Implementing the Falsified Medicines Directive:

Changes to the EU Regulatory Framework for APIs

Unit "Quality, Safety and Efficacy of Medicinal Products"

European Commission

ICH Q7
Training Course

Health and Consumers

Outline

- Falsified medicines legislation
- API:
  - Rationale and summary of the new EU rules
  - State of play
  - Taking stock

Directive on Falsified Medicines – FMD

2011/62/EU (in force since January 2013)

Manufacturers of active substances

- **New rules for import of APIs:**
  - ✓ Written confirmation on GMP or
  - ✓ Country is listed by the Commission
- **Registration of API stakeholders**
- **Strengtened API inspections**
- **GMP and GDP for APIs**

Manufacturers of medicines

- **Safety features**
  - ✓ Unique identifier
  - ✓ Anti-tampering device
  - ✓ On prescription medicinal products
- **On-site audit of API manufacturers**
- **GMP for certain excipients**

Distributors

- **Obligation to report incidents of falsification**
- **EU database of all authorised distributors**
- **New GDP guidelines**

Online pharmacies

- **Common logo / trust mark**
- **Awareness campaign**

EU RULES FOR ACTIVE PHARMACEUTICAL INGREDIENTS

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Definition of API

Any substance or mixture of substances intended to be **used in the manufacture of a medicinal product** and **that, when used in its production, becomes an active ingredient of that product** intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.

New Rules on API import

Starting point:

- Trust and cooperation between regulators in key regions
- Not “identical rules” as in the EU, but “equivalent protection”
- Internationally-accepted guidelines (ICH, WHO, PIC/S)

New Rules on API import

Objectives:

- Objectives:
  - **Increased compliance** with good manufacturing practices for all API manufacturers;
  - Adding **official oversight** to the business-to-business controls
  - Promote **dialogue and cooperation** on good manufacturing practices at global level.

New Rules on API import

Non-EU country

"Written confirmation" needed

EU country

unless:

- Non-EU country is 'listed' ("waiver 1")

or, exceptionally*

- EU GMP certificate following inspection by an EU country ("waiver 2")

*** to secure supplies of medicines**

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New Rules on API import
"Written Confirmation":

- Confirming compliance of the plant with GMP or equivalent rules
- Issued by the competent authority of the exporting non-EU country
- Issued per site and API (not per batch or consignment)
- One written confirmation can cover several APIs
- Duration of validity is established by exporting non-EU country
- Template is here:

http://ec.europa.eu/health/files/eudralex/vol-4/2012_06_19_template.pdf

New Rules on API import

"Waiver 1" : non-EU country is "listed"

List is set up by the European Commission following a ***request from a non-EU country***

The list is based on an ***assessment*** *of equivalence of:*

- **GMP rules**
- **Regularity of inspections**
- **Effectiveness of enforcement of GMP**
- **Rapid alert system for non-compliant producers**

New Rules on API import
"Listing"

So far, nine countries have submitted requests, 6 have been listed, 2 assessments are ongoing

- **CH, AUS, JPN, US, BRA and IL** have been listed;
- **SGP** has not been listed for the moment;
- **NZ** and **KOR** assessments are on-going.

New Rules on API import

"Waiver 2": "Exceptional circumstances"

*"**Exceptionally**", and where this is necessary to ensure the availability of medicines, the need for the written confirmation can be waived by a EU Member State if a EU Member State has inspected the plant and found it compliant.*

To date, 16 Member States are using this waiver

STATE OF PLAY

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New Rules on API import

State of Play:

- Rules smoothly entered into force on 2 July 2013
- Most API sites are **covered with written confirmation** or exempted because of "listing" of the non-EU country.
- The **renewal** of written confirmations is also proceeding timely, without disruption of supply.
  - We encourage third countries to renew written confirmations **on the basis of new inspections**
- The Commission is following-up with third country authorities the **GMP non-compliance** of API sites covered by W-Cs.

New Rules on API import
Taking stock (I):

SUCCESS STORY!

- **No shortages** (but we stay vigilant).
- **Improved monitoring of APIs** at EU level (inspections, registration of manufacturers, distributors and brokers).
- **Increased compliance** to GMP for API at EU and international level – increased awareness and surveillance.
- **Improved communication** with EU national competent authorities and industry on APIs.

New Rules on API import
Taking stock (II):

SUCCESS STORY!

- **Strengthened regulatory dialogue** with non-EU countries to:
  - Fight **GMP-non compliance**;
  - Increase **regulatory supervision** of API sites;
  - **Promote awareness** and training on the new EU rules.

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FREQUENTLY ASKED QUESTIONS

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Do I need a written confirmation to import a substance X into the EU?

Whether a written confirmation is needed or not to import a specific substance into the EU depends on the final use of the substance.

A written confirmation is only required **if the substance is to be used as active pharmaceutical ingredient** in the production of medicines.

What happens when an API site covered by a written confirmation is found GMP non-compliant by a EU authority?

A statement of non-compliance (NCS) is issued and entered in the publicly accessible database EudraGMDP: http://eudragmdp.eudra.org/inspections/gmpc/index.do

A NCS **supersedes the corresponding written confirmation** (if it exists) issued by the non-EU country.

In practice:

EU Member States will suspend the acceptance of the written confirmation for the site in question until GMP compliance is restored.

Additional information published by the European Commission

- *"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*

Thank you

sante-pharmaceuticals-d6@ec.europa.eu

(new email!!!)