

# Summary of Concept Paper: Implementing Act on the Requirements for the Assessment of the Regulatory Framework Applicable to the Manufacturing of Active Substances of Medicinal Products for Human Use

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*This summary was prepared by the Rx-360 Monitoring and Reporting Working Group which tracks regulatory, legislative and policy developments relevant to pharmaceutical/medical device supply chain integrity. The summary is not intended to serve as comprehensive and formal interpretation or guidance (and should not replace your own review and analysis of any referenced source documents). If you have questions, please contact Maureen Hardwick, Rx-360 Secretariat, at 202.230.5133 or [maureen.hardwick@dbr.com](mailto:maureen.hardwick@dbr.com).*

# Publication Details

- Released by the European Commission Health and Consumer Directorate-General on December 7, 2011 for comment
- Comment deadline is March 23, 2012

# Background

- Directive 2011/62/EU introduces EU-wide rules for the importation of active substances
- Per Directive 2011/83/EC, Article 46b(2), active substances are to be imported only if, inter alia, they are accompanied by a written confirmation from the competent authority of the exporting third country which, as regards the plant manufacturing the exported active substance, confirms that the standards of good manufacturing practice and control of the plant are equivalent to those in the EU

# Background

- Requirement for written confirmation is waived for third countries listed by the Commission in accordance with Article 111b of Directive 2001/83/EC
- To be listed, the Commission, shall, at the request of the third country, assess whether the **regulatory framework applicable to active substances and the respective control and enforcement activities** ensure a level of public health protection equivalent to that of the EU ('the equivalence assessment')
- If equivalency is confirmed, the Commission shall include the third country in a list

# Background

- The equivalence assessment includes:
  - the country's rules for GMP
  - the regularity of inspections to verify compliance with GMP
  - the effectiveness of enforcement of GMP
  - the regularity & rapidity of information provided by the third country regarding non-compliant producers of active substances
- Article 111b(2) of Directive 2001/83/EC provides that the Commission adopt an implementing measure to apply these requirements
- This concept paper has been generated for public consultation with a view to preparing the implementing act in the Directive

# Consultation Topics for Comment

1. Equivalence Assessment of the Rules for GMP
2. Equivalence Assessment of the Regularity of Inspections to Verify Compliance with GMP and the Effectiveness of Enforcement of GMP
3. Regularity and Rapidity of Information Provided by the Third Country Relating to Non-Compliant Producers of Active Substances
4. Other Issues
  - 4.1 Form of assessment
  - 4.2 Interface with existing mechanisms
  - 4.3 Regular verification
  - 4.4 Date of application
- Annex: Audit checklist for joint programme for EEM GMP Inspectorates

# Equivalence Assessment of the Rules for GMP

- Directive 2001/83/EC, Article 111b(1)(a), obliges the Commission, in its equivalence assessment, to take particular account of the third country's rules for GMP
- In this context and pending adoption of a delegated act on the principles and guidelines of GMP for active substances, EU rules to be taken into account are in Eudralex Volume 4, Part II of the good manufacturing guideline

# Equivalence Assessment of the Regularity of Inspections to Verify Compliance with GMP and Effectiveness of Enforcement of GMP

- Directive 2001/83/EC, Article 111b(1)(b), obliges the Commission, in its equivalence assessment, to take particular account of:
  - the regularity of inspections to verify compliance with GMP, and
  - the effectiveness of enforcement of GMP
- The regulatory framework for inspections of manufacturing plants of active substances is taken into account (Directive 2001/83/EC, Article 52A(4) and Article 111(1b))

# Equivalence Assessment of the Regularity of Inspections to Verify Compliance with GMP and Effectiveness of Enforcement of GMP

- Applicable rules for the risk-based approach provided for in Directive 2001/83/EC, Article 111(1b) are set out in the *‘Compilation of Community Procedures, Procedures related to GMP inspection – guidance on occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials’*.
- Points 1-9 & 11 of the audit checklist provided in the concept paper Annex could be used to facilitate the equivalence assessment
  - Checklist is currently used in the existing Joint Audit Programme for GMP Inspectorates of the Heads of Medicines Agencies (‘HMA’), the EMA, and the GMP/GDP inspectors working group

# Regularity and Rapidity of Information Provided by the Third Country Relating to Non-Compliant Producers of Active Substances

- Requirement objective – ensure the EU Member States are timely informed on possible quality incidents which occur in the third country, as these may have impact on the quality of medicinal products in the EU market
- To ensure equivalence, it could be considered that the third country
  - participates in and contributes to the ‘*Community information and rapid alert system*’, and
  - communicates any suspension or withdrawal of an authorisation granted, based on non-compliance with GMP, to the EU

# Other Issues:

## Form of assessment

- Per Directive 2001/83/EC, Article 111b(1), the equivalence assessment shall take the form of:
  - a review of relevant documentation
  - an on-site review of the third country's regulatory system, unless a mutual recognition agreement (MRA) is in place covering the manufacturing of active substances
  - an observed inspection of one or more of the third country's manufacturing sites for active substances (if necessary)

# Other Issues:

## Interface with existing mechanisms

- The Commission performs the assessment and verification of equivalence in cooperation with the Agency and Member States
- In this context, in order to avoid unnecessary duplication of work and to build on existing mechanisms and expertise, the intent is to take into consideration the following (where available and appropriate):
  - MRAs on GMP for medicinal products that also cover the manufacturing of active substances
  - Regulatory alignment with applicable guidance of the ICH of Technical Requirement for Registration of Pharmaceuticals for Human Use
  - Existing assessment programs

# Other Issues:

## Interface with existing mechanisms

- Examples of existing assessment programs:
  - The Joint Audit Programme used for assessing European Union's authorities and MRA partners; and
  - The Assessment and Reassessment Programmes of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)

# Other Issues:

## Regular verification

- Per Directive 2001/83/EC Article 111b(3), the Commission shall regularly verify whether the conditions of GMP equivalence are fulfilled
  - First verification to take place no later than 3 years after the country has been included in the list

# Other Issues:

## Date of application

- Rules on importation of active substances apply as of July 2, 2013

# Thank you

**For More Information**



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