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

DRAFT SUBMITTED FOR PUBLIC CONSULTATION

Stakeholders are invited to comment on this draft by 30 April 2013 at the latest. Responses should be sent preferably by e-mail to sanco-pharmaceuticals-d6@ec.europa.eu, or by post to Unit SANCO/D/6, DM24 02/050, BE-1049 Brussels.

When sending your comments and responses, you should state whether you are a stakeholder association or a private individual. If you represent an association, please indicate clearly what type of association this is (active substance manufacturer, medicinal products manufacturer, importer etc.). If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50 million annual turnover and fewer than 250 employees).

All comments and responses will be made publicly available on the 'Europa website' on pharmaceuticals once the consultation period is over. If you do not wish your contribution to be made public please indicate this clearly and specifically in the documentation you send us (i.e. not just in the covering letter or e-mail). In this case, only an indication of the contributor will be disclosed.

Professional organisations are invited to register in the Union's Register for Interest Representatives (<http://europa.eu/transparency-register/>) set up as part of the European Transparency Initiative to provide the Commission and the public at large with information about the objectives, funding and structures of interest representatives.

Scope



1. For the purpose of these guidelines, the distribution of active substances for medicinal products for human use (hereafter 'active substances') is the procuring, import, holding, supplying or exporting active substances.
2. Activities consisting of re-packaging, re-labelling or dividing up of active substances are manufacturing activities and as such are subject to the guidelines on Good Manufacturing Practice of active substances.

Quality System

3. Distributors of active substances should develop and maintain a quality system setting out responsibilities, processes and risk management principles.
4. The quality system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities.
5. The size, structure and complexity of distributor's activities should be taken into consideration when developing or modifying the quality system.

Personnel

6. A management representative should be appointed in each distribution point, who should have defined authority and responsibility for ensuring that a quality system is implemented and maintained. He should fulfil his responsibilities personally.
7. Key personnel involved in the warehousing of active substances should have the appropriate ability and experience to guarantee that active substances are properly stored and handled.
8. Personnel should be trained in relation to the duties assigned to them and the training sessions recorded.

Documentation

9. All documentation should be made available on request of competent authorities. Electronic documentation should comply with Chapter 5.4 of Part II of Eudralex, the Rules Governing Medicinal Products in the European Union, Volume 4 (*EU Guidelines to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use* – hereafter 'EU-GMP'), or its Annex 11 (Guidelines on Computerised Systems).

Orders

10. Where active substances are procured from a distributor of active substances, that distributor should be registered according to Article 52(a) of Directive 2001/83/EU.

Procedures

11. Written procedures should describe the different operations which may affect the quality of the active substances or of the distribution activity: 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, records, including records of clients orders, returned products, recall plans, etc. These procedures should be approved, signed and dated by the person responsible for the quality system.

Records

12. Records should be made at the time each operation is taken ~~and in such a way that all significant activities or events are traceable.~~ Records should be clear and readily available. They should be retained for a period of five years at least.

13. 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 original manufacturer. 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. Documents that should be retained and available include:

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders
- Bills of lading, transportation and distribution records
- Receipt documents
- Name or designation of active substance
- Manufacturer's batch number
- ~~All authentic~~ Certificates of Analysis, including those of the original manufacturer
- Retest or expiry date

Premises and equipment

14. Premises and equipment should be suitable and adequate to ensure proper ~~conservation~~, protection (e.g. narcotics) and distribution of active substances. Monitoring devices, where used, should be calibrated.

Receipt

15. Areas for receiving active substances should protect deliveries from bad weather during unloading. The reception area should be separate from the storage area. Deliveries should be examined at receipt in order to check that containers are not damaged, all security seals are present and that the active substance and the consignment correspond to the order.
16. Active substances subject to specific storage measures (e.g. narcotics, products requiring a specific storage temperature or humidity) should be immediately identified and stored in accordance with written instructions and with relevant legislative provisions.
17. Where the distributor suspects that an active substance procured or imported by him is falsified, he should inform the national competent authority in which he is registered.

Storage

18. Active substances should normally be stored apart from other ~~goods~~ and under the conditions specified by the manufacturer (e.g. controlled temperature and humidity when necessary). These conditions should be monitored periodically and records maintained. The records should be reviewed regularly by the person responsible for the quality system.
19. When specific temperature or humidity storage conditions are required, storage areas should be equipped with recorders or other devices that will indicate when the specific temperature or humidity range has not been maintained. Control should be adequate to maintain all parts of the relevant storage area within the specified temperature or humidity ranges.
20. 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.
21. There should be a system to ensure stock rotation ('first expiry (retest date) first out') with regular and frequent checks that the system is operating correctly. Products beyond their expiry date or shelf-life should be ~~separated~~ from usable stock and not be supplied.
22. Active substances with broken seals, damaged packaging, ~~or~~ suspected of possible contamination should be withdrawn from saleable stock, and if not

immediately destroyed, they should be ~~kept in a~~ clearly ~~separated area~~ so that they cannot be sold in error or contaminate other goods.

23. ~~Shortages that requires registered importers to notify relevant customers of any interruption to supply that the importer or distributor becomes aware of.~~

Deliveries to customers

24. Supplies within the EU should be made only to registered distributors of active substances according to Article 52a of Directive 2001/83/EU or to authorised manufacturers according to Article 40 of Directive 2001/83/EU.
25. Active substances should be transported in such a way that:
- a) their identification is not lost;
 - b) they do not contaminate, and are not contaminated by other products or materials;
 - c) adequate precautions are taken against spillage, breakage or theft;
 - d) they are ~~secure and~~ not subjected to unacceptable degrees of heat, cold, light, moisture or other adverse influence, nor to attack by micro-organisms or pests.
26. Where transportation of the active substance is contracted out the distributor should ensure that the contract acceptor knows and follows the appropriate transport and storage conditions.
27. Active substances requiring controlled temperature storage should also be transported by appropriately specialized means.
28. A system should be in place by which the distribution of each batch of active substance can be readily determined to permit its recall.

Transfer of Information

29. Distributors should transfer ~~all quality or regulatory information~~ received from an active substance manufacturer to the customer, and from the customer to the active substance manufacturer.
30. 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.

31. The distributor should also provide the identity of the original active substance manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorised agents, depending on the legal relationship between the authorised agents and the original active substance manufacturer. (In this context "authorised" refers to authorised by the manufacturer.)
32. The specific guidance for Certificates of Analysis is included in Section 11.4 of Part II of the EU-GMP.

Returns

33. Returned active substances should be identified as such and quarantined.
34. If the conditions under which returned active substances have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, they should be destroyed by appropriate means.
35. Active substances which have left the care of the distributor, should only be returned to saleable stock if:
 - a) the active substance is in the original unopened container(s) and in good condition;
 - b) it is demonstrated that the active substance have been stored and handled under proper conditions;
 - c) the remaining shelf life period is acceptable;
 - d) they have been examined and assessed by a person authorised to do so.
36. 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. Special attention should be given to products requiring special storage conditions. If necessary, advice should be sought from the manufacturer of the active substance.
37. Records of returned active substances should be maintained. For each return, documentation should include:
 - Name and address of the consignee
 - Active substance batch number and quantity returned
 - Reason for return

- Use or disposal of the returned active substance

38. Only appropriately trained and authorised personnel should release active substances to be returned to stock. Active substances returned to saleable stock should be placed such that the 'first expiry (re-test date) first out' system operates effectively.

Complaints and Recalls

39. All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

40. Complaint records should include:

- Name and address of complainant
- Name (and, where appropriate, title) and phone number of person submitting the complaint
- Complaint nature (including name and batch number of the active substance)
- Date the complaint is received
- Action initially taken (including dates and identity of person taking the action)
- Any follow-up action taken
- Response provided to the originator of complaint (including date response sent)
- Final decision on active substance batch or lot

41. 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 to competent authorities of the Member States on whose territory the products were distributed.

42. ~~If the situation warrants,~~ 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 regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

43. ~~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).
44. In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.
45. There should be a written procedure that defines the circumstances under which a recall of an active substance should be considered.
46. 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.

Self-inspections

45. The distributor should conduct and record self-inspections in order to monitor the implementation of and compliance with this guideline.