API – the new approach for third countries – what are the consequences – should we expect shortage of medicinal products in the country? Perspectives from an acceding country

EU28: SCIENCE MEDICINES HEALTH, A REGULATORY SYSTEM FIT FOR THE FUTURE

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Medicinal products: quality, safety and efficacy

Directorate General for Health and Consumers

Health and Consumers

The European Union (EU) Directive 2011/62/EU - main contents

Obligatory safety features	*Actors in the supply chain*	***Active substances, quality***	*‚Online pharmacies‘*

Structure of talk

API:

- Rationale for the rules
- Summarising the rules
- State of play (focus of the talk)

Other aspects in relation to GMP and GDP

RULES FOR ACTIVE PHARMACEUTICAL INGREDIENTS

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.

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

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 for imported API

*** to secure supplies of medicines**

New rules on API

"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
“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**

So far, seven countries have submitted requests

New rules on API
“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.

State of play

- **Countries that have informed us of the intent to issue "written confirmation", or that have started issuing "written confirmation":** India, China, Israel, Mexico, Canada, Taiwan, Turkey, South Africa, Ukraine; Korea; Singapore; Russia
- **Countries that have applied for "listing":** Switzerland, Israel, Singapore, Australia, Japan, U.S., Brazil
- **Strengthened coordination of inspections (EMA) on the basis of survey of the heads of medicines agencies**

Actions needed by the different actors

- **Finished dosage manufacturers in the EU:** To inform suppliers in third countries of incoming rules
- **EU-authorities:** To inform of incoming rules; verify whether additional Member State inspections are needed to ensure supply
- **Suppliers in third country:** To obtain 'written confirmation' for the manufacturing plant
- **Non-EU country authorities:** To prepare for issuing the written confirmation; assess possibility to request Commission to be 'listed'

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

European Commission

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

Other aspects in relation to GMP and GDP

- GDP (medicinal products)
- GDP for API
- Risk assessment for excipients
- GMP for API

http://ec.europa.eu/health/human-use/falsified_medicines/index_en.htm

Many thanks!

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