Based on Article 139 paragraph 8 of the Law on medicines („Official gazette of Montenegro“ No 080/20) have been published

GUIDELINES ON GOOD DISTRIBUTION PRACTICE OF MEDICINAL PRODUCTS FOR HUMAN USE

PART I

INTRODUCTION

These Guidelines are based on Article 84 and Article 85b (3) of Directive 2001/83/EC[1], which was implemented with the law governing medicines and bylaws for its implementation.

The Commission has published EU Guidelines on Good Distribution Practice (GDP) in 1994[2]. Revised guidelines were published in March 2013[3] 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[4].

This version corrects factual mistakes identified in subchapters 5.5 and 6.3 of the revised guidelines. It also gives more explanations on the rationale for the revision as well as a date of coming into operation.

It replaces the guidelines on GDP published in March 2013.

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. Compliance with these Guidelines will ensure control of the distribution chain and consequently maintain the quality and the integrity of medicinal products.

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

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

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[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67.
[2] Guidelines on Good Distribution Practice of medicinal products for human use, OJ C 63, 1.3.1994, p. 4.
[3] Guidelines of 7 March 2013 on Good Distribution Practice of medicinal products for human use, OJ C 68, 8.3.2013, p. 1.
[4] Directive 2011/62/EU of the European Parliament and of the Council amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of falsified medicinal products, OJ L 174, 1.7.2011, p. 74.

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

The definition of wholesale distribution does not depend on whether that distributor is established or operating in specific customs areas, such as in free zones or in free warehouses. All obligations related to wholesale distribution activities (such as exporting, holding or supplying) also apply to these distributors. Relevant sections of these Guidelines should also be adhered to by other actors involved in the distribution of medicinal products.

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.

GLOSSARY

Terms used in these guidelines shall have following meaning:

1) Good Distribution Practice (GDP) is that part of quality assurance which ensures that the quality of medicinal products is maintained throughout all stages of the supply chain from the site of manufacturer to the pharmacy or person authorised or entitled to supply medicinal products to the public;

2) Export procedure is a procedure, which allow goods to leave the customs territory of the Montenegro;

3) Falsified medicinal product[5] is 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 authorisation holder; or

(c) its history, including the records and documents relating to the distribution channels used;

4) Free zones and free warehouses[6] are parts of the customs territory of the Montenegro or premises situated in that territory and separated from the rest of it in which:

(a) foreign goods are considered, for the purpose of import duties and commercial policy import measures, as not being on 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) domestic goods for which such provision is made under special 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;

5) Holding is storing medicinal products;

6) Transport is moving medicinal products between two locations without storing them for unjustified periods of time;

7) Procuring is obtaining, acquiring, purchasing or buying medicinal products from manufacturers, importers or other wholesale distributors;

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[5]Article 1 paragraph 33 of Directive 2001/83/EC.

[6] Articles 166 to 181 of Council Regulation (EEC) No 2913/92 of 12 October 1992 establishing the Community Customs Code (OJ L 302, 19.10.1992, p. 1).

8) Qualification is 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);

9) Supplying are all activities of providing, selling, donating medicinal products to wholesalers, pharmacists, or persons authorised or entitled to supply medicinal products to the public;

10) Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle;

11) Quality system is 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);

12) Validation is 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).

CHAPTER 1 — QUALITY MANAGEMENT

1.1. Principle

Wholesale distributors must maintain a quality system setting out responsibilities, processes and risk management principles in relation to their activities[7]. 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 organisation's management and requires their leadership and active participation and should be supported by staff commitment.

1.2. Quality system

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 maintains its quality and integrity and remains within the legal supply chain during storage and/or transportation.

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.

A responsible person should be appointed by the management, who should have clearly specified authority and responsibility for ensuring that a quality system is implemented and maintained.

The 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.

[7] Article 80 (h) of Directive 2001/83/EC.

The size, structure and complexity of distributor's activities should be taken into consideration when developing or modifying the quality system.

A change control system should be in place. This system should incorporate quality risk management principles, and be proportionate and effective.

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) records are made contemporaneously;

(v) deviations from established procedures are documented and investigated;

(vi) appropriate corrective and preventive actions (commonly known as 'CAPA') are taken to correct deviations and prevent them in line with the principles of quality risk management.

1.3. Management of outsourced activities

The quality system should extend to the control and review of any outsourced activities related to the procurement, holding, supply or export of medicinal products. These processes should incorporate quality risk management and include:

(i) assessing the suitability and competence of the contract acceptor to carry out the activity and checking authorisation status, if required;

(ii) defining the responsibilities and communication processes for the quality-related activities of the parties involved;

(iii) monitoring and review of the performance of the contract acceptor, and the identification and implementation of any required improvements on a regular basis.

1.4. Management review and monitoring

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

(i) measurement of the achievement of quality system objectives;

(ii) assessment of performance 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 and audits; and external assessments such as inspections, 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 system;

(v) changes in business environment and objectives.

The outcome of each management review of the quality system should be documented in a timely manner and effectively communicated internally.

1.5. Quality risk management

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.

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 in guideline Q9 of the International Conference on Harmonisation ('ICH').

CHAPTER 2 — PERSONNEL

2.1. Principle

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 wholesale distributor is responsible. Individual responsibilities should be clearly understood by the staff and be recorded.

2.2. Responsible person

The wholesale distributor must designate a person as responsible person. The responsible person should meet the qualifications and all conditions provided for by the law governing medicines and bylaws for its implementation, in accordance with the EU legislation[8]. A degree in pharmacy is desirable. The responsible person should have appropriate competence and experience as well as knowledge of and training in GDP.

The responsible person should fulfil their responsibilities personally and should be continuously contactable. The responsible person may delegate duties but not responsibilities.

The written job description of the responsible person should define their authority to take decisions with regard to their responsibilities. The wholesale distributor should give the responsible person the defined authority, resources and responsibility needed to fulfil their duties.

The responsible person should carry out their duties in such a way as to ensure that the wholesale distributor can demonstrate GDP compliance and that public service obligations are met.

The responsibilities of the responsible person include:

(i) ensuring that a quality management system is implemented and maintained;
(ii) focusing on the management of authorised activities and the accuracy and quality of records;

[8] Article 79(b) of Directive 2001/83/EC.

(iii) ensuring that initial and continuous training programmes are implemented and maintained;

(iv) coordinating and promptly performing any recall operations for medicinal products;

(v) ensuring that relevant customer complaints are dealt with effectively;

(vi) ensuring that suppliers and customers are approved;

(vii) approving any subcontracted activities which may impact on GDP;

(viii) ensuring that self-inspections are performed at appropriate regular intervals following a prearranged programme and necessary corrective measures are put in place;

(ix) keeping appropriate records of any delegated duties;

(x) deciding on the final disposition of returned, rejected, recalled or falsified products;

(xi) approving any returns to saleable stock;

(xii) ensuring that any additional requirements imposed on certain products by law on medicines and bylaws for its implementation, in accordance with the EU legislation, are adhered to[9].

2.3. Other personnel

There should be an adequate number of competent personnel involved in all stages of the wholesale distribution activities of medicinal products. The number of personnel required will depend on the volume and scope of activities.

The organisational structure of the wholesale distributor should be set out in an organisation chart. The role, responsibilities, and interrelationships of all personnel should be clearly indicated.

The role and responsibilities of employees working in key positions should be set out in written job descriptions, along with any arrangements for deputising.

2.4. Training

All personnel involved in wholesale distribution activities should be trained on the requirements of GDP. They should have the appropriate competence and experience prior to commencing their tasks.

Personnel should receive initial and continuing training relevant to their role, based on written procedures and in accordance with a written training programme. The responsible person should also maintain their competence in GDP through regular training.

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

Personnel dealing with any products which require more stringent handling conditions should receive specific training. Examples of such products include hazardous products, radioactive materials, products presenting special risks of abuse (including narcotic and psychotropic substances), and temperature-sensitive products.

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

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[9] Article 83 of Directive 2001/83/EC.

2.5. Hygiene

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

CHAPTER 3 — PREMISES AND EQUIPMENT

3.1. Principle

Wholesale distributors must have suitable and adequate premises, installations and equipment in accordance with the law governing medicines and bylaws for its implementation, in accordance with the EU legislation[10], so as to ensure proper storage and distribution of medicinal products. In particular, the premises should be clean, dry and maintained within acceptable temperature limits.

3.2. Premises

The premises should be designed or adapted to ensure that the required storage conditions are maintained. They should be suitably secure, structurally sound and of sufficient capacity to allow 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.

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

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

Products pending a decision as to their disposition or products that have been removed from saleable stock should be segregated either physically or through an equivalent electronic system. This includes, for example, any product suspected of falsification and returned products. Medicinal products received from a third country but not intended for the Union market should also be physically segregated. Any falsified medicinal products, expired products, recalled products and rejected products found in the supply chain should be immediately physically segregated and stored in a dedicated area away from all other medicinal products. The appropriate degree of security should be applied in these areas to ensure that such items remain separate from saleable stock. These areas should be clearly identified.

Special attention should be paid to the storage of products with specific handling instructions as specified in accordance with the law governing medicines and bylaws for its implementation. Special storage conditions (and special authorisations) may be required for such products (e.g. narcotics and psychotropic substances).

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

Radioactive materials and other hazardous products, as well as products presenting special safety risks of fire or explosion (e.g. medicinal gases, combustibles, flammable liquids and solids), should be stored in one or more dedicated areas in accordance with the special law and appropriate safety and security measures.

Receiving and dispatch bays should protect products from prevailing weather conditions. There should be adequate separation between the receipt and dispatch and storage areas. Procedures should be in place to maintain control of inbound/outbound goods. Reception areas where deliveries are examined following receipt should be designated and suitably equipped.

Unauthorised access to all areas of the authorised premises should be prevented. Prevention measures would usually include a monitored intruder alarm system and appropriate access control. Visitors should be accompanied.

Premises and storage facilities should be clean and free from litter and dust. Cleaning programmes, instructions and records should be in place. Appropriate cleaning equipment and cleaning agents should be chosen and used so as not to present a source of contamination.

Premises 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.

Rest, wash and refreshment rooms for employees should be adequately separated from the storage areas. The presence of food, drink, smoking material or medicinal products for personal use should be prohibited in the storage areas.

3.2.1. Temperature and environment control

Suitable equipment and procedures should be in place to check the environment where medicinal products are stored. Environmental factors to be considered include temperature, light, humidity and cleanliness of the premises.

An initial temperature mapping exercise should be carried out on the storage area before use, under representative conditions. Temperature monitoring equipment should be located according to the results of the mapping exercise, ensuring that monitoring devices are positioned in the areas that experience the extremes of fluctuations. 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. For small premises of a few square meters which are at room temperature, an assessment of potential risks (e.g. heaters) should be conducted and temperature monitors placed accordingly.

3.3. Equipment

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

Equipment used to control or to monitor the environment where the medicinal products are stored should be calibrated at defined intervals based on a risk and reliability assessment.

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

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

Adequate records of repair, maintenance and calibration activities for key equipment should be made and the results should be retained. Key equipment would include for example cold stores, monitored intruder alarm and access control systems, refrigerators, thermo hygrometers, or other temperature and humidity recording devices, air handling units and any equipment used in conjunction with the onward supply chain.

3.3.1. Computerised systems

Before a computerised system is brought into use, it should be demonstrated, through appropriate validation or verification studies, that the system is capable of achieving the desired results accurately, consistently and reproducibly.

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 principles, objectives, security measures, system scope and main features, how the computerised system is used and the way it interacts with other systems.

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

Data should be secured by physical or electronic means and protected against accidental or unauthorised modifications. Stored data should be checked periodically for accessibility. Data should be protected by backing up at regular intervals. Back up data should be retained for the period stated at least for five years at a separate and secure location.

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

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.

Equipment and processes should be respectively qualified and/or validated before commencing use and after any significant changes, e.g. repair or maintenance.

Validation and qualification reports should be prepared summarising the results obtained and commenting on any observed deviations. Deviations from established procedures should be documented and further actions decided to correct deviations and avoid their reoccurrence (corrective and preventive actions). The principles of 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.

CHAPTER 4 — DOCUMENTATION

4.1. Principle

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.

4.2. General

Documentation comprises all written procedures, instructions, contracts, records and data, in paper or in electronic form. Documentation should be readily available/retrievable.

With regard to the processing of personal data of employees, complainants or any other natural person, law on the protection of individuals applies, in accordance with the Directive 95/46/EC[11] to the processing of personal data and to the free movement of such data.

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

Procedure should be approved signed and dated by the responsible person. Documentation should be approved, signed and dated by appropriate authorised persons, as required. It should not be hand-written; although, where it is necessary, sufficient space should be provided for such entries.

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.

Documents should be retained at least for five years. Personal data should be deleted or anonymised as soon as their storage is no longer than necessary for the purpose of distribution activities.

Each employee should have ready access to all necessary documentation for the tasks executed.

Attention should be paid to using valid and approved procedures. Documents should have unambiguous content; title, nature and purpose should be clearly stated. Documents should be reviewed regularly and kept up-to-date. Version control should be applied to procedures. After revision of a document, a system should exist to prevent inadvertent use of the superseded version. Superseded or obsolete procedures should be removed from workstations and archived.

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[11] OJ L 281, 23.11.1995, p. 31.

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

Records must include at least the following information: date; name of the medicinal product; quantity received, supplied or brokered; name and address of the supplier, customer, broker or consignee, as appropriate; and batch number.

Records should be made at the time each operation is undertaken.

CHAPTER 5 — OPERATIONS

5.1. Principle

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 minimise the risk of falsified medicinal products entering the legal supply chain.

All medicinal products distributed in the Montenegro by a wholesale distributor must be covered by a marketing authorisation in accordance with the law governing medicines, unless prescribed otherwise by this law).

Any distributor, other than the marketing authorisation holder, who imports a medicinal product from another Member State must notify the marketing authorisation holder and the Institute for medicines and medical devices (hereinafter; the Institute). [12]

All key operations described below should be fully described in the quality system in appropriate documentation.

5.2. Qualification of suppliers

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 in accordance with the law governing medicines[13].

Wholesale 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 authorisation[14].

Where medicinal products are obtained from another wholesale distributor, the receiving wholesale distributor, must verify that the supplier complies with the principles and guidelines of good distribution practices and that they hold an authorisation for example by

[12] Article 76 paragraph 3 of Directive 2001/83/EC.
[13] Article 80(b) of Directive 2001/83/EC.
[14] Article 40 paragraph 3 of Directive 2001/83/EC.

using the Union database. 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[15].

Appropriate qualification and approval of suppliers, should be performed prior to any procurement of medicinal products. This should be controlled by a procedure and the results documented and periodically rechecked.

When entering into a new contract with new suppliers, the wholesale distributor should carry out 'due diligence' checks in order to assess the suitability, competence and reliability of the other party. Attention should be paid to:

(i) the reputation or reliability of the supplier;
(ii) offers of medicinal products more likely to be falsified;
(iii) large offers of medicinal products which are generally only available in limited quantities; and
(iv) out-of-range prices.

5.3. Qualification of customers

Wholesale distributors must ensure they supply medicinal products only to persons who are themselves in possession of a wholesale distribution authorisation or who are authorised or entitled to supply medicinal products to the public.

Checks and periodic rechecks may include: requesting copies of customer's authorisations according to the law, verifying status on an authority website, requesting evidence of qualifications or entitlement according to the law etc.

Wholesale distributors should monitor their transactions and investigate any irregularity in the sales patterns of narcotics, psychotropic substances or other dangerous substances. Unusual sales patterns that may constitute diversion or misuse of medicinal product should be investigated and reported to competent authorities where necessary. Steps should be taken to ensure fulfilment of any public service obligation imposed upon them.

5.4. Receipt of medicinal products

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

Medicinal products requiring special storage or security measures should be prioritised and once appropriate checks have been conducted they should be immediately transferred to appropriate storage facilities.

Batches of medicinal products intended for the Montenegro should not be transferred to saleable stock before assurance has been obtained in accordance with written procedures, that they are authorised for sale. For imported batches, prior to their transfer to saleable stock, the

[15] Article 80 paragraph 4 of Directive 2001/83/EC.

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

5.5. Storage

Medicinal products and, if necessary, healthcare products should be stored separately from other products likely to alter them and should be protected from the harmful effects of light, temperature, moisture and other external factors. Particular attention should be paid to products requiring specific storage conditions.

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

Warehousing operations must ensure appropriate storage conditions are maintained and allow for appropriate security of stocks.

Stock should be rotated according to the 'first expiry, first out' (FEFO) principle. Exceptions should be documented.

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 unless the package is designed to allow such storage (such as for some medicinal gas cylinders).

Medicinal products that are nearing their expiry date/shelf life should be withdrawn immediately from saleable stock either physically or through other equivalent electronic segregation.

Stock inventories should be performed regularly taking into account law governing medicines and bylaws for its implementation requirements. Stock irregularities should be investigated and documented.

5.6. Destruction of obsolete goods

Medicinal products intended for destruction should be appropriately identified, held separately and handled in accordance with a written procedure.

Destruction of medicinal products should be in accordance with the law governing waste management for handling, transport and disposal of such products.

Records of all destroyed medicinal products should be retained for a defined period.

5.7. Picking

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.

5.8. Supply

For all supplies, a document (e.g. delivery note) must be enclosed stating the date; name and pharmaceutical form of the medicinal product, batch number; quantity supplied; name and address of the supplier, name and delivery address of the consignee[16] (actual physical storage premises, if different) and applicable transport and storage conditions. Records should be kept so that the actual location of the product can be known.

5.9. Export to third countries

The export of medicinal products falls within the definition of 'wholesale distribution'[17]. A person exporting medicinal products must hold a wholesale distribution authorisation or a manufacturing authorisation. This is also the case if the exporting wholesale distributor is operating from a free zone.

The rules for wholesale distribution apply in their entirety in the case of export of medicinal products. However, where medicinal products are exported, they do not need to be covered by a marketing authorisation of the Institute or Union or a Member State). Wholesalers should take the appropriate measures in order to prevent these medicinal products reaching the Montenegro market. Where wholesale distributors supply medicinal products to persons in third countries, they shall ensure that such supplies are only made to persons who are authorised or entitled to receive medicinal products for wholesale distribution or supply to the public in accordance with the applicable legal and administrative provisions of the country concerned.

CHAPTER 6 — COMPLAINTS, RETURNS, SUSPECTED FALSIFIED MEDICINAL PRODUCTS AND MEDICINAL PRODUCT RECALLS

6.1. Principle

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 Institute. An assessment of returned medicinal products should be performed before any approval for resale. A consistent approach by all partners in the supply chain is required in order to be successful in the fight against falsified medicinal products.

6.2. Complaints

Complaints should be recorded with all the original details. A distinction should be made between complaints related to the quality of a medicinal product and those related to distribution. In the event of a complaint about the quality of a medicinal product and a potential product defect, the manufacturer and/or marketing authorisation holder should be informed without delay. Any product distribution complaint should be thoroughly investigated to identify the origin of or reason for the complaint.

A person should be appointed to handle complaints and allocated sufficient support personnel.

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[16] Article 82 of Directive 2001/83/EC.

[17] Article 1 paragraph 17 of Directive 2001/83/EC.

If necessary, appropriate follow-up actions (including CAPA) should be taken after investigation and evaluation of the complaint, including where required notification to the Institute in accordance with the law governing medicines.

6.3. Returned medicinal products

Returned products must be handled according to a written, risk-based process taking into account the product concerned, any specific storage requirements and the time elapsed since the medicinal product was originally dispatched. Returns should be conducted in accordance with the law governing medicines and bylaws for its implementation and contractual arrangements between the parties.

Medicinal products which have left the premises of the distributor should only be returned to saleable stock if all of the following are confirmed:

(i) the medicinal products are in their unopened and undamaged secondary packaging and are in good condition; have not expired and have not been recalled;
(ii) medicinal products returned from a customer not holding a wholesale distribution authorisation or from pharmacies authorised to supply medicinal products to the public should only be returned to saleable stock if they are returned within an acceptable time limit, for example 10 days;
(iii) it has been demonstrated by the customer that the medicinal products have been transported, stored and handled in compliance with their specific storage requirements;
(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 the product was supplied to that customer (via copies of the original delivery note or by referencing invoice numbers, etc.) and the batch number is known, and that there is no reason to believe that the product has been falsified.

Moreover, for medicinal products requiring specific temperature storage conditions such as low temperature, returns to saleable stock can only be made if there is documented evidence that the product has been stored under the authorised storage conditions throughout the entire time. If any deviation has occurred, a risk assessment has to be performed, on which basis the integrity of the product can be demonstrated. The evidence should cover:

(i) delivery to customer;
(ii) examination of the product;
(iii) opening of the transport packaging;
(iv) return of the product to the packaging;
(v) collection and return to the distributor;
(vi) return to the distribution site refrigerator.

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

Stolen products that have been recovered cannot be returned to saleable stock and sold to customers.

6.4. Falsified medicinal products

Wholesale distributors must immediately inform the Institute and the marketing authorisation holder of any medicinal products they identify as falsified or suspect to be falsified[18]. A procedure should be in place to this effect. It should be recorded with all the original details and investigated.

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

6.5. Medicinal product recalls

The effectiveness of the arrangements for product recall should be evaluated regularly (at least annually).

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

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

Any recall operation should be recorded at the time it is carried out. Records should be made readily available to the Institute or other competent authorities.

The distribution records should be readily accessible 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, batch numbers and quantities delivered), including those for exported products and medicinal product samples.

The progress of the recall process should be recorded for a final report.

CHAPTER 7 — OUTSOURCED ACTIVITIES

7.1. Principle

Any activity covered by the GDP guide that is outsourced should be correctly defined, agreed and 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.

7.2. Contract giver

The contract giver is responsible for the activities contracted out.

The contract giver is responsible for assessing the competence of the contract acceptor to successfully carry out 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 commencement of, and whenever there has been a change

[18] Article 80(i) of Directive 2001/83/EC.

to, the outsourced activities. The frequency of audit should be defined based on risk depending on the nature of the outsourced activities. Audits should be permitted at any time.

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.

7.3. Contract acceptor

The contract acceptor should have adequate premises and equipment, procedures, knowledge and experience, and competent personnel to carry out the work ordered by the contract giver.

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 by the contract giver or the contract acceptor. 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.

The contract acceptor should refrain from any activity which may adversely affect the quality of the product(s) handled for the contract giver.

The contract acceptor must forward any information that can influence the quality of the product(s) to the contract giver in accordance with the requirement of the contract.

CHAPTER 8 — SELF-INSPECTIONS

8.1. Principle

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

8.2. Self-inspections

A self-inspection programme should be implemented covering all aspects of GDP and compliance with the regulations, guidelines and procedures within a defined time frame. Self-inspections may be divided into several individual self-inspections of limited scope.

Self-inspections should be conducted in an impartial and detailed way by designated competent company personnel. Audits by independent external experts may also be useful but may not be used as a substitute for self-inspection.

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

CHAPTER 9 — TRANSPORTATION

9.1. Principle

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 utilised when planning transportation.

9.2. Transportation

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 recipient of the affected medicinal products. A procedure should also be in place for investigating and handling temperature excursions.

It is the responsibility of the wholesale 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.

There should be written procedures in place for the operation and maintenance of all vehicles and equipment involved in the distribution process, including cleaning and safety precautions.

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.

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

For emergency deliveries outside normal business hours, persons should be designated and written procedures should be available.

Where transportation is performed by a third party, the contract in place should encompass the requirements of Chapter 7. Transportation providers 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 minimise the duration of temporary storage while awaiting the next stage of the transportation route.

9.3. Containers, packaging and labelling

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.

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; the qualification status of the packaging and the validation status of the shipping containers.

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.

9.4. Products requiring special conditions

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

Medicinal products comprising highly active and radioactive materials should be transported in safe, dedicated and secure containers and vehicles. The relevant safety measures should be in accordance with international agreements and special law.

For temperature-sensitive products, qualified equipment (e.g. thermal packaging, temperature-controlled containers or temperature-controlled vehicles) should be used to ensure correct transport conditions are maintained between the manufacturer, wholesale distributor and customer.

If temperature-controlled vehicles are used, the temperature monitoring equipment used during transport should be maintained and calibrated at regular intervals. Temperature mapping under representative conditions should be carried out and should take into account seasonal variations.

If requested, customers should be provided with information to demonstrate that products have complied with the temperature storage conditions.

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.

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

The process for delivery of sensitive products and control of seasonal temperature variations should be described in a written procedure.

CHAPTER 10 — SPECIFIC PROVISIONS FOR BROKERS[19]

10.1. 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[20].

Brokers are subject to a registration requirement in accordance with the law governing medicines. They must have a permanent address and contact details in the Montenegro or Member State where they are registered[21]. They must notify the Institute of any changes to those details without unnecessary delay.

By definition, brokers do not procure, supply or hold medicines. Therefore, requirements for premises, installations and equipment as set out in law governing medicines and bylaws for its implementation and all other rules that apply to wholesale distributors also apply to brokers.

10.2. Quality system

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

The quality system should include an emergency plan which ensures effective recall of medicinal products from the market ordered by the manufacturer or the Institute or carried out in cooperation with the manufacturer or marketing authorisation holder for the medicinal product concerned[22]. The Institute must be immediately informed of any suspected falsified medicines offered in the supply chain[23].

10.3. Personnel

[19] Article 85b paragraph 3 of Directive 2001/83/EC.
[20] Article 1 paragraph 17a of Directive 2001/83/EC.
[21] Article 85b of Directive 2001/83/EC.
[22] Article 80(d) of Directive 2001/83/EC.
[23] Article 85b paragraph 1 subparagraph 3 of Directive 2001/83/EC.

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

10.4. Documentation

The general provisions on documentation in Chapter 4 apply.

In addition, at least the following procedures and instructions, along with the corresponding records of execution, should be in place:

(i) procedure for complaints handling;
(ii) procedure for informing the Institute and marketing authorisation holders of suspected falsified medicinal products;
(iii) procedure for supporting recalls;
(iv) procedure for ensuring that medicinal products brokered have a marketing authorisation;
(v) 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;
(vi) records should be kept either in the form of purchase/sales invoices or on computer, or in any other form for any transaction in medicinal products brokered and should contain at least the following information: date; name of the medicinal product; quantity brokered; name and address of the supplier and the customer; and batch number.

Records should be made available to the Institute, for inspection purposes, least for five years.

PART II

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

Introduction

These guidelines are based on the fourth paragraph of Article 47 of Directive 2001/83/EC[24], which was implemented with the law governing medicines and bylaws for its implementation (hereinafter: GDP for active substances).

They follow the same principles that underlie the guidelines of EudraLex Volume 4, Part II, Chapter 17, with regard to the distribution of active substances and the Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use[25].

These guidelines provide stand-alone guidance on Good Distribution Practice (GDP) for importers and distributors of active substances for medicinal products for human use. They complement the rules on distribution set out in the guidelines of EudraLex Volume 4, Part II, and apply also to distributors of active substances manufactured by themselves.

Any manufacturing activities in relation to active substances, including re-packaging, re-labelling or dividing up, are subject to Commission Delegated Regulation (EU) No 1252/2014[26] and EudraLex Volume 4, Part II.

Additional requirements apply to the importation of active substances, as laid down in Article 46b of Directive 2001/83/EC.

GLOSSARY

Terms used in these guidelines shall have following meaning:

1) Batch is a specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval;

2) Batch number is a unique combination of numbers, letters and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined;

3) Brokering of active substances are all activities in relation to the sale or purchase of active substances that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person;

4) Calibration is the demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements;

5) Consignee is the person to whom the shipment is to be delivered whether by land, sea or air;

6) Contamination is the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or active substance during production, sampling, packaging or repackaging, storage or transport;

7) Distribution of active substances are all activities consisting of procuring, importing, holding, supplying or exporting of active substances, apart from brokering;

8) Deviation is departure from an approved instruction or established standard;

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[24] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67.

[25] OJ C 343, 23.11.2013, p. 1.

[26] Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parlia-ment and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use (OJ L 337, 25.11.2014, p. 1).

9) Expiry date is the date placed on the container/labels of an active substance designating the time during which the active substance is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used;

10) Falsified active substance is any active substance with a false representation of:

a) its identity, including its packaging and labelling, its name or its components as regards any of the ingredients and the strength of those ingredients;

b) its source, including its manufacturer, its country of manufacture, its country of origin; or

c) its history, including the records and documents relating to the distribution channels used;

11) Holding is storing of active substances;

12) Procedure is a documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the distribution of an active substance;

13) Procuring is obtaining, acquiring, purchasing or buying active substances from manufacturers, importers or other distributors;

14) Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of an active substance across the product lifecycle;

15) Quality system is the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met (ICH Q9);

16) Quarantine is the status of materials isolated physically or by other effective means pending a decision on the subsequent approval or rejection;

17) Retest date is the date when a material should be re-examined to ensure that it is still suitable for use;

18) Supplying are all activities of providing, selling, donating active substances to distributors, pharmacists, or manufacturers of medicinal products;

19) Signed (signature) is the record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature;

20) Transport (transportation) is moving active substances between two locations without storing them for unjustified periods of time;

21) Validation is a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

CHAPTER 1 — SCOPE

1.1. These guidelines apply to distribution of active substances, as defined in Article 1(3a) of Directive 2001/83/EC, for medicinal products for human use. According to that provision, an active substance is any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.

1.2. For the purpose of these guidelines, distribution of active substances shall comprise all activities consisting of procuring, importing, holding, supplying or exporting active substances, apart from brokering.

1.3. These guidelines do not apply to intermediates of active substances.

CHAPTER 2 — QUALITY SYSTEM

2.1. Distributors of active substances should develop and maintain a quality system setting out responsibilities, processes and risk management principles. Examples of the processes and applications of quality risk management can be found in EudraLex Volume 4, Part III: GMP related documents, ICH guideline Q9 on Quality Risk Management (ICH Q9).

2.2. The quality system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. It should ensure that:

(i) active substances are procured, imported, held, supplied or exported in a way that is compliant with the requirements of GDP for active substances;
(ii) management responsibilities are clearly specified;
(iii) active substances are delivered to the right recipients within a satisfactory time period;
(iv) records are made contemporaneously;
(v) deviations from established procedures are documented and investigated;
(vi) appropriate corrective and preventive actions, commonly known as 'CAPA', are taken to correct deviations and prevent them in line with the principles of quality risk management;
(vii) changes that may affect the storage and distribution of active substances are evaluated.

2.3. The size, structure and complexity of the distributor's activities should be taken into consideration when developing or modifying the quality system.

CHAPTER 3 — PERSONNEL

3.1. The distributor should designate a person at each location where distribution activities are performed who should have defined authority and responsibility for ensuring that a quality system is implemented and maintained. The designated person should fulfil his responsibilities personally. The designated person can delegate duties but not responsibilities.

3.2. The responsibilities of all personnel involved in the distribution of active substances should be specified in writing. The personnel should be trained on the requirements of GDP for active substances. They should have the appropriate competence and experience to ensure that active substances are properly handled, stored and distributed.
3.3. Personnel should receive initial and continuing training relevant to their role, based on written procedures and in accordance with a written training programme.

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

CHAPTER 4 — DOCUMENTATION

4.1. Documentation comprises all written procedures, instructions, contracts, records and data, in paper or in electronic form. Documentation should be readily available or retrievable. All documentation related to compliance of the distributor with these guidelines should be made available on request of the Institute.

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, unambiguous language and be free from errors.

4.3. 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.

4.4. Each employee should have ready access to all necessary documentation for the tasks executed.

Procedures

4.5. Written procedures should describe the distribution activities which affect the quality of the active substances. This could include receipt and checking of deliveries, storage, cleaning and maintenance of the premises (including pest control), recording of the storage conditions, security of stocks on site and of consignments in transit, withdrawal from saleable stock, handling of returned products, recall plans, etc.

4.6. Procedures should be approved, signed and dated by the person responsible for the quality system.

4.7. Attention should be paid to the use of valid and approved procedures. Documents should be reviewed regularly and kept up to date. Version control should be applied to procedures. After revision of a document a system should exist to prevent inadvertent use of the superseded version. Superseded or obsolete procedures should be removed from workstations and archived.

Records

4.8. Records should be clear, be made at the time each operation is performed and in such a way that all significant activities or events are traceable. Records should be retained for at least 1 year after the expiry date of the active substance batch to which they relate. For active substances with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

4.9. Records should be kept of each purchase and sale, showing the date of purchase or supply, name of the active substance, batch number and quantity received or supplied, and name and address of the supplier and of the original manufacturer, if not the same, or of the shipping agent and/or the consignee. Records should ensure the traceability of the origin and destination of products, so that all the suppliers of, or those supplied with, an active substance can be identified. Records that should be retained and be available include:

(i) identity of supplier, original manufacturer, shipping agent and/or consignee;
(ii) address of supplier, original manufacturer, shipping agent and/or consignee;

(iii) purchase orders;
(iv) bills of lading, transportation and distribution records;
(v) receipt documents;
(vi) name or designation of active substance;
(vii) manufacturer's batch number;
(viii) certificates of analysis, including those of the original manufacturer;
(ix) retest or expiry date.

CHAPTER 5 — PREMISES AND EQUIPMENT

5.1. Premises and equipment should be suitable and adequate to ensure proper storage, protection from contamination, e.g. narcotics, highly sensitising materials, materials of high pharmacological activity or toxicity, and distribution of active substances. They should be suitably secure to prevent unauthorised access. Monitoring devices that are necessary to guarantee the quality attributes of the active substance should be calibrated according to an approved schedule against certified traceable standards.

CHAPTER 6 — OPERATIONS

Orders

6.1. Where active substances are procured from a manufacturer, importer or distributor established in the Montenegro, that manufacturer, importer or distributor should be registered according to the law governing medicines.

Receipt

6.2. Areas for receiving active substances should protect deliveries from prevailing weather conditions during unloading. The reception area should be separate from the storage area. Deliveries should be examined at receipt in order to check that:

(i) containers are not damaged;
(ii) all security seals are present with no sign of tampering;
(iii) correct labelling, including correlation between the name used by the supplier and the in-house name, if these are different;
(iv) necessary information, such as a certificate of analysis, is available; and
(v) the active substance and the consignment correspond to the order.

6.3. Active substances with broken seals, damaged packaging, or suspected of possible contamination should be quarantined either physically or using an equivalent electronic system and the cause of the issue investigated.

6.4. Active substances subject to specific storage measures, e.g. narcotics and products requiring a specific storage temperature or humidity, should be immediately identified and stored in accordance with written instructions and with law governing medicines and bylaws for its implementation.

6.5. Where the distributor suspects that an active substance procured or imported by him is falsified, he should segregate it either physically or using an equivalent electronic system and inform the Institute and other competent authority.

6.6. Rejected materials should be identified and controlled and quarantined to prevent their unauthorised use in manufacturing and their further distribution. Records of destruction activities should be readily available.

Storage

6.7. Active substances should be stored under the conditions specified by the manufacturer, e.g. controlled temperature and humidity when necessary, and in such a manner to prevent contamination and/or mix up. The storage conditions should be monitored and records maintained. The records should be reviewed regularly by the person responsible for the quality system.

6.8. When specific storage conditions are required, the storage area should be qualified and operated within the specified limits.

6.9. The storage facilities should be clean and free from litter, dust and pests. Adequate precautions should be taken against spillage or breakage, attack by micro-organisms and cross-contamination.

6.10. There should be a system to ensure stock rotation, e.g. 'first expiry (retest date), first out', with regular and frequent checks that the system is operating correctly. Electronic warehouse management systems should be validated.

6.11. Active substances beyond their expiry date should be separated, either physically or using an equivalent electronic system, from approved stock and not be supplied.

6.12. Where storage or transportation of active substances is contracted out, the distributor should ensure that the contract acceptor knows and follows the appropriate storage and transport conditions. There must be a written contract between the contract giver and contract acceptor, which clearly establishes the duties of each party. The contract acceptor should not subcontract any of the work entrusted to him under the contract without the contract giver's written authorisation.

Deliveries to customers

6.13. Supplies within the EU should be made only by distributors of active substances registered according to the law governing medicines to other distributors, manufacturers or to dispensing pharmacies.

6.14. Active substances should be transported in accordance with the conditions specified by the manufacturer and in a manner that does not adversely affect their quality. Product, batch and container identity should be maintained at all times. All original container labels should remain readable.

6.15. A system should be in place by which the distribution of each batch of active substance can be readily identified to permit its recall.

Transfer of information

6.16. Any information or event that the distributor becomes aware of, which have the potential to cause an interruption to supply, should be notified to relevant customers.

6.17. Distributors should transfer all product quality or regulatory information received from an active substance manufacturer to the customer and from the customer to the active substance manufacturer.

6.18. The distributor who supplies the active substance to the customer should provide the name and address of the original active substance manufacturer and the batch number(s) supplied. A copy of the original certificate of analysis from the manufacturer should be provided to the customer.

6.19. The distributor should also provide the identity of the original active substance manufacturer to the Institute upon request. The original manufacturer can respond to the Institute directly or through its authorised agents. (In this context 'authorised' refers to authorised by the manufacturer.)

6.20. The specific guidance for certificates of analysis is detailed in Section 11.4 of Part II of Eudralex Volume 4.

CHAPTER 7 — RETURNS, COMPLAINTS AND RECALLS

Returns

7.1. Returned active substances should be identified as such and quarantined pending investigation.

7.2. Active substances which have left the care of the distributor, should only be returned to approved stock if all of the following conditions are met:

(i) the active substance is in the original unopened container(s) with all original security seals present and is in good condition;
(ii) it is demonstrated that the active substance has been stored and handled under proper conditions. Written information provided by the customer should be available for this purpose;
(iii) the remaining shelf life period is acceptable;
(iv) the active substance has been examined and assessed by a person trained and authorised to do so;
(v) no loss of information/traceability has occurred.

This assessment should take into account the nature of the active substance, any special storage conditions it requires, and the time elapsed since it was supplied. As necessary and if there is any doubt about the quality of the returned active substance, advice should be sought from the manufacturer.

7.3. Records of returned active substances should be maintained. For each return, documentation should include:

(i) name and address of the consignee returning the active substances;

(ii) name or designation of active substance, active substance batch number and quantity returned;

(iii) reason for return;

(iv) use or disposal of the returned active substance and records of the assessment performed.

7.4. Only appropriately trained and authorised personnel should release active substances for return to stock. Active substances returned to saleable stock should be placed such that the stock rotation system operates effectively.

Complaints and recalls

7.5. All complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure. In the event of a complaint about the quality of an active substance the distributor should review the complaint with the original active substance manufacturer in order to determine whether any further action, either with other customers who may have received this active substance or with the Institute, or both, should be initiated. The investigation into the cause for the complaint should be conducted and documented by the appropriate party.

7.6. Complaint records should include:

(i) name and address of complainant;

(ii) name, title, where appropriate, and phone number of person submitting the complaint;

(iii) complaint nature, including name and batch number of the active substance;

(iv) date the complaint is received;

(v) action initially taken, including dates and identity of person taking the action;

(vi) any follow-up action taken;

(vii) response provided to the originator of complaint, including date response sent;

(viii) final decision on active substance batch.

7.7. Records of complaints should be retained in order to evaluate trends, product related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action. These should be made available during inspections by the Institute.

7.8. Where a complaint is referred to the original active substance manufacturer, the record maintained by the distributor should include any response received from the original active substance manufacturer, including date and information provided.

7.9. In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

7.10. There should be a written procedure that defines the circumstances under which a recall of an active substance should be considered.

7.11. The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how

the recalled material should be treated. The designated person (cf. Section 3.1) should be involved in recalls.

CHAPTER 8 — SELF-INSPECTIONS

8.1. The distributor should conduct and record self-inspections in order to monitor the implementation of and compliance with these guidelines. Regular self-inspections should be performed in accordance with an approved schedule.

FINAL PROVISIONS

On the day of publication of these guidelines, the Guidelines of good practice in the distribution of medicines published on the website of the Ministry of Health on November 14, 2012 cease to be valid.

These guidelines shall enter into force on the day of their publication on the website of the Institute and the Ministry of Health, except for the provisions of item 3.2, paragraph 4, third sentence in Chapter 3; item 4.2, paragraph 9 and paragraph 10 the words: “or which has been the subject of mediation” in Chapter 4; item 5.1 paragraph 3, items 5.2 paragraph 2 and paragraph 3 second sentence, item 5.9 paragraph 2 second and third sentences in Chapter 5 and Chapter 10 of the First Part of this Guideline, which apply from the date of Montenegro's accession to the EU.

D I R E C T O R

dr Milorad Drljević