Practical implementation of the Falsified Medicines Directive

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Content

- Development of the Directive
- Overview of main changes
- Ongoing works at EU level
- Challenges for stakeholders and NCAs

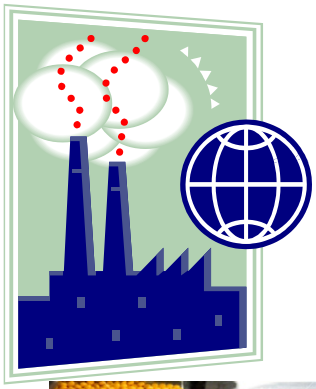
Development of the Directive

- **2007**: falsified medicinal products in the legal chain in some Member States
- **2008**: heparin adulteration
- **2008**: public consultation in preparation of a legal proposal to combat counterfeit medicines for human use
- **2009-2010***:* discussions on the proposal from the European Commission, at the Council WP of Pharmaceuticals and Medical Devices
- **2011**: the Directive is published on the Official Journal the 1st of July
- **2013***:* entry into force of most of the new provisions

MP manufacture

MP distribution

Supply to the public



AS manufacture

AS distribution

MP manufacture

ACTIVE SUBSTANCES (AS) SUPPLY CHAIN

Overview of the main changes

- **Active substances and excipients**
- **Distribution** of medicinal products
- **Safety features**
- **Internet**

Definition of falsified medicinal product

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;*

*(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.*

*This definition does not include **unintentional quality defects** and is without prejudice to **infringements of intellectual property rights**.*

Active substances (AS) and excipients

- Definitions
- **MMSS to ensure compliance with GMP& GDP** of the manufacture, import and distribution of AS in its territory
- New GDP for AS
- **National registry** of manufacturers, importers, and distributors
- **Exchange of information** and EU databases
- **Importation of AS from third countries**
- MAH evaluation of appropriate **GMP for excipients**

Distribution of medicinal products

- **Extension of the controls to all agents** in the supply chain (brokers, wholesalers in free-trade zones…)
- **New requirements** for wholesalers

  Quality system
  Suppliers verification
  Notification of any suspicion of medicinal products falsification
  Safety features verification
  Export requirements

- **Exchange of information** and EU databases
- **New GDP guidelines**

Brokers

- **Brokering of medicinal products:**
  - Physical handling excluded
  - Independent negotiation on behalf of a third party
- **Requirements:**
  - Only authorised medicinal products
  - Contact address in the EU
  - Record keeping of the transactions
  - Emergency plan for recalls & quality system
  - Notification to NCA of suspicions of falsified medicinal products
  - Registration at the NCA (public registry)
- **Subject to inspections**

Safety features (I)

- **With the purpose of :**
  - Verify authenticity
  - Identify individual packs
  - Serve as tamper evidence

- **To be borne by:**
  - Medicinal products subject to prescription unless low falsification risk
  - Not for medicinal products without prescription unless at risk of falsification

- **Possibility to extend the scope of the application of safety features by MMSS** (reimbursement or pharmacovigilance)

Safety features (II)

- Conditions for the removal/cover of safety features (by manufacturers) and responsibilities

- Commission to adopt delegated act with the objective of establishing detailed rules for safety features defining:
  - Characteristics and technical specifications
  - Lists of medicinal products to bear safety features
  - Modalities for the verification
  - Repository systems holding this information

- Transitional period, revision of its efficacy, Commission previous study (technical options/verifications/repository)

Internet

- Conditions for the sale at a distance to the public of medicinal products
- Medicinal products must comply with the legislation of the Member State of destination
- Common logo (Commission implementing act)
- Website of each Member State
  - Information on legislation and different conditions on Member States
  - Information on the purpose of common logo
  - List of persons and websites offering medicinal products for sale at distance
  - Risk of internet illegal sales
  - Hyperlink to EMA website
- EMA website: link to MMSS websites & similar information about logo and risks

Ongoing works at regulators' level

Activities in cooperation:

EMA

Good Manufacturing Practice/Good Distribution Practice Inspectors Working Group (GMP/GDP IWG)

Commission

Delegated/implementing acts and experts groups

HMA

Task Force on the Falsified Medicines Directive (HMA-TF-FMD)

Working Group of Enforcement Officers (WGEO)

NCAs on their own:

Legal transposition and implementation of the new provisions

EMA GMP/GDP IWG works (I)

- Development and implementation of new modules of EudraGMP
- Revision of relevant paragraphs of GMP guidelines to adapt them to the new legislation
- New GDP guidelines for APIs
- Risk assessment guideline to establish appropriate GMPs for excipients
- Documents harmonisation: new formats
- …

GMP/GDP IWG works (II): GDP drafting group

- New EU GDP guideline draft
- Guideline on Training and Qualification of Inspectors Performing Inspections of Wholesale Distributors
- Format for:
  - Wholesale Distributors Authorisation,
  - GDP Certificate and
  - Statement of non-compliance
- GDP Inspection Procedure
- GDP Inspection Report
- Issuance of GDP certificate
- …

New GDP guidelines

- Commission guidelines
- Table of contents:
  - Introduction
  - 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 Recalls
  - Chapter 7 Contract Operations
  - Chapter 8 Self Inspections
  - Chapter 9 Transportation
  - Chapter 10 Specific Provisions for Brokers

- Published the 8th of March 2013 in the Official Journal
- Entry into force: 6 months after publication

Compilation of Community Procedures updated in july 2012

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000156.jsp&mid=WC0b01ac05800296cb)

Commission works (I)

- **Delegated act establishing Principles and Guidelines of GMP for AS**
  - Concept paper for public consultation (2011)
  - MMSS expert group first meeting September 2012
  - Regulation to be published in 2013?

- **Delegated act on the detailed rules for a unique identifier for medicinal products for human use and its verification**
  - Concept paper for public consultation (finished in April 2012)
  - MMSS Experts group meetings (December 2011 and September 2012)
  - Stakeholders meeting (December 2011)
  - Adoption 2014?

Commission works (II)

- **Implementing act: Requirements for the assessment of the regulatory framework applicable to the manufacturing of AS**
  - Concept paper for public consultation (finished in March 2012)
  - Assessments of third countries ongoing with the collaboration of NCAs

- **Implementing act: Criteria to be considered and verifications to be made when assessing the potential falsified character of medicinal products introduced into the EU but not intended to be placed on the market**
  - Concept paper for public consultation (finished in December 2012)
  - MMSS expert group first meeting September 2012

- **Implementing act: Design of the common logo for legally-operating online-websites, including the technical, electronic, cryptographic requirements**
  - Concept paper for public consultation (finished in January 2013)

Commission works (III)

- **Implementation of the new rules on importation of AS**
  - Draft template public consultation for the written confirmation: (finished in June 2012)
  - **Template for the written confirmation** has been published in Part III of EudraLex Vol 4.
  - Questions-and-answers" document: http://ec.europa.eu/health/human-use/quality/index_en.htm
  - Information leaflet: http://ec.europa.eu/health/files/documents/active_pharmaceutical_ingredients_leaflet_en.pdf


European Commission

New rules on importing
active pharmaceutical ingredients
into the European Union

...Who issues the written confirmation?
Written confirmation is issued by the regulatory authority of the country where the manufacturing site is located. You need to request it from that authority.

...Does written confirmation need to be issued for each batch/consignment?
No. Written confirmation is issued per manufacturing plant and for each active substance(s) manufactured on that site.

...Does each imported consignment have to be accompanied by written confirmation?
Yes. However, it may be a copy of the written confirmation issued by the regulatory authority.

...Are there exceptions from the written confirmation requirement?
The Commission publishes a list of countries which, following their request, have been assessed and are considered as having equivalent rules for good manufacturing practices to those in the EU. Active substances manufactured in such countries do not require a written confirmation.

...Do I need written confirmation, even though my manufacturing site has recently been inspected by an EU Member State or by the European Directorate for the Quality of Medicines (EDQM) of the Council of Europe?
Yes. The process of written confirmation is independent of such inspection activities. However, exceptionally and where necessary to ensure the availability of medicinal products, following inspections by an EU Member State, a Member State may decide to waive the need for a written confirmation for a period not exceeding the validity of the GMP certificate.

...Is written confirmation also required where there is a 'mutual recognition agreement' between my country and the EU?
Yes. The process of written confirmation is independent of the existence of 'mutual recognition agreements'.

The European Union (EU) has reformed the rules for importing into the EU active substances for medicinal products for human use.

As of 2 January 2013, all imported active substances must have been manufactured in compliance with standards of good manufacturing practices (GMP) at least equivalent to the GMP of the EU. The manufacturing standards in the EU for active substances are those of the 'International Conference for Harmonisation' – ICH Q7.

As of 2 July 2013, this compliance must be confirmed in writing by the competent authority of the exporting country. This document must also confirm that the plant where the active substance was manufactured is subject to control and enforcement of good manufacturing practices at least equivalent to that in the EU.

The template for such written confirmation can be found overleaf. This must accompany the active substance being imported into the EU.

More information is available here:
http://ec.europa.eu/health/human-use/quality/index_en.htm

Health and Consumers

HMA TF-FMD (I)

Mission/ Mandate

- Follow up, coordination, support for an harmonised approach for NCAs when bringing into force FMD or its delegated/implementing acts.
- Elaboration of common positions of NCAs, when needed, for strategic issues
- Cooperation with the current GMP/GDP Inspectors Working Group and HMA Working Group of Enforcement Officers (WGEO)

Composition: representatives from 19 NCAs

HMA TF-FMD (II)

Workplan: 5 workstreams

- Safety features
- Importation of AS
- Introduction of medicinal products
- Registry of brokers
- Distance sales
- Inspection resources

HMA WGEO

Activities included in Strategy 2011-2015

- Common understanding of the concept of a falsified medicine.
- Risk assessment template for wholesalers and brokers to conduct due diligence on new suppliers
- Development of best practices on controlling medicines introduced into the EU (imports for exports), in cooperation with customs
- Coordination of surveillance of illicit sale of medicines over the internet
- Guidance on open source internet investigations for the purpose of uncovering illegal websites and identifying the persons/companies responsible
- Templates for assessment of the potential vulnerability of products being falsified
- Develop an Anti-Counterfeit Stakeholder meeting concept – national group, membership and objectives (extension of Network & SPOC concept).
- Model for meetings between enforcement officers and consumer's organizations (Article 118b)
- Develop a falsified medicine case study analysis template

Challenges for stakeholders: implemention of the new rules (I)

- **New requirements for manufacturers of MP:**
  - New controls for AS supply chain and excipients
  - Notification of any suspicion of medicinal products falsification
  - Importation of AS from third countries
- **New requirements for manufacturers, importers & distributors of AS:**
  - National registry
    - Register prior to initiate the activity
    - Annual update
    - Notification of modifications
  - Subject to inspections from NCAs

Challenges for stakeholders: implementation of the new rules (II)

- **Additional requirements for wholesalers:**
  - Quality system (responsibilities, processes and risk management measures)
  - GDP certification
  - Notification of any suspicion of medicinal products falsification
  - Authorisation of wholesalers in free trade zones or free warehouses
  - Adaptation to the new GDP guidelines

- **Brokers:**
  - New requirements
  - Registry

Challenges for NCAs: implementation of the new rules (I)

Databases and exchange of information:

- **Registry of AS manufacturers/importers/distributors**:
  - Set up of the registry
  - Transmission of information to Union database

- **Wholesalers Registry**:
  - Set up of the registry
  - Transmission of information to Union database

- **Brokers registry**:
  - Set up of the registry
  - Publication in the national website

Challenges for NCAs: implementation of the new rules (II)

Other new activities:

- Authorisation of **wholesalers in free trade zones or bonded warehouses**
- **GDP certification of all wholesalers**
- Controls on **APIs importation**
- Cooperation with customs authorities on the **control of the 'introduction'** of medicinal products (not intended for the EU market)

Other tasks:

- Update of current procedures & quality system

Challenges for NCAs: implementation of the new rules (III)

Inspections:

Periodic inspections of:

- Local & 3rd countries manufacturers of medicinal products
- Local wholesalers
- Local Manufacturers/Importers/Distributors of AS

When *suspecting noncomplicance*

- Manufacturers/Distributors of AS in 3rd countries
- Importers/Manufacturers of excipients
- MAH & brokers of medicinal products

Inspectors resources & qualification!

Challenges for NCAs: implementation of the new rules (IV)

Internet sales:

- Conditions for the sale at a distance to the public of medicinal products (regulation)

- National website after publication of EU common logo
  - Information on legislation and different conditions on Member States
  - Information on the purpose of common logo
  - List of persons and websites offering distant sale of medicinal products
  - Risk of internet illegal sales
  - Hyperlink to EMA website

- Raising awareness about illegal websites

But these are difficult times…

Economic crisis: both NCAs and stakeholders are facing problems to get additional human or material resources

Potential solutions

- Increase efficiency
- Resources allocation
- HMA network to avoid duplication of efforts
- …

But with the new measures we will:

- Increase the quality of medicinal products (AS & excipients)
- Reinforce the supply chain against penetration of falsified MP/AS
- Increment the protection of our citizens when buying medicinal products in internet

Thank you & welcome!