EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – Quality, safety and efficacy

PHARM 613

PHARMACEUTICAL COMMITTEE
22 October 2012

Subject: **Implementation of the new rules on importation of active substances**

Agenda item 2. c)

1. BACKGROUND

The 'Falsified Medicines Directive' 2011/62/EU has been adopted in June 2011 and published on 1 July 2011. It introduces (for the first time) EU-wide rules for the importation of active substances for medicines for human use. As of 2 January 2013, all active substances have to be manufactured in accordance with good manufacturing practice (GMP), or (if imported) with equivalent rules.

As of 2 July 2013, the import of these substances is only possible if:

- **Option 1**: the consignment is accompanied by a 'written confirmation' by the authority of the third country that the plant manufacturing active substances operates in compliance with EU-'good manufacturing practice', or with equivalent rules, and is subject to equivalence rules for control and inspections; or

- **Option 2**: the third country has been listed by the Commission as a country with an equivalent system of supervision and inspection as in the EU; or

- **Option 3**: exceptionally, and where necessary to ensure the availability of medicinal products, the need for the written confirmation can be waived by a Member State if a Member State has inspected the specific plant.

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2. STATE OF PLAY OF IMPLEMENTATION AT EU-LEVEL

The Commission, in cooperation with the Agency, has taken a multitude of measures in order to prepare for the incoming rules:

2.1. 'Written confirmation'

The Commission has published, in July 2012, the template of the 'written confirmation'.

Care has been taken to ensure that the template of the 'written confirmation' is not creating additional bureaucracy, and that it is compliant with international documents.

2.2. 'Questions and answers' (Q&A) document

The Commission has published an extensive Q&A document in order to address issues frequently raised in contacts between stakeholders with the Commission.

It is planned to add Q&As to the document (see annex 1). Are there any objections from the delegates?

2.3. 'Listing' of third countries

2.3.1. List of third countries

The Commission has received (state of play: 28/9/12) four requests from third countries to be listed. An overview of the state of play is here: http://ec.europa.eu/health/human-use/quality/index_en.htm#ias

These equivalence assessments are ongoing. In this respect, the Commission draws also on expertise of the "Food and Veterinary office" of DG SANCO. The Commission is going to cooperate also with the Agency and the competent authorities of the Member States.

To streamline the equivalence assessments the Commission has set up a 'road-map' (see annex 2). It is planned to publish this 'road-map' shortly on the respective Commission website.

2.3.2. Implementing act

In the context of the 'listing', the Commission is put under an obligation to adopt an 'implementing act' to apply the requirements for the 'equivalence assessment'.

Work on this implementing act is advanced: The Commission has notified, in accordance with the EU Agreement on Technical Barriers to Trade the draft text of the implementing act. The text is available, under the reference G/TBT/N/EU/62, here: http://docsonline.wto.org/gen_search.asp?searchmode=simple

The final draft will be submitted to the Standing Committee for an opinion in early 2013.

This draft Commission Decision is **not** a prerequisite for the purpose of 'listing' third countries in accordance with Article 111b of Directive 2001/83/EC. Rather, in parallel to the adoption of this draft Commission Decision the Commission continues to assess equivalence following requests from third countries in accordance with Article 111b(1) of Directive 2001/83/EC.

2.4. Awareness raising – general

The Commission has published an 'information leaflet' explaining, in plain, simple words, the incoming rules. The leaflet is here:

http://ec.europa.eu/health/files/documents/active_pharmaceutical_ingredients_leaflet_en.pdf

Delegates are invited to ensure that the leaflet is also posted on the websites of the appropriate national body or bodies.

2.5. Awareness raising – multilateral and bilateral

The Commission has informed of the incoming new rules in over 30 multilateral and bilateral meetings at all levels of seniority.

A specific focus is India and China, who are the largest exporters of active substances into the EU.

2.6. 'Mapping' of critical supply sites

The Commission has requested the Agency to 'map' the supply-sites of active substances for centrally-authorised medicinal products and to identify whether and which medicinal products are 'at risk'.

The Agency has shared its methodology with Member States.

Delegates are invited to ensure that Member States perform a similar 'mapping'.

In addition, the Commission has requested industry to supply it with accurate information about the number of 'active' sites in third countries supplying active substances for medicinal products for human used into the EU.

3. RISK-MANAGEMENT

Despite all these measures situations may arise where a (a) non-listed third country (b) does not issue a 'written confirmation', while the site where the exported active substances is manufactured was never inspected (c) by a EU Member State.

The Commission excludes, for legal, technical and political reasons, the possibility to postpone the entry into force of the new rules.

Therefore, it is crucial for industry, the Commission, the Agency, and Member States to take risk-preventive measures.

3.1. Measures to be taken by EU-industry

Manufacturers of medicinal products in the EU should take the following steps:

- Industry should 'map' the sources of their active substances and ensure that the active substance supplier provides it with the 'written confirmation'. As the 'written confirmation' has a validity set by the issuing third country, the importer of the active substance should ask the written confirmation to the authority in the third country immediately.

3.2. Measures taken by the Commission

- The Commission continues to assess swiftly all third countries which request to be listed.

- The Commission continues to raise awareness of the incoming rules and ensures that the implementation is not unnecessarily burdensome.

3.3. Measures taken by the Agency

- The Agency is currently conducting the 'mapping' referred to in point 2.6..

3.4. Measures to be taken by Member States

- Member States should step up inspections of active substance manufacturing sites in third countries. This is done in cooperation with the Agency (Article 111(1) of Directive 2001/83/EC). When planning those activities, a risk-mapping similar to that done by the Agency should be carried out.

Delegates are invited to comment on these risk-management measures.

Annex 1: Additional "Q&A" of the Commission Questions and Answers Document

Q&A 18a: Question: Regarding the written confirmation of 'equivalent' standards of good manufacturing practice, can the issuing authority of the non-EU country base itself on inspection results from EU authorities or other authorities applying equivalent standards for good manufacturing practice, such as US FDA?

Answer: Yes.

Q&A 18b: Question: Regarding the written confirmation of 'equivalent' standards of good manufacturing practice, can the issuing authority of the non-EU country base itself on inspections conducted in the past?

Answer: Yes. It is not necessary to conduct an inspection specifically for the purpose of issuing the 'written confirmation'.

Q&A 29a: Question: How does a non-EU country request to be listed?

Answer: The request is made by way of a letter to the responsible Director-General, Ms Paola Testori Coggi (Paola.Testori@ec.europa.eu, office B232 07/058, BE-1049 Brussels, Belgium). It should contain the relevant information for conducting the 'equivalence assessment'. A list of that information is published here: http://ec.europa.eu/health/human-use/quality/index_en.htm#ias.

In the alternative, the request is made by way of a short letter to the responsible Director-General, and the relevant information is sent as follow-up information to the responsible service within the Commission (sanco-pharmaceuticals-d6@ec.europa.eu).

Q&A 29b: Question: By when should the request to be listed be made?

Answer: The request should be listed as soon as possible. It is strongly recommended to make the request before end-2012.

If the request is made late, it may be impossible to conclude the equivalence-assessment before the date of application of the rules in July 2013.

Annex 2: Standard 'Roadmap' for the 'equivalence-assessment' of the Commission provided for in Article 111b of Directive 2001/83/EC

1. Request by Third Country (TC) to COM to be listed in accordance with Article 111b of Directive 2001/83/EC

    - The request should contain the information set out in appendix 1.

2. Acknowledgement of receipt by COM

    - Highlighting the need for additional information (where necessary);

    - Requesting contact details of a person at operational level (if not yet submitted).

3. COM establishes 'assessment team' consisting of SANCO-D, SANCO-F (FVO), EMA, Member States

    - Requesting availability of MS through GMDP/IWG

4. Desk-based assessment of equivalence of rules in the TC (led by SANCO-D)

    - Assessment of legislation, guidance documents, standards, etc.

    - Taking account of membership in relevant international fora (ICH, PIC/S, etc.)

    - Possibly telephone-conferences with TC for clarifications

    - See appendix 2.

5. Decision whether on-site review and observed inspection is required, in accordance with Article 111b(1) of Directive 2001/83/EC

6. Fixing of meetings with competent authority in the TC and observed inspections

7. Trip of assessment team to TC

8. (Where a visit has been performed) Draft report submitted to TC detailing findings, conclusions (including significance), and recommendations on improvement

9. Issuing (or not) COM Decision including a TC in the 'list' referred to in Article 111b of Directive 2001/83/EC

Appendix 1: Documentation/information submitted with a request for listing

1. The identity of the national body responsible for registration/authorisation API manufacturers and carrying out inspections in those sites.

2. Contact details of person at operational level for technical follow-up questions.

3. The national legislation, implementing provisions and other relevant information relating to the manufacture of APIs (including the registration/authorisation of manufacturers) in order to ensure quality and purity of the active substances. Copies of legislation and implementing provisions should be provided and the relevant sections highlighted. If the legislation is not in one of the working languages of the Commission (English, French or German), a translated version should be provided.

4. Information as to whether these provisions are identical with internationally-agreed guidelines, such as those of the ICH Q7 or WHO and, if not identical, where precisely they differ.

5. The national legislation, implementing provisions and other relevant information relating to inspections of API manufacturers, including the risk prioritisation process for selecting sites to be inspected and the frequency of inspections.

6. The total number and list of registered API manufacturers in the country and (where numbers are available) those exporting APIs to the EU. Please also list those sites which have been inspected in the last calendar year and in this calendar year to date.

7. The total number of inspectors and the average number of API sites inspected annually per inspector.

    - the minimum qualifications required of inspectors;
    - the professional training required to be followed by inspectors;
    - the inspection procedures;
    - the format of the inspection report;
    - actions taken to follow-up inspections findings;
    - the enforcement powers and sanctions available.

8. Information (and reference) whether the legislative and implementing provisions referred to in points 2 and 4 apply to sites manufacturing APIs *exclusively* destined for export.

9. The legislative and implementing provisions relating to the importers and the import of APIs into your country.

10. (In the case there is an MRA in place which covers APIs) An overview of any legislative and implementing provisions which have been adopted or which have entered into force subsequent to conclusion of the MRA.

11. The prospective timetable for the inspections of API manufacturers for the next 12 months (to plan the on-site visit).

12. (Where already in place) The mechanisms in order to ensure regular and rapid provision of information by the third country to the EU in relation to non-compliant producers of APIs

Appendix 2: Criteria for verification

	Relevant EU-rules	Issues of substance	Remarks
Rules for GMP for active substances	Part II of Volume 4 of EudraLex Rules on biological and steriles		= ICH Q7 = WHO GMP for API
Regularities of inspections	Compilation of Community Procedures (CoComP)		
Effectiveness of enforcement	Directive 2001/83/EC CoComP		
Registration/authorisation requirement for manufacturers, importers			
Inspections		Inspection resources, the qualification and training of inspectors, inspection procedures, inspection strategies and mechanisms to address conflicts of interest, inspection performance standards, enforcement powers, alert and crisis mechanisms, and analytical capacity	See work conducted by the compliance group of the GMP/GDP inspectors working group, as well as work of PIC/S
Other enforcement issues			
Third country's arrangements in order to ensure regular and rapid provision of information by the third country to the EU in relation to non-compliant producers of active substances.			