EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Pharmaceuticals

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IMPLEMENTING ACT ON THE REQUIREMENTS FOR THE ASSEMENT OF THE REGULATORY FRAMEWORK APPLICABLE TO THE MANUFACTURING OF ACTIVE SUBSTANCES OF MEDICINAL PRODUCTS FOR HUMAN USE

CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

INTRODUCTION

1. On 1 July 2011, Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products was published.[1] This Directive amends Directive 2001/83/EC on the Community Code relating to medicinal products for human use.[2]

2. Directive 2011/62/EU introduces EU-wide rules for the importation of active substances:[3] According to Article 46b(2) of Directive 2001/83/EC, active substances shall only be imported if, *inter alia*, the active substances 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 Union.

3. The requirement of a written confirmation is waived for third countries listed by the Commission in accordance with Article 111b of Directive 2001/83/EC.

4. 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** in the third country ensure a level of protection of public health equivalent to that of the Union (hereinafter: 'the equivalence assessment').[4]

5. If the assessment confirms equivalence, the Commission shall adopt a decision to include the third country in a list.[5]

6. In the equivalence assessment particular account shall be taken of:

   - the country's rules for good manufacturing practice (GMP);
   - the regularity of inspections to verify compliance with GMP;
   - the effectiveness of enforcement of GMP;

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1 OJ L 174, 1.7.2011, p. 74

2 OJ L311, 28.11.2001, p. 67. A consolidated version of Directive 2001/83/EC including the amendments by Directive 2011/62/EU is here: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20110721:EN:PDF

3 For the definition of active substance, see Article 1(3a) of Directive 2001/83/EC.

4 Article 111b of Directive 2001/83/EC.

5 Article 111b of Directive 2001/83/EC.

- the regularity and rapidity of information provided by the third country relating to non-compliant producers of active substances.

7. Article 111b(2) of Directive 2001/83/EC provides that the Commission adopts an implementing measure to apply these requirements.

8. This concept paper is being rolled out for public consultation with a view to preparing this implementing act.

9. The adoption of the implementing act is scheduled for 2013.

CONSULTATION TOPICS

1. EQUIVALENCE ASSESSMENT OF THE RULES FOR GMP

10. Article 111b(1)(a) of Directive 2001/83/EC obliges the Commission, in its equivalent assessment, to take particular account of the third country's rules for GMP.

11. In this context, and pending the adoption of a delegated act on the principles and guidelines of good manufacturing practice for active substances[6], the EU rules to be taken into account are contained in Part II of the good manufacturing practice guideline of the EU (Eudralex Volume 4).[7]

Consultation item n°1: Please comment.

2. EQUIVALENCE ASSESSMENT OF THE REGULARITY OF INSPECTIONS TO VERIFY COMPLIANCE WITH GMP AND THE EFFECTIVENESS OF ENFORCEMENT OF GMP

12. Article 111b(1)(b) of Directive 2001/83/EC 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.

13. In the equivalence assessment, the regulatory framework for inspections of manufacturing plants of active substances is taken into account. This regulatory framework is set out in Article 52a(4) and Article 111(1b) of Directive 2001/83/EC.

14. Moreover, regarding the risk-based approach provided for in Article 111(1b) of Directive 2001/83/EC, the applicable rules are set out in the '*Compilation of Community Procedures, Procedures related to GMP inspections – guidance on*

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6 See third paragraph of Article 47 of Directive 2001/83/EC.

7 http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials'.[8]

15. To facilitate the equivalence assessment, points 1-9 and 11 of the audit checklist in the Annex to this concept paper could be used. This audit checklist is used in the existing Joint Audit Programme[9] for GMP Inspectorates of the Heads of Medicines Agencies ('HMA'), the European Medicines Agency ('the Agency') and the GMP/GDP inspectors working group.[10]

Consultation item n°2: Please comment.

3. REGULARITY AND RAPIDITY OF INFORMATION PROVIDED BY THE THIRD COUNTRY RELATING TO NON-COMPLIANT PRODUCERS OF ACTIVE SUBSTANCES

16. The objective of this requirement is to make sure that the Member States in the European Union are timely informed of possible quality incidents which occur in the third country, as these may have an impact on the quality of medicinal products placed on the EU market.

17. To ensure equivalence, it could be considered that the third country

- participates in and contributes to the '*Community information and rapid alert system*';[11] and
- communicates any suspension or withdrawal of an authorisation granted, based on non-compliance with GMP, to the EU.

Consultation item n°3: Please comment.

4. OTHER ISSUES

4.1. Form of assessment

18. According to Article 111b(1) of Directive 2001/83/EC, the equivalence assessment shall take the form of:

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8 http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf, page 64.

9 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/joint_audit_programme.jsp&mid=WC0b01ac058006e06f&murl=menus/regulations/regulations.jsp&jsenabled=true

10 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000161.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296c9&jsenabled=true

11 Cf. Compilation of Community Procedures: Procedures Related to Rapid Alerts - Procedure for Handling Rapid Alerts Arising From Quality Defects (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf, p. 19.

- 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 that covers the manufacturing of active substances; and

- if necessary, an observed inspection of one or more of the third country's manufacturing sites for active substances.

4.2. Interface with existing mechanisms

19. The Commission performs the assessment and verification of equivalence in cooperation with the Agency and the Member States.[12]

20. In this context, in order to avoid unnecessary duplication of work, and in order to build on existing mechanisms and expertise, it is intended to take into consideration, where available and appropriate, the following:

    - MRAs on GMP for medicinal products which cover also the manufacturing of active substances;

    - Regulatory alignment with applicable guidance of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ('ICH');[13]

    - Existing assessment programs such as

        – 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').[14]

4.3. Regular verification

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

4.4. Date of application

22. The rules on importation of active substances apply as of 2 July 2013.[15]

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12 Article 111b(4) of Directive 2001/83/EC.

13 http://www.ich.org/

14 http://www.picscheme.org/

15 Article 2(2)(a) of Directive 2011/62/EU.

Consultation item n° 4: Please comment on the issues raised in point 4 ('other issues').

Consultation item n° 5: Please raise any other issue or comment you would wish to make which has not been addressed in the consultation items above.

Stakeholders are invited to comment on this consultation paper, and especially on the boxed text, by 23 March 2012 at the latest. Responses should be sent preferably by e-mail to sanco-pharmaceuticals@ec.europa.eu, or by post to Unit SANCO/D/3, BREY 10/114, BE-1049 Brussels.

When sending your comments and responses, you should state whether you are a stakeholder association or a private individual. If you represent an association, please indicate clearly what type of association this is (patient, API manufacturer, medicinal products manufacturer, API importer, medicinal products importer etc.). If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50 million annual turnover and fewer than 250 employees).

All comments and responses will be made publicly available on the 'Europa website' on pharmaceuticals once the consultation period is over. If you do not wish your contribution to be made public please indicate this clearly and specifically in the documentation you send us (i.e. not just in the covering letter or e-mail). In this case, only an indication of the contributor will be disclosed.

Professional organisations are invited to register in the Union's Register for Interest Representatives (http://ec.europa.eu/transparency/regrin/) set up as part of the European Transparency Initiative to provide the Commission and the public at large with information about the objectives, funding and structures of interest representatives.

Annex: Audit checklist for joint audit programme for EEA GMP Inspectorates

Summary of the Audit Checklist			
Component	**Sub-component**	**Importance**	**Evaluation method**
1 - Legislative and Regulatory Requirements and Scope	1A - Empowering legislation	Critical	Documentation review
	1B - Conflict of interest	Very important	Documentation review On-site evaluation at Inspectorate
2 - Regulatory directives and policies	2A - Procedures for designating inspectors	Very important	Documentation review
	2B - Enforcement Policies	-	Evaluated as part of sub-component 7B
	2C - Code of conduct/ Code of ethics	Very important	Documentation review
	2D - Training certification policies/guidelines	-	Evaluated as part of sub-component 4C
	2E - Alert/crisis management policies/procedures/guidelines	-	Evaluated as part of sub-component 8A
	2F - Organisational structure	-	Evaluated as part of sub-component 11A
3 - GMP Standards	3A - Details/ scope of GMP	Critical	Documentation review
	3B - Process validation	-	Evaluated as part of sub-component 3A
4 - Inspection resources	4A - Staffing: Initial qualification	Very important	Documentation review On-site evaluation at Inspectorate
	4B - Number of inspectors	Very important	Documentation review On-site evaluation at Inspectorate
	4C - Training programme	Very important	Documentation review On-site evaluation at Inspectorate
	4D - QA mechanism to assure effectiveness of training programme	-	Evaluated as part of sub-component 4C
5 - Inspection procedures	5A - Inspection strategy	Very important	Documentation review On-site evaluation at Inspectorate
	5B - Pre-inspection preparation	Very important	Documentation review On-site evaluation at Inspectorate Observed inspections
	5C - Format and content of inspection reports	Very important	Documentation review Observed inspections
	5D - Inspection methodology	-	Evaluated as part of sub-components 5E
	5E - SOP for conducting inspections	Critical	Documentation review Observed inspections
	5F - Inspection procedures - Post-inspection activities	Very important	Documentation review On-site evaluation at Inspectorate Observed inspections
	5G - Inspection procedures – Storage of inspection data	Important	Documentation review Observed inspections
6 - Inspection performance standard	6A - Performance standards	Very important	Documentation review On-site evaluation at Inspectorate
7 - Enforcement powers and procedures	7A - Provision for written notice of violations	-	Evaluated as part of sub-component 7B
	7B - Non-compliance management	Critical	Documentation review On-site evaluation at Inspectorate
	7C - Appeal mechanism	Important	Documentation review On-site evaluation at Inspectorate
	7D - Other measures	-	Evaluated as part of sub-components 7B
8 - Alert and crisis systems	8A - Alert mechanisms	Critical	Documentation review On-site evaluation at Inspectorate
	8B - Crisis management mechanisms	-	Evaluated as part of sub-component 8A
	8C - Alert performance standards	Important	Documentation review
9 - Analytical capability	9A - Access to laboratories	Critical	Documentation review On-site evaluation at Laboratory
	9B - SOPs for analytical support	Very important	Documentation review On-site evaluation at Laboratory On-site evaluation at Inspectorate
	9C - Validation of analytical methods	Very important	Documentation review On-site evaluation at Laboratory
10 - Surveillance programme	10A - Sampling and audit procedure	Very important	Documentation review On-site evaluation at Laboratory On-site evaluation at Inspectorate
	10B - Recall monitoring	-	Evaluated as part of sub-component 7B
	10C - Consumer complaint system	Very important	Documentation review On-site evaluation at Inspectorate
	10D - Adverse reaction reporting system/ procedures	-	Not evaluated - not considered within the scope of a GMP compliance programme.
	10E - Drug product defect reporting system/ procedures	-	Evaluated as part of sub-component 10C

11 - Quality management system	11A - Quality management system	Critical	Documentation review On-site evaluation at Inspectorate On-site evaluation at Laboratory