Wholesaling & Distribution & the GMPs

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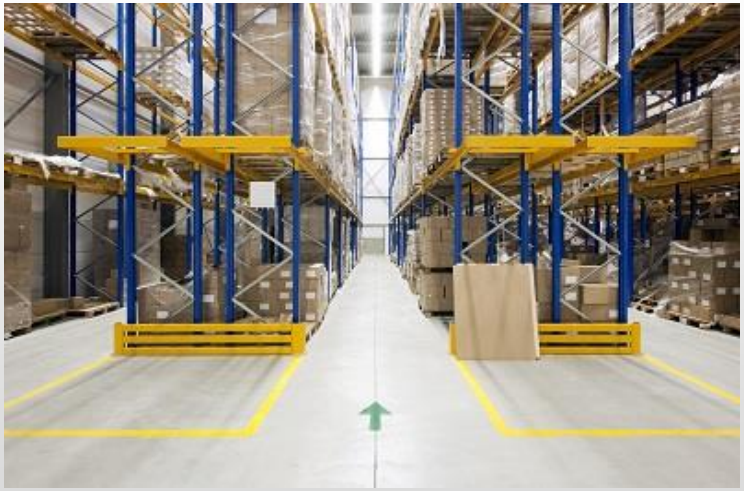
Overview

- Wholesaling & distribution of Medicines (FPs) in the EU
- New EU GDP Guidelines – Expectations
- How complicated can the supply chain be?
- GDP Inspection findings in EU
- Differences in GDP expectations - other GDP guidelines
- Falsified Medicines Directive - important Changes in EU
- Distribution of APIs & Excipients in EU



Wholesale & Distribution in EU

- Wholesalers in EU – UK & Ireland vs rest of EU
- Licensing situation – standardized Authorizations across EU for GDP
- Inspections and Inspectorates (MS)
- Certificates of Compliance – the EUDRA data base
- Inspectors & Training
- Wholesale sites (different types) and Personnel
- What is an RP and what are the expectations

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A "new" EU GDP Guideline

- New EU GDP in guide (2013/C 68/01)- for human medicines:
  - Legal basis; Articles 84 & 85 of Directive 2001/83/EC
  - Article 1(17) if distributing medicines must hold a WDA

- Wholesale distributors must maintain a quality management system which:
  - Sets out responsibilities and processes and
    Risk Management principles in relation to activities
  - Activities must be clearly defined and systematically reviewed
  - Critical steps in processes justified and where relevant *validated*

As well as including organizational structure, procedures, processes and resources the Quality System must ensure confidence that the delivered product maintains its **quality and integrity** and remains within the **legal supply chain** during storage and/or transportation.

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EU GDP Guidelines & QMS Expectations

Some significant changes to expectations quality and integrity of product:

- Management review – system of objectives and performance monitored by 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 inspection findings and customer audits
- A change control system should be in place – system incorporates QRM principles. QRM to be applied to e.g. transport, to returns, to equipment/qualification and validation
- Key systems and processes to be identified and subject to verification and/or validation e.g. systems such as: computers, storage, picking and packing processes, recalls, complaints, transport & qualification of customers – reports to be documented and to be available for inspection
- Contract arrangements fully specified & documented

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The EU GDP Guidelines - Definitions

Legal basis is Directive 2001/83/EC - some issues for the legal supply chain

- Definition of wholesaling and what this means in practice:
  - Wholesaling of medicinal products in EU is all activities consisting of:
    - Procurement - buying
    - Holding - storage
    - Supply - selling
    - Export – outside EEA
  - Definition of what a broker is and the requirements for brokers:
    - Sale or purchase activities without actually handling the medicines

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How complicated can the supply chain be?

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EU GDP – Clarification

Wholesalers

Maintain a Quality System detailing responsibilities and QRM measures
Report immediately actual or suspected falsified products
Have systems to verify suppliers have appropriate authorization or registration

Brokers

Maintain a Quality System & comply with GDP (and accept inspection)
Trade only those products subject to an EU marketing authorization
Register with NCA of MS where established

Member States

Issue certificates of compliance or non compliance as appropriate
Record wholesaler distribution authorization in a community data base
Establish and publish a register of persons brokering medicinal products

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GDP Inspection findings

- Categorization of deficiencies – compilation of community procedures
- Number of inspections & number of findings in each category
- How findings are utilized
    - Publication of deficiencies (related to GDP guide)
    - GDP Symposium & Consultative Committee
    - Publication of guidelines and blogs
- Critical and significant deficiencies
- Impact of significant findings – what it means:
    - To the WDA(H)
    - To the Responsible person
- Common deficiencies (basic GDP, expanded guideline & new models)

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Inspection findings and Eudra GMDP data base

Common deficiencies

- Quality System (aspects of risk management, change control & deviation management)
- Storage Temperatures
- Transport conditions
- Qualification checks
- Customer returns

Of more significance

- Failure by RP in his/her duties

Ref. Philip Neale GDP Operations Manager
Common Deficiencies since 2013/C 343/01
MHRA GDP Symposium 2014

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Other GDP Guidelines

PIC/S guide chapters aligned with EU GDP i.e.

- Chapter 1 Quality Management
- Chapter 2 Personnel
- Chapter 3 Premises and Equipment
- Chapter 4 Documentation
- Chapter 5 Operations
- Chapter 6 Complaints, Returns, Suspected Falsified Medicinal Products and Product Recalls
- Chapter 7 Outsourced Activities
- Chapter 8 Self-Inspections
- Chapter 9 Transportation

Similarities – QRM fully integrated & key tool in implementing requirements

Differences – No responsible person & no mention of brokers

http://www.good-distribution-practice-group.org/gdp_news_04435_PIC-S-adopts-EU-GDP-Guidelines.html

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GDP Guidelines & Australia

Differences EU and PIC/S vs Australia:

- A QMS with integrated QRM
- Self-inspection audits expected
- Increased level of control & documentation around processes e.g. computers, maintenance of equipment, calibration segregation and quarantine
- Increased validation/verification and calibration expectations
- Outsourced activities and processes to be checked for compliance
- Written contracts for contract storage sites
- All suppliers and customers must be verified as part of legitimate supply chain
- Transportation to be verified e.g. in relation to temperature sensitive medicines

Ref Kathy Walsh PharmOut June 2014

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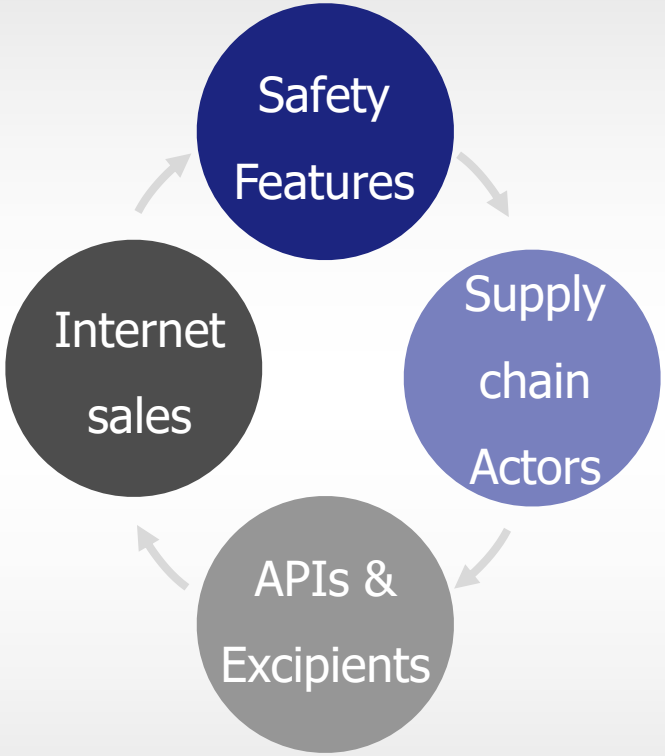
Falsified Medicines Directive (2011/62/EU)

Secure integrity & authenticity (unique identifier). Obligation to report suspected falsified material



Extends Wholesale authorization to export to third countries & concept of Brokering

Introduction of a common internet logo

GMP Expectations around APIs and Excipients

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Falsified Medicines Directive
Some important aspects

- Details GMP expectations for manufacturers (verification of integrity & authenticity of APIs and excipients)
- Introduces the concept of brokering and registration in EEA
- Introduces GDP Certificates of Compliance – EUDRA GMDP
- Requires enhanced qualification checks of suppliers and customers
- Batch numbers to be recorded for product bearing safety features
- Obligations on licence holders to *report* any suspected falsified medicines
- Introduces additional safety features to seals and pack identification (verification of authenticity) – from 2019!

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GDP Guide for Active Substances & New rules for Import of APIs

EU GDP guide for APIs is a document based on Part 11 of EU GMP guide and the (earlier) EU Guide to GDP

- Covers guidelines for all activities of procuring, importing, holding, supply or exporting active substances
- This applies to distributors both within the EEA (exporting to Third Countries) and to those outside EEA (exporting to EEA)

New rules for Import of APIs (see also Chapter 5 EU GMP Guide)

- List of third country authorities – assessment to ensure "equivalence"
- Non Listed country – written statement from exporting authority

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Excipients – Risk Assessment Guidelines for Excipient GMP

It is the MAHs responsibility to ensure all excipients used are suitable. They must:

- Determine and evaluate what the appropriate GMP is
- Determination should be by the use of a formalized risk assessment process as laid out in the EC guidelines
- This formalized risk assessment process should take into account the requirements under other appropriate quality systems as well as the source and intended use of the excipient and any previous quality defects

MIA Holders must ensure that appropriate standards of GMP are actually applied and document the measures taken

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APIs & Excipients – what it means in practice

- Manufactures, Importers and distributors of APIs in an EU MS to register activity with NCA (update details annually)
- Manufactures of APIs to comply with EU GMP for actives and distributors to comply with EU GDP for actives
- Only actives that have been manufactured in accordance with standards of GMP at least equivalent to those in EU to be imported and used
- Manufacturer of Finished Product to verify compliance with GMP & GDP by audit of manufacturer, importer and/or distributor sites
- Manufacturers to ensure excipients are suitable for use in medicinal products by determination of what the appropriate GMP is, that this is applied and all actions documented

Above to be checked during inspection

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Conclusion

- There are some significant changes to EU GDP guidelines
- These changes are reflected in inspection findings
- The supply chain can be complex
- Increased regulation has and is being introduced to ensure effective control of the supply chain
- The regulations themselves can be complex

Useful links

EU GDP Guide
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:068:0001:0014:EN:PDF

EMA (EU GMP Guide)*
http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Eudra GMDP
http://eudragmdp.ema.europa.eu/inspections/displayHome.do

MHRA Blog
http://mhrainspectorate.blog.gov.uk/category/good-distribution-practice/

***See EU GMP Guide Part III for**

- Q9 Quality Risk Management
- Template for the 'written confirmation' for active substances exported to the European Union for medicinal products for human use (Version 2, January 2013)
- Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use

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Glossary

QRM – Quality Risk Management
EEA –European Economic Area
MS – Member States
HMR – Human Medicines Regulation
SI – Statutory Instrument
FMD –Falsified Medicines Directive
WDA(H) – Wholesale Distribution Authorisation
MAH – Marketing Authorisation Holders
MIA - Marketing Import Authorisation
FP – Finished Product
RP – Responsible Person

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Thank you for your time. Questions?

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