Reviewing the GDPs

Preparing a supplier for an inspection

Dealing with EU's new unannounced supplier visits

FURTHER CHALLENGES

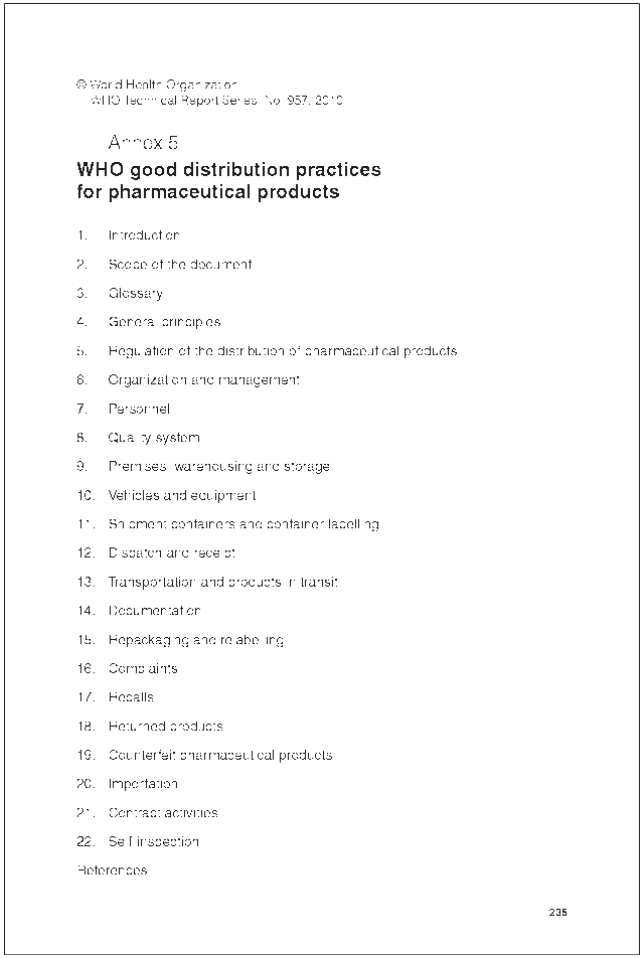
Good Distribution Practices

WHO Technical Report Series, No. 957, Annex 5

3 broad activities under GDPs:

- handling (incl. transporting)
- storing
- distributing

Identifies records to retain and recommended length of time for all suppliers in your supply chain



WHO Technical Report Series, No. 957, 2010

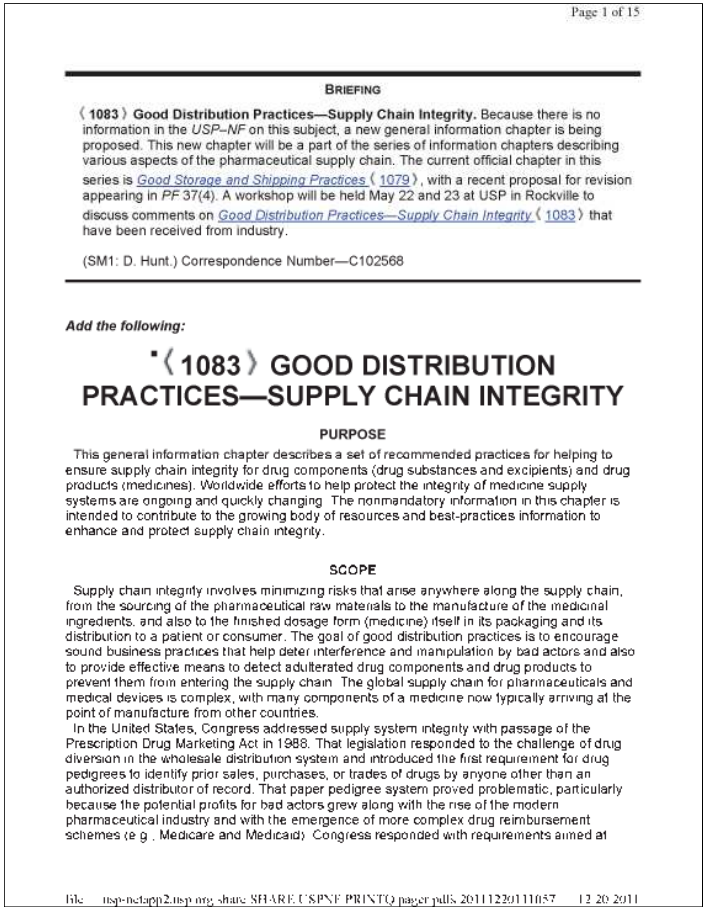
Annex 5

WHO good distribution practices for pharmaceutical products

Good Distribution Practices

USP standard 1083 (draft 2011)

- heavy emphasis on anti-counterfeiting measures
- also suggestions on combating theft, product diversions



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BRIEFING

〈1083〉 **Good Distribution Practices—Supply Chain Integrity.** Because there is no information in the *USP–NF* on this subject, a new general information chapter is being proposed. This new chapter will be a part of the series of information chapters describing various aspects of the pharmaceutical supply chain. The current official chapter in this series is *Good Storage and Shipping Practices* 〈1079〉, with a recent proposal for revision appearing in *PF* 37(4). A workshop will be held May 22 and 23 at USP in Rockville to discuss comments on *Good Distribution Practices—Supply Chain Integrity* 〈1083〉 that have been received from industry.

(SM1: D. Hunt.) Correspondence Number—C102568

Add the following:

〈1083〉 GOOD DISTRIBUTION PRACTICES—SUPPLY CHAIN INTEGRITY

PURPOSE

This general information chapter describes a set of recommended practices for helping to ensure supply chain integrity for drug components (drug substances and excipients) and drug products (medicines). Worldwide efforts to help protect the integrity of medicine supply systems are ongoing and quickly changing. The nonmandatory information in this chapter is intended to contribute to the growing body of resources and best-practices information to enhance and protect supply chain integrity.

SCOPE

Supply chain integrity involves minimizing risks that arise anywhere along the supply chain, from the sourcing of the pharmaceutical raw materials to the manufacture of the medicinal ingredients, and also to the finished dosage form (medicine) itself in its packaging and its distribution to a patient or consumer. The goal of good distribution practices is to encourage sound business practices that help deter interference and manipulation by bad actors and also to provide effective means to detect adulterated drug components and drug products to prevent them from entering the supply chain. The global supply chain for pharmaceuticals and medical devices is complex, with many components of a medicine now typically arriving at the point of manufacture from other countries.

In the United States, Congress addressed supply system integrity with passage of the Prescription Drug Marketing Act in 1988. That legislation responded to the challenge of drug diversion in the wholesale distribution system and introduced the first requirement for drug pedigrees to identify prior sales, purchases, or trades of drugs by anyone other than an authorized distributor of record. That paper pedigree system proved problematic, particularly because the potential profits for bad actors grew along with the rise of the modern pharmaceutical industry and with the emergence of more complex drug reimbursement schemes (e.g., Medicare and Medicaid). Congress responded with requirements aimed at

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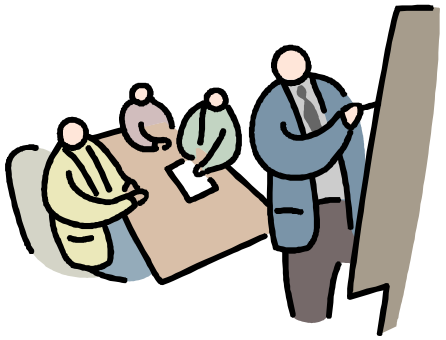
FOR CRITICAL SUPPLIERS ONLY

Prepare a Supplier for FDA

Focus on critical suppliers (CMOs, CROs) that might receive an FDA inspection

Cover 3 topics

1. Logic behind FDA supplier inspections
2. Overall inspection process
3. How to prepare and respond (including coordination with you)



Prepare a Supplier for FDA

“How to Prepare” points:

- responsibilities under the contract
- key documents to have on hand
- best practices for inspectional logistics
- best practices for behavior during the inspection (responding to questions, etc.)
- verify you will be involved in any formal response
- timelines for follow-ups with your organization (weekly meetings and teleconferences, etc.)
- consider conducting a “dry run” using an independent consultant as a mock auditor or trainer

EU Announced Visits

MDD Supplier Management

- The MDD has provisions for unannounced visits
- The plan is to implement the provisions and extend them to suppliers starting in April 2014
- Your Notified Body could make unannounced visits:
  - to your facility
  - to your supplier's facility

Medical Device Directive

- Annex II EC Declaration Of Conformity
- Quality System
- 3.3 The assessment procedure must include an assessment, on a representative basis, … and, in duly substantiated cases, on the premises of the manufacturer's suppliers and/or subcontractors to inspect the manufacturing processes.

Medical Device Directive

- Annex II EC Declaration Of Conformity
- Surveillance
- 5.4 In addition, the notified body may pay **unannounced visits to the manufacturer**. At the time of such visits, the notified body may, where necessary, carry out or ask for tests in order to check that the quality system is working properly. It must provide the manufacturer with an inspection report and, if a test has been carried out, with a test report.

Notified Body Visits

- EU Commission Recommendation on Audits
- 2(c) To verify the day-to-day compliance with legal obligations, notified bodies should, in addition to the initial, surveillance, or renewal audits, visit the manufacturer or, if this is likely to ensure more efficient control, one of its subcontractors in charge of processes which are essential for ensuring compliance with legal requirements (‘critical subcontractor’) or a supplier of crucial components or of the entire devices (both: ‘crucial supplier’) without prior notice (‘unannounced audits’) in accordance with Annex III.

Notified Body Visits

- EU Commission Recommendation on Audits
- Annex III Paragraph 2
- Notified bodies may, instead of or in addition to visiting the manufacturer, visit one of the premises of the manufacturer's critical subcontractors or crucial suppliers if this is likely to ensure more efficient control. This applies in particular if the main part of the design development, manufacturing, testing, or another crucial process is located with the subcontractor or supplier.

Terms

- *Critical subcontractor* means a subcontractor in charge of processes which are essential for ensuring compliance with legal requirements

- *Crucial supplier* is:
  - a) a supplier of crucial components OR
  - b) a supplier of the entire device

Notified Body Visits

- EU Commission Recommendation on Audits
- Annex III General Advice
- Unannounced audits in premises of the manufacturer or its critical subcontractors or crucial suppliers should be foreseen in the contractual arrangements between the notified bodies and the manufacturers. If a visa is needed to visit the country where the manufacturer is located, the contractual arrangements should contain, as an annex, an invitation to visit the manufacturer at any time and an invitation which leaves the date of signature and the date of visit open (to be filled-in by the notified body). The contractual arrangements should also contain, as an annex, similar invitations issued by the critical subcontractors or crucial suppliers.

Recommendation

- Learn your Notified Body's plan for unannounced visits
- Many of them will start implementation in 2014
- As part of your discussion, learn their plans for suppliers
  - Be prepared to identify your critical subcontractors and crucial suppliers
  - Inform your suppliers as appropriate

The Medical Device Regulation

Final Draft

- The EU intends to replace the product directive, MDD, AIMD, and IVDD, with two regulations, MDR, and IVDR.

- The timing is not clear, but publication in the Official Journal will probably be in May 2017.

- This starts a transition period:
  - Three years for the EU-MDR
  - Five years for the EU-IVDR

- The final draft of each regulation is available
  - The EU-MDR final draft is the basis for the subsequent information

Recitation

- The regulations start with a list of “Whereas” clauses, often called the recitations.

- (52) The position of notified bodies vis-à-vis manufacturers should be strengthened, including with regard to their right and duty to carry out unannounced on-site audits and to conduct physical or laboratory tests on devices to ensure continuous compliance by manufacturers after receipt of the original certification.

Economic Operators

- Article 2 Definitions
  - *Economic Operator* means a manufacturer, an authorized representative, an importer, a distributor, or the person referred to in Article 22(1) and 22(3);
  - Any firm that uses CE Mark products as part of a system or procedure pack [Article 22(1)]
  - Any firm that sterilizes a system or a procedure pack [Article 22(3)]
- Some of the EU-MDR requirements, not unannounced audits, may change if the economic operator is an SME, *i.e.,* micro, small and medium-sized enterprise

Market Surveillance

- The regulators (Notified Bodies, Competent Authorities, the Commission, *etc*.) conduct market surveillance

- The manufacturer (and other economic operators) conduct post-market surveillance

- Article 93 Market surveillance activities
- Section 3(b) says Competent Authorities "shall carry out both announced and, if necessary, unannounced inspections of the premises of economic operators, as well as suppliers and/or subcontractors, and, where necessary, at the facilities of professional users".

Notified Bodies

- Article 52 Conformity assessment procedures
- Section 14(b) says, “the minimum frequency of unannounced on-site audits and sample tests to be conducted by notified bodies in accordance with Section 3.4 of Annex IX, taking into account the risk-class and the type of device”

Notified Bodies

- Annex IX Conformity Assessment Based on a Quality Management System and on Assessment of Technical Documentation
- Section 3.4 says, “The notified body shall randomly perform at least once every five years unannounced audits on the site of the manufacturer and, where appropriate, of the manufacturer's suppliers and/or subcontractors, which may be combined with the periodic surveillance assessment referred to in Section 3.3. or be performed in addition to that surveillance assessment. The notified body shall establish a plan for such unannounced on-site audits but shall not disclose it to the manufacturer.”

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