EU Good Distribution Practices

Presented By: Santosh Savarkar
Alembic Pharmaceuticals Ltd
Disclaimer

The views and opinions expressed in the workshop are those of the individual presenter / participants and should not be attributed to organisers or an organization with which the presenter is employed.

- This presentation is **NOT intended to outline regulatory** expectations...
Agenda

- Definition
- Background
- Why GDP is such important?
- Overview of GDP Guidance and Dir. 2011/62/EU...
- Key new areas covered by the GDP Guide
- Typical queries raised by EU agencies.
Pharmaceutical distribution is the process starting from
The procurement,
purchase...
holding...
storing...
selling...
supplying...
importing / exporting or
movement of pharmaceutical products, with the exception of the dispensing or providing pharmaceutical products directly to a patient...
Definition

- Good Distribution Practices, 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.
Background

- EU Commission have revised the Guideline on Good Distribution Practices.
- The new GDP was published in November 2013.
- GDP guidance was in place from 1994.
- Amendment of GDP was essential inline with amendment of EC Dir. 2001/83/EC, since there was an alarming level of falsified medicinal products entering in EU for past few years.
- The EC Directorate for public health and risk assessment issued Dir. 2011/62/EU dated 8th June, 2011; amending Dir. 2001/83/EC

Revised guideline published in March 2013 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 revised Dir.2011/62/EU.

Factual mistakes identified in subchapters 5.5 – storage of medicinal products and 6.3 – handling recalls have been corrected and new version issued in Nov 2013 replaces guidance issued in March 2013.
Why GDP is Such an Important?
1990s, when India opens its economy, many EU players started looking for tapping Indian pharmaceutical manufacturers’ potential & initiated...

- Outsource of non-core activities
- Manufacture, analytics, distribution, storage etc...
- Markets have globalised and new territories opened up or added in EU...
Supply chain...

Sourcing of RMs – Global or Local

APIs – Domestic or preferably In-House

Manufacturing – Outsourcing in India or China

Logistics arrangement to EU destination

EU Warehousing – QC Testing and QP Release by MAH
Issues...!!!

- Heparin, supplied by Baxter, found to be adulterated, with reports of 574 adverse events and nine patient deaths estimated...
- J&J/McNeil placed under a ‘Consent Decree’ after recalls associated with supply chain issues.
- Shortages in US/EU supply chains result in governments and general public questions...!!
Issues...!!!

- Abbott suffered by $4m diagnostics theft in USA (June 2011)
- Eli Lilly warehouse thieves make off with $76m haul (March 2011)
- Operation Singapore, 2 million doses of counterfeit medicine enter UK supply chain in 2006/7
- FDA is still concerned that the drug supply is increasingly vulnerable to diversion of legitimate drugs (ie stolen or sold illegally)

Rx-360 Newsletter September 28 2011
What are principles of wholesaling in the EU?

DIRECTIVE 2001/83/EC Art. 76 -85

The aim of this Directive is to control the falsified medicines through various measures at different stages:

**Addition of safety features** for Prescription Medicines and for Non-prescription products at risk of falsification.

**Supply Chain & Good Distribution Practices** for wholesale distribution of medicinal products in the Union extending Regulation to **brokers**.

Also includes import from 3rd country for re-export of medicinal products to 3rd country (products ‘introduced’ in EU)
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.

- **Art.76 - Distribution of medicinal products only with Marketing Authorization (MA)**
- **Art.77 - Need of an Wholesale Authorization issued by competent authority (CA)**
- **Art.78 - Timeline for decision of CA to grant the authorization : 90 days**
Art.79 - Minimum Requirements for obtaining the authorization:

- Suitable premises,
- Systems/ procedures and installations, equipments
- Trained, competent Staff
- Responsible Person
- Fulfilling obligations as defined in Art. 80
DIRECTIVE 2001/83/EC with amendment Dir. 2011/62/EC

- Art. 80 - Minimum requirements (running the business)
  Suitable premises, installations and equipment accessible to the persons responsible for inspecting them...
- Supply chain only from and to the partners with wholesale authorization
- Emergency plan for recall – Mock recall for verification
- Records of purchase/sales or any other transaction, achieved for at least 5 years (blood, blood products: 30 years)

- **Compliance with the principles of GDP**
DIRECTIVE 2001/83/EC with amendment Dir. 2011/62/EC

- Art. 81 - Mutual acceptance of Wholesale authorizations within the member states of the EU. Any obligations imposed on wholesaler of another EU country exceeding the national requirements forbidden
- Art 82 Minimum requirements of information on the delivery slip to persons entitled to supply the public (i.e. pharmacies)
- Art 83 Special National requirements concerning Narcotic/psychotropic substances within their territory, Medicinal products derived from blood, Immunological medicinal products, Radiopharmaceuticals

- **Art 84 Commission shall publish the GDP Guidance**
- Art 85 Applicable to homeopathic medicinal products
Is this G.... DP or B.... DP?
Let’s see requirements of EU GDP guidance ....
EU Good Distribution Practices...

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 1</td>
<td>QUALITY MANAGEMENT</td>
</tr>
<tr>
<td>Chapter 2</td>
<td>PERSONNEL</td>
</tr>
<tr>
<td>Chapter 3</td>
<td>PREMISES AND EQUIPMENT</td>
</tr>
<tr>
<td>Chapter 4</td>
<td>DOCUMENTATION</td>
</tr>
<tr>
<td>Chapter 5</td>
<td>OPERATIONS</td>
</tr>
<tr>
<td>Chapter 6</td>
<td>COMPLAINTS, RETURNS, SUSPECTED FALSIFIED MEDICINAL PRODUCTS AND MEDICINAL PRODUCT RECALLS</td>
</tr>
<tr>
<td>Chapter 7</td>
<td>OUTSOURCED ACTIVITIES</td>
</tr>
<tr>
<td>Chapter 8</td>
<td>SELF-INSPECTIONS</td>
</tr>
<tr>
<td>Chapter 9</td>
<td>TRANSPORTATION</td>
</tr>
<tr>
<td>Chapter 10</td>
<td>SPECIFIC PROVISIONS FOR BROKERS</td>
</tr>
</tbody>
</table>
Chapter 1 Quality Management
Management Review and Monitoring...
“The management should have a formal process for reviewing the quality system on a periodic basis. The review should include:
→ Evaluation and assurance of quality system objectives;
→ Assessment of quality 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 & audits;
Chapter 1 Quality Management

Management Review and Monitoring...

→ External assessments such as inspections, findings and customer audits;
→ Emerging regulations, guidance and quality issues that can impact the quality management system
→ Innovations that might enhance the quality system;
→ Changes in business environment and objectives.”
→ The outcome of each management review of the quality system should be documented in a timely manner & effectively communicated internally.
Chapter 2 Personnel

“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 responsibility should be clearly understood by the staff and be recorded.”

Clarifies role of Responsible Person, approved organogram, laid down job descriptions and expectations on staff training and hygiene.

New...

- The Responsible Person should fulfil his responsibilities personally and should be accountable. The responsible person may delegate duties but not responsibilities.
- Training and retraining of staff as per schedule...
- Personnel hygiene.
Chapter 3 - Premises & Equipment

“Wholesale distributors must have suitable and adequate premises, installations and equipment, so as to ensure proper storage and distribution of medicinal products. In particular, they should be Clean, Dry & Maintained within specified Temperature conditions and limits.”

Expectation on details of Premises, Temperature mapping, Electronic system to segregate stock & qualification & validation of equipment.

Key new areas:
• Records to be kept of repair, maintenance & calibration of key equipment.
• Validation of Computer Systems.
• Qualification and Validation of key equipment.
Chapter 3 Premises and Equipment

Computerised Systems

Appropriate validation or verification studies, that the system is capable of achieving the

• A written detailed description of the system should be available.
• The document should describe the principles, objectives, security measures & the way it interacts with other systems.
• Authorized to do so accidental or un-authorised modifications.
• Stored data should be checked periodically back up data should be retained for the period stated in national legislation but
• Procedures to be followed if the system fails or breaks down should be
Chapter 3 Premises and Equipment

Computerized Systems

To use the Computerized system, it has to be demonstrated that it provides solution consistently & with required reproducibility. (including diagrams where appropriate). Its functionality, security and risk assessment should be done as per EU GMP annex 11 requirements.

Any manual intervention for the computerized system would lead to the appropriate investigation, technical justification and assessment of risk associated with the deviation...
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.
“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”

Key new areas:
- The documentation should be in language understood by the users and operators
- Version control for procedures and emphasis on ensuring documentation is up to date
“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.”
Chapter 5 Operations

This requirement is laying down significant delaying of service providers / suppliers / warehouse etc...

Main areas covered but not limited to...
• Verifying the supplier that it is GDP compliant...
• Due diligence checks on the supplier
• stock statements reviews to identify any misuse or diversion of medicines
• Requirement for a control report when sourcing goods from EEA States
• Requirement for First Expiry First out – FEFO , rather than FIFO
• Stock inventories should be performed regularly
• Exporting medicines out of the EEA requires a wholesale authorisation and GDP has to be applied
Chapter 6 Complaints, Returns, suspected falsified Medicinal Products and Medicinal Product Recalls

“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 competent authorities. An assessment of returned medicinal product should be performed before any approval for resale. A consistent approach amongst all partners within the supply chain is required in order to be successful in the fight against falsified medicinal products.”

No significant changes to current requirements.

The new guide suggests 10 days may be an acceptable time limit to return medicines that have been outside the Licensed chain.

*Stolen medicines that are recovered cannot be returned to saleable stock.*
Chapter 7 Outsourced activities

“Any activity covered by the GDP Guide that is outsourced should be correctly Defined, Agreed & 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.”

Requirements for contracts between parties where GDP has been outsourced are set very clear. Outsourced activities should be audited as a part of management review. Audits by independent external experts may be useful but should not be substituted for self-inspection!!
Chapter 8 Self-Inspections

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

Expectations:

- Self inspections can be carried out by staff other than RP. An independent external audit is recommended.
- The reports should be subject to CAPA principles.
Chapter 9 Transportation

“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.”
Chapter 9 Transportation

A significant expansion on the requirements to control distribution channel. It is expected that products should be shipped according to the labelled conditions and that excursions are reported. There are detailed requirements for shipping temperature sensitive items. Contracted transporters should be informed of storage conditions.

Key new areas:

• Medicines to be shipped within label conditions
Chapter 9 Transportation

• Temperature excursions should be reported and investigated
• Risk assessments of delivery routes to identify when temperature control is needed.
• Dedicated vehicles to be used where possible.
  Procedures to cover use of non dedicated vehicles.
• A contract to be in place with transporters as required by Chapter 7.
Chapter 9 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.

- 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.
Chapter 9 Transportation

- 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.

- Where transportation is performed by a third party, the contract in place should encompass the requirements of Chapter 7. Transporters 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.
Chapter 9 Transportation

- Provision should be made to minimise the duration of temporary storage while awaiting the next stage of the transportation route.”

“Containers should bear labels providing sufficient information on handling and storage requirements & 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.”
Chapter 10 Specific Provisions for Brokers

“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. Brokers are subject to a registration requirement. They must have a permanent address and contact details in the Member State where they are registered. They shall notify the competent authority of any changes thereof without unnecessary delay.

By definition, brokers do not procure, supply or hold medicines. Therefore, requirements for premises, installations and equipment as set out in Directive 2001/83/EC do not apply. However, all other rules in Directive 2001/83/EC that apply to wholesale distributors also apply to brokers.”

Sets out the requirements for records and procedures required for brokers. This is a new area not previously required.
A. Cold storage qualification was found lacking in that the following was not defined:
   • The position of the monitoring devices (OQ & PQ).
   • The associated cold spot and location of routine monitoring probe (OQ & PQ)
   • The rationale for the duration of mapping (OQ & PQ)
   • The alarm set points (IQ/OQ)
   • The simulated loaded of the chamber during (PQ)
B. Supplier (Brokers) management was not defined in the procedure.
C. Handling of Product Recall, fails to consider mock recall to verify the suitability of procedure.
D. Handling of Product Recall, fails to consider that a Deviation could result in the initiation of a Recall
E. SOP for technical agreements fails in addressing requirement to have TA with suppliers and brokers and service providers involved in logistics
Acknowledgement

- Presentations by
  - Tony Orme, Senior GDP Inspector, UK
  - Dr. Martin Melzer - Pharmacist / GMP Inspector, Germany
  - By Director of Pharmacy Affairs, U.S. FDA
  - S.M. Mudda, Micro Labs Limited, Bangalore
  - EU GDP Guideline dated 5 November 2013
  - Hedley Rees, Biotech PharmaFlow, UK
Thank You