Implementing the Falsified Medicines Directive:

Changes to the EU Regulatory Framework for APIs

Patrizia Tosetti

Unit "Quality, Safety and Efficacy of Medicinal Products"

European Commission

"GMP for APIs" Training Course
Bruxelles
19 September 2014

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

Health and
Consumers

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**

Health and Consumers

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, eight countries have submitted requests, 4 have been listed, 3 assessments are ongoing

- **CH, AUS, JPN** and the **US** have been listed;
- **SGP** has not been listed for the moment;
- **IL** has recently modified its legislation and formally asked COMM to be reconsidered for listing; the assessment is ongoing;
- Brazil and New Zealand 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, 13 Member States have notified to the Commission their intention to use this waiver

STATE OF PLAY

Health and
Consumers

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.
- 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.
- **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.

Health and Consumers

FREQUENTLY ASKED QUESTIONS

Health and
Consumers

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.

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

sanco-pharmaceuticals-d6@ec.europa.eu