Supply Chain Security and Good Distribution Practice:

Essential for Pharmaceutical Excipients

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In green the formal IPEC Europe Committees, note that the Certification Committee is no longer existing since the creation of EXCiPACT asbl

In purple, the ad hoc Committees. The Risk Assessment TF was created end of 2011 to establish guidelines. The International Aff TF was created in 2013 to work on IPEC Federation topics. The Event Committee is revamped every year with new members with the main goal to organise the annual seminar.
Content

• Definitions and the why of Supply Chain Management and GDP

• Supply chain incidents

• Processes and relevant aspect in the supply chain

• Frequently observed problems

• A practical approach to the guidelines

• Ongoing revision of current guidelines
Definition – Supply Chain Management

http://en.wikipedia.org/wiki/Supply_chain_management:

„Supply chain management is the management of the flow of goods. It includes the movement and storage of raw materials, work-in-process inventory, and finished goods from point of origin to point of consumption. Interconnected or interlinked networks, channels and node businesses are involved in the provision of products and services required by end customers in a supply chain.”
Why do we talk about supply chain of Pharmaceutical Starting Materials?

High quality of a medicinal product

Starting Material

• Stable quality
• No contamination
• Meets expectations
  • Traceability
  • Supply chain integrity
  • Liability and confidence
Current Situation

• Supply Chain Management and Good Distribution Practice principles are underlying
  • changes and
  • new developments
  since publishing the related guides

• Incidents of recent time create awareness for further improvement of actual guides
Critical Incidents

• 2006 in China and Panama
  • 10 death after injection of Armillarisin caused by a diethylene glycol contamination
    • source: “propylene glycol”
  • >200 death through diethylene glycol contamination in glycerol

• 2008 Heparin in China
  • > 60 patients killed in the USA
  • falsification: contaminant was over-sulfated chondroitin sulfate
  • complex supply chain of Heparin from many sources in China

• 2012 Sorbitol online sale
  • 1 patient killed in Italy
  • wrong label: sodium nitrite was sold under the name Sorbitol used as sugar substitute
Excipient Supply Chain to Panama:
46 barrels of glycerin

Producer: Hengxiang, China

Distributor 1: Beijing, China

Distributor 2: Barcelona, Spain

Distributor 3: Panama

User: Panama

What happened?

- No testing of product
- Re-labeling at any stage
- Producer hidden at any stage
- COA always copied on another letterhead
- Upgrading of technical grade glycerin to pharmaceutical grade

1) Walt Bogdanich and Jake Hooker, From China to Panama, a trail of poisoned medicine, International Herald Tribune May 5, 2007; http://www.iht.com
Why Supply chain security and Good Distribution Practice?

- Regulation
  - EU: 2011/62/EU and EU GMP Guidelines Part I (chapter 5)
  - US: FDASIA
  - China
  - WHO GTDP Guide

- General development in a globalised world
  - Quality defects harmed people
  - More players in the market, more complex supply chains
  - Majority of suppliers are not original manufacturers
  - More risks could be identified in starting materials supply chain

- Good Practices and shared responsibility through-out the entire supply chain
Steps and Processes in the Excipient Supply Chain

Raw materials Supplier → Transportation / Shipment → Manufacturer of Excipient → Transportation / Shipment → Distributor 0 …to… n → Transportation / Shipment → User Producer of Medicinal Products

- Raw materials Supplier
- Manufacturer of Excipient: Production (GMP), Warehousing / Storage, Packaging, Labelling, Testing, CoA
- Distributor: Warehousing / Storage, Re-Packaging, Re-Labelling, Re-Testing, CoA
- User Producer of Medicinal Products

DOCUMENTATION
Frequently observed problems

- Complexity of supply chain
- Who is the original manufacturer?
- Transparency of everybody involved in a supply chain
- Traceable, authentic and complete documentation
- Qualification and understanding of personnel at distributor
- Quality and robustness of quality systems
- Lack of standards in transport, storage and packaging activities

Measures to solve the problems:

- Apply Good Distribution Practices principles
  - WHO GTDP Guidelines
  - IPEC GDP Guide for Pharmaceutical Excipients (www.ipec-europe.org)
  - EXCiPACT GDP Certification (www.excipact.org)
„Trusted Supply Chain Partners“

• Requirements
  • Regulatory compliance
  • Voluntary application of standards
  • Transparency back to the original manufacturer
  • Quality of documentation
  • Qualified personnel
  • GMP/GDP compliant quality system

It is the responsibility of the manufacturing authorisation holder!

• How to find?
  → Auditing
  → GMP certificates of competent authorities
  → Third party certification
GDP relevant aspects in excipient supply chain

- (Cross-)Contamination prevention
- Traceability
- Analytical data
  - COA
- Documentation
- Stability / Integrity of quality
- Change Control
How does WHO GTDP / IPEC GDP Guide help to meet these needs?

Extract from IPEC GDP Guide – I. Introductory Note

• The **WHO GTDP** document provides the *general principles of good practices* in the pharmaceutical starting materials supply chain.

• This **IPEC (GDP)** document should provide the *practical approach* with examples that provide guidance on the application of WHO GTDP principles.
Content of these Guidelines

WHO GTDP for Pharmaceutical Starting Materials
IPEC GDP Guide for Pharmaceutical Excipients

• Quality management
• Organization and Personnel
• Premises
• Warehousing and Storage
• Equipment
• Documentation
• Repacking and Relabeling
• Complaints
• Recalls
• Returned goods
• Handling of non-conforming materials
• Dispatch and Transportation
• Contract activities
GDP relevant aspects in excipient supply chain

- Traceability
- Analytical data
  - COA
- Change Control
- Documentation
- Stability / Integrity of quality
- (Cross-)Contamination prevention
Traceability

- 1 Quality Management
- 6 Documentation
- 7 Repackaging and relabelling
- 13 Contract activities
1 Quality Management

1.4 All parties involved in the manufacture and supply chain must share responsibility for the quality and safety of the materials and products to ensure that they are fit for their intended use.

1.6 Where electronic commerce (e-commerce) is used defined procedures and adequate systems should be in place to ensure traceability (...).
6 Documentation

6.3 Original Certificates of Analysis (COAs) should accompany materials supplied by manufacturers to suppliers. (…) A distributor should not change the original title and data of the COA or other quality documents. Whenever possible, the original manufacturer’s documentation should be used, or transcription of data should be verified. (…)

6.5 The original manufacturer and intermediaries handling the material should always be traceable and the information available to authorities and end-users, downstream and upstream.

6.6 Mechanisms should exist to allow for transfer of information (…) between a manufacturer and a Customer (…).
7 Repackaging and relabelling

7.2 Special attention should be given to the following points (...)

- maintaining batch integrity (...)
  Where new batch numbers are assigned, traceability to original batch numbers should be ensured by proper documentation. (...)

- maintaining product identity and integrity.
  All repackaging and relabelling processes should be designed and carried out (...) to ensure full traceability of the excipients back to the original manufacturer and traceability downstream to the final customer. (...)

Traceability
7 Repackaging and relabelling

7.5 In all cases the original COA of the original manufacturer should be provided. If retesting is done, both the original and the new COA should be provided. The batch referred to on the new COA should be traceable to the original COA.

7.11 Procedures should be in place to ensure maintenance of the identity and quality of the material by appropriate means, both before and after repackaging operations.

These procedures should include documented traceability downstream and upstream.
13 Contract activities

13.3 All contract acceptors should comply with the requirements in these guidelines. Special consideration should be given (...) to maintaining traceability.
Contamination Prevention

• 2 Organization and Personnel

• 3 Premises

• 4 Warehousing and Storage

• 5 Equipment

• 7 Repackaging and relabelling

• 12 Dispatch and Transport
2 Organization and Personnel

2.6 Personnel who may be exposed to materials from open containers should maintain good hygiene, (...) be equipped with an appropriate protective outfit (...).

To protect excipients from contamination by personnel activities such as handling of unpacked excipient (...) personnel should:

• wear clean protective apparel (...)
• store and consume food, drink, (...) in certain designated areas;
• (...) personal hygiene training (...)

Contamination Prevention
3 Premises

3.1 (…) Their layout and design must (…) permit effective cleaning and maintenance in order to avoid cross-contamination, mix-ups, build-up of dust or dirt and, in general, any adverse effect on the quality of materials.

3.3 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, rodents or other animals.

3.5 There should normally be a separate sampling area (…) in a controlled environment. (…) Adequate cleaning procedures should be in place for the sampling areas.
4 Warehousing and Storage

4.3 Receipt and dispatch bays should be equipped with the means to protect materials from the weather. (...)

4.9 Special attention should be given to the design, use, cleaning and maintenance of all equipment for bulk handling and storage. (...)

4.10 Spillages should be cleaned as soon as possible. (...)

4.13 Storage areas should be clean and free from accumulated waste and from vermin. (...)

5 Equipment

5.2 The layout, design and use of equipment must (...) permit effective cleaning and maintenance to avoid cross-contamination, build-up of dust or dirt and any adverse effect on the quality of materials.

5.7 Washing and cleaning equipment should be chosen and used such that it cannot be a source of contamination.

5.8 Dedicated equipment should be used where possible when handling (...) materials. Where non-dedicated equipment is used cleaning validation should be performed. (...) Multi-purpose equipment should only be used again after verification of the cleaning efficiency. Cleaning efficiency should be verified by e.g.:

• testing the final rinse after cleaning for residues of the previous product or,
• (...) in order to avoid contamination and carry-over of previously processed products.
7 Repackaging and relabelling

7.2 Special attention should be given to the following points:

- prevention of contamination (…) and mix-ups; (…)
- good sanitation and hygiene practices; (…)

Contamination (…) should be avoided by using suitable equipment and cleaning procedures. (…)
Environmental conditions and repackaging procedures should be designed to avoid contamination (…) during repackaging (…) operations. Filtered air in the repackaging area should considered where necessary (…). Protective clothing for the operators should be clearly defined.
7 Repackaging and relabelling

7.7 The re-use of containers should be discouraged unless they have been cleaned using a validated procedure. (…)

Returned containers may have unknown residues from other than the intended use. Therefore, use of new containers is recommended for excipients. However, if containers are reused, a procedure should demonstrate a rationale for cleaning procedures for specific excipients and their different types of container. (…)

7.8 Materials should be repackaged only if efficient environmental control exists to ensure that there is no possibility of contamination, cross-contamination, degradation, physicochemical changes and/or mix-ups. (…)
12 Dispatch and Transport

12.1 (...) The transport process should not adversely affect the materials. Transport conditions and the equipment to be used should be defined according to the characteristics of the products. (…)

12.4 Procedures should be in place to ensure proper cleaning and prevention of cross-contamination when (...) bulk or packed materials are transported. Best practice for bulk transport is to use dedicated equipment and defined handling processes. If this is not possible, the type of transport equipment and suitable supplies (...) should be specified. (...) Cleaning procedures with documented evidence of their efficiency should be used between loadings of different materials. (…)
Ongoing Revisions of current Guidelines

- IPEC Good Distribution Guide 2006
- General Chapter USP <1083> Good Distribution Practices (newly created)
<table>
<thead>
<tr>
<th></th>
<th>What to change / add …</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>@1</td>
<td>Include <strong>Risk Management</strong></td>
<td>Currently missing and became standard in several industries</td>
</tr>
<tr>
<td>@1</td>
<td>Include <strong>Supplier Management</strong></td>
<td>Need to be more detailed than currently mentioned, to ensure authenticity and traceability of supply chain</td>
</tr>
<tr>
<td>@1</td>
<td>Add <strong>independency of quality unit</strong></td>
<td>Part of all GxP principles</td>
</tr>
<tr>
<td>@1, 8, 11</td>
<td><strong>Preventive actions</strong>, including verification of effectiveness</td>
<td>CAPA state of the art and essential quality system element</td>
</tr>
</tbody>
</table>
Thank you for your attention

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