Falsified Medicines Directive
Presentation Outline

• Changes in pharmaceutical supply chains and the challenges these present
• Overview of counterfeit incidents in the UK and worldwide
• Key elements of the Falsified Medicines Directive and its implementation
• Overview of the key changes to the EU Guide to GDP
Supply Chains – 20th Century

Manufacturer → Pharmacy

Wholesale Dealer
Falsified Medical Products Situation - UK

Wholesale - Anti-cholesterol, Anti-inflammatory, Anti-platelet, Alopecia, Erectile Dysfunction, Rheumatoid Arthritis, HIV.

Pharmacy - Anti-cholesterol, Anti-platelet, Anti-psychotic, Erectile dysfunction, Prostate cancer, Appetite suppressants, Chronic asthma.

Clinical Trial - Anti-platelet
Operation Singapore

Most serious known case of Counterfeit Medicines penetrating the European Supply Chain

- 72,000 packs, 2.1 million doses, retail value £4.7m
- 3 medicines, 7 separate batches
- 4 Class 1 recalls
- MHRA seized 40,000 packs before reaching pharmacies
- Further 7000 packs recovered following recalls
- 25,000 packs (700,000 doses) reached pharmacies and patients
- Products contained between 50% - 80% of API together with unknown impurities
- No known fatalities or adverse reactions.
- Counterfeits indistinguishable from genuine through visual identification alone
Operation Singapore
Counterfeit Medicines
Operation Singapore - Flow of counterfeits
Operation Singapore - Flow of money

UK

Luxembourg

Mauritius

China
Supply Chain Risks - Counterfeits
Analysis of UK Incidents

- Usually manufactured in the Far East
- Complex global supply and money laundering routes
- Shipped to an EU port where Customs clearance is obtained
- UK Freight carriers collect product and deliver to customer in the UK
- Transactions often negotiated by unlicensed brokers or traders operating outside the UK
- A holder of a wholesale dealer licence facilitates introduction into the legitimate supply chain
- Insufficient ‘due diligence’ conducted by purchaser.
Falsified Medicines Directive

- Safety features
- Internet sales
- Active Substances
- Excipients

Actors in the supply chain

Directive 2011/62/EU on falsified medicinal products

MHRA
Regulating Medicines and Medical Devices
Falsified Medicinal Product - Definition

Any medicinal product with a false representation of:

a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients; or

b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or

c) its history, including the records and documents relating to the distribution channels used.
• The ‘safety features' will enable wholesale distributors and pharmacists:
  – to verify the authenticity of the medicinal product,
  – to identify individual packs,
  – to verify, by means of a device, whether the outer packaging has been tampered with.

• compulsory for prescription-only medicines and for some non-prescription medicines

• The characteristics and technical specifications of the 'safety features', will be laid down in implementing measures expected 2014.

• Member States will have three further years after adoption to put requirements in place ~ 2017.
• Wholesale distributors:
  – already regulated under EU rules
  – will be listed in an EU database
  – subject to Good Distribution Practices (GDP) for all activities performed on the EU territory
  – required to verify that they are dealing with authorised suppliers by checking for MIA, WDA, Registrations
  – required to report any suspicion of falsification.

• Brokers:
  – i.e. persons who are trading in medicines without physically handling them
  – not previously regulated under EU rules
  – require permanant address in EU and must register
  – have obligations similar to those of wholesale distributors.
• Requirements apply to active substances manufactured, imported or distributed in the EU (including those intended for export).

• Must comply with GMP and GDP for Active Substances (AS)

• Mandatory audits performed by manufacturing authorisation holder or third party contractor.

• All EU active substance manufacturers, importers, distributors must be register with the competent authority where they are established

• If imported the rules on Active Substance importation must be complied with

• European Commission publishing GDP for Active Substances.
New rules on Active Substance import after 2nd July 2013

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<tr>
<th>Baseline Situation</th>
<th>Waiver 1</th>
<th>Waiver 2 “exceptional circumstances”</th>
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<td>• API exporting country has no proven equivalence to EU GMP system</td>
<td>• API exporting country is on EC list of GMP equivalent countries</td>
<td>• Medicines availability issue in the EU, <strong>AND</strong>&lt;br&gt;• Existing EU GMP certificate (&lt;3 years), <strong>AND</strong>&lt;br&gt;• EC informed</td>
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<td><strong>regardless of available EU-GMP or local GMP certificate</strong></td>
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<td><strong>Written confirmation of compliance by exporting 3rd country</strong></td>
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• Manufacturing Authorisation holders to ascertain the appropriate good manufacturing practice for the excipients they use through a formalised risk assessment

• Risk Assessment Guidelines for Excipient GMP to be published by the European Commission
• May only be undertaken by persons entitled to supply medicines to the public, who are registered and have a permanent address

• The website must include details of the supplier, link to a national website, and common European logo on each page.

• Member States may restrict internet sales under national legislation

• The medicinal products supplied have to be authorised in the Member State of destination

• Each Member State must have its own national website listing those entitled to supply via internet & other relevant information

• EMA must also have a website, with links to national websites

• The new requirements - to be registered and display a common internet logo, will come into force one year after the common logo has been agreed.
Applicability to Clinical Trials Supply

• Will not impact on the manufacture of Investigational Medicinal Products
  – unless such products are already the subject of a valid Marketing Authorisation.

• Audit of the supply chain for Active Substances and excipients
  – good practice but is not a regulatory requirement

• Sourcing, storage and supply of comparator products
  – FMD and GDP apply up to the point they are supplied for use in a clinical trial.
Manufacturers Specials Licence Holders

- FMD requirements do not extend to the manufacture of unlicensed specials i.e. no requirement:
  - for the API to be manufactured or distributed in accordance with GMP or GDP for active substances,
  - to audit the active substance suppliers, or
  - check that they are registered.

- However manufacturers, importers and distributors of active substances must register irrespective of what the active substance is to be use for.

- **BUT** where holders of a Manufacturers Special Licence are importing active substance solely for their own use in the manufacture of unlicensed medicinal products **they do not need to register as an active substance importer.**
• Reflects more complex supply chains of the 21st Century.

• Came into force on 8th September 2013
Chapter 1 – Quality Management

• Increased emphasis on the quality systems
• Quality Risk Management
• Change control
• CAPA
• Management Review and Monitoring.

Chapter 2 – Personnel

• Role of the Responsible Person
• Organisational charts & job descriptions
• Staff training

Chapter 3 – Premises and Equipment

• Premises requirements
• Temperature mapping
• Systems for electronic stock segregation
• Qualification and validation of equipment.
Chapter 4 – Documentation

- All written procedures, instructions, contracts, records and data, in paper or in electronic form.
- Document management and control.

Chapter 5 – Operations

- Checking bona fides of suppliers and customers
- Introduction of due diligence
- Export now covered by GDP.

Chapter 6 – Complaints, Returns, Suspected Falsified Medicinal Products and Medicinal Product Recalls

- No significant changes to current requirements.
Chapter 7 – Outsourced Activities

• Contracts between parties where GDP has been outsourced
• Audits to be undertaken
• Contracted out activities covered by the quality system and subject to regular review.

Chapter 8 – Self Inspection

• Conduct and recording
• Audit reports to be made available to management and other relevant personnel.
Chapter 9 – Transportation

• Products should be shipped according to the labelled conditions
• Excursions to be reported.
• Risk assessment of delivery routes
• Qualification of packaging and validation of shipping containers.

Chapter 10 – Specific Provisions for Brokers

• Sets out the requirements for the quality system, personnel and documentation.
Falsified Medical Products
What to look out for

- Subtle differences in printed colours and lettering
- Smudges or small spattering of ink
- Different look feel or even smell to the packaging
- Packaging which is not as neatly folded as normal
- Does the packaging differ from its normal shiny or matt finish?
- Heavier or lighter embossing of batch numbers
- Different formats in batch numbers or codes
- Differences in size, type or placement of security seals
- General quality of the packaging materials used

- Don’t let appearances deceive you, sometimes the falsified product may be the one with higher quality packaging!
Summary

- Falsified medicinal products are a global concern.

- Within Europe the Falsified Medicines Directive aims to strengthen the current EU legislation to better protect the public from the threats posed by fake medicines.

- Implementation of the FMD impacts on all actors in the pharmaceutical supply chain and introduces many new requirements.

- The FMD doesn’t directly impact on Specials manufacturers or the manufacture of Investigational Medicinal Products
  - But the storage and supply of medicinal products is subject to the new GDP guidelines and the FMD and vigilance is required at all stages within the supply chain.
Thank You
Useful References

• MHRA Falsified Medicines Directive Webpage

• MHRA Case Referrals Centre
  – casereferrals@mhra.gsi.gov.uk
  – tel +44 (0)20 3080 6330
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