IRISH MEDICINES BOARD

Starting Materials Changes from FMD

GMP Information Day / 27th September 2012

Anne Hayes

FMD Legislation

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Directive 2011/62/EC

amending Directive 2001/83/EC

addresses issues of quality of active substances, as well as issues of 'falsified medicines'

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Objective:

Increased compliance with good manufacturing practices for all API manufacturers

Date of application:

2 January & 2 July 2013

Basic principles

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Equal rules for all APIs, whether manufactured in the EU or imported

Strengthened business-to-business control:

Mandatory audits conducted by medicines manufacturers or third party contactors

Strengthening official control:

- Building on mutual trust and cooperation
- In line with global regulatory guidelines (WHO, ICH)

New rules for imported API

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Non-EU country

- Written confirmation needed

EU country

unless:

- country is 'listed'

  or, exceptionally*

- EU GMP certificate following inspection by a Member State

* to secure supplies of medicines

New rules for Imported API

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Option 1 for import: Written confirmation

- **API can be imported only if it is accompanied by a written confirmation confirming GMP compliance of the plant**
- Issued by the competent authority of the exporting third country
- Template published by Commission: http://ec.europa.eu/health/files/eudralex/vol-4/2012_06_19_template.pdf

New rules for Imported API

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Option 2 for import: Country is "listed"

List is set up by the European Commission following a **request from a third 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, two countries have submitted request

New rules for Imported API

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Option 3 for import: 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 Member State if a Member State has inspected the plant and found it compliant

Actions needed by the different actors

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Finished dosage manufacturer in the EU: To inform supplier of incoming rules

Supplier in third country: To obtain 'written confirmation' for the manufacturing plant

Third country authority: To prepare for issuing the written confirmation; assess possibility to request Commission to be listed

Medicines authority in MSs: To verify whether additional Member State inspections are needed to ensure supply

Increased risk of API & product shortages

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A very high proportion of active substances used in EU are sourced from third countries

Some third country authorities may not able to issue the written confirmations

There is a risk that APIs from those countries will not be legitimately imported as of 2 July 2013 resulting in product shortages

- Preliminary analysis put approximately 200 CAPs & 1000s of nationally authorised products at risk

Increased risk of API & product shortages

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EU GMP certificates are held by only 100-200 active substance manufacturers located in third countries

EU resources for inspections are limited, in particular for active substances

What is being done by Agencies?

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EMA is performing a risk analysis for centrally authorised products

MSs will be doing this for nationally authorised products too

Purpose of the Risk Analysis: To identify and prioritise products that might be at risk of shortage

Products clearly at risk are those with API manufactured only in a third country and finished product manufactured exclusively in the EEA (not biological and/or veterinary)

What do companies & agencies need to do?

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Step1. Screen and classify your products as:

- Green: not at risk
- Amber: potentially at risk
- Red: clearly at risk

Step 2. Carry out a detailed analysis of red & amber products

Risk rank at site level based on location and EEA inspection status Source: EudraGMP

Outcome: list of active substance manufacturing sites in third countries ranked by risk category

Detailed Analysis – Step 2.1

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Probability

Rating	The API site :
1	has been inspected by an EEA competent authority for the relevant active substance
2	has been inspected by an EEA competent authority for a different APIs or Finished Product operations
3	has not been inspected by an EEA competent authority

Severity

Rating	
1	The API site is located in a listed country
2	The API site is located in a third country that is not listed (with MRA or without MRA)

Detailed Analysis – Step 2.2

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Risk matrix

Severity/ Probability	1	2
1	1	2
2	2	4
3	3	6

Risk ranking: level of risk calculated as **R = P x S**

- R = 1 to 3: low risk
- R = 4: medium risk
- R = 6: high risk

Outcome: sites in the highest risk category classified for criticality (prioritisation)

Step 3: Criticality analysis of sites from the highest risk category from step 2.2

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Stock level	**Rating**
Less than 3 months	4
3 months to 1 year	3
1 year to 2 years	2
More than 2 years	1

API site located in a third country	**Rating**
Site in use	2
Back-up site	1

Number of active substances manufactured	**Rating**
3 or more	3
2	2
1	1

Step 3: Criticality analysis

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Supplier criticality Σ(Cn) calculated from criticality of stock + site + number APIs

Risk priority number (RPN) = S x P x Σ(Cn) = score

Step 4 – Prioritisation by Agencies

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Involve clinical experts in the risk analysis in order to take into consideration the clinical relevance of products in case of shortage

The results of the risk analysis from step 3 and step 4 will have to be combined in order to make a final decision on the actions to be taken

Excipients - FMD

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Manufacturers have to establish and document the risk profile of all excipients used and ensure that they are suitable by determining what is the appropriate good manufacturing practice

Via a formalised risk assessment

Taking into account appropriate quality system requirements, sources and intended use and previous quality defects

Excipients - FMD

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Guidelines on the formalised risk assessment under development at GMPD IWG

Public consultation expected @ end of year

Implementation date: 2nd January 2013

Summary

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New FMD rules for API come into force on 2nd January and 2nd July 2013

Impacts on medicines for humans but not investigational medicinal products (IMPs)

Importation requirement will very likely result in API shortages

Risk mitigation measures will be required by manufacturers and agencies to ensure continued supply of medically necessary products

From 2nd Jan 2013 manufacturers (MIA holders) are required to conduct risk assessments on excipients used in commercial medicines