which such provision is made under Community legislation governing specific fields qualify, by virtue of being placed in a free zone or free warehouse, for measures normally attaching to the export of goods.
Holding	Keeping or storing medicinal products.
Procuring	Obtaining, acquiring, purchasing or buying

[27] Article 1, point 33 of Directive 2001/83/EC
[28] Articles 166 to Article 181 of Council Regulation (EEC) No 2913/92 of 12 October 1992 establishing the Community Customs Code

	medicinal products from manufacturers, importers or other wholesale distributors.
Qualification	Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification. (Defined in EudraLex Volume 4 Glossary to the GMP Guidelines)
Responsible Person	The responsible person is the qualified person designated as responsible, meeting the conditions provided for by the legislation of the Member State concerned. (Defined in Article. 79(b) of Directive 2001/83/EC, as amended)
Supplying	All activities of providing /selling / donating medicinal products to wholesalers; pharmacists; or persons authorised or entitled to supply medicinal products to the public.
Quality Risk Management	A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.
Quality System	The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met. (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Q9)
Validation	Action of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification). (Defined in EudraLex Volume 4 Glossary to the GMP Guidelines)
Wholesale distribution[29]	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. (Defined in Article 1 of Directive 2001/83/EC, as amended)

[29] Article 1 point 17 of Directive 2001/83/EC