



PHARMACEUTICAL COMMITTEE
27 March 2013

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

Agenda item 3c, 2nd indent

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.

2. STATE OF PLAY OF IMPLEMENTATION AT EU-LEVEL

The Commission has reached out to a multitude of stakeholders and third country governments in order to raise awareness of the incoming rules. Annex 1 contains a state of play for information.

3. UPDATE OF Q&A DOCUMENT

In the context of the implementation of the rules the Commission has published and revised a "Questions and Answers" ("Q&A") document.

Annex 2 contains additional Q&As.

It is planned to add these Q&As to the Q&A document (see <u>annex 2</u>). Are there any objections from the delegates?

Annex 1:

New rules on API quality in the EU; Preparation with regard to exporting third countries – state of play (top 18 API exporters to the EU, plus South Africa and Ukraine)¹

Third country	Number of API manufacturing sites supplying EU ²	Option 1 (written confirmation) or option 2 (listing)	State of play
India	496	Option 1	Good progress, but more work needed – in particular by industry stakeholders. IND government has announced that the 'Drug Controller General' (i.e. central agency) is going to issue 'written confirmation'. Implementation guidelines have been published. ³
China	438	Option 1	Good progress, but more work needed – in particular by industry stakeholders. CHN has announced ⁴ that it will issue written confirmation. A ' notice ⁵ has previously been published. However, SFDA has already informed COM that it would not issue 'written confirmation' for manufacturing sites which are not under SFDA's supervision. This concerns about 30 sites. EMA is coordinating the inspections of these sites (option 3).
U.S.	186	Option 2	Situation under control. On-site audit visit by COM in mid-May 2013. The US FDA has issued a supportive public statement . ⁶
Japan	108	Option 2	Situation under control. On-site audit visit by COM in mid-April 2013.
Switzerland	67	Option 2	Situation under control. Listed.
Korea	37	Option 1	Situation under control. Korea has issued written confirmation.
Israel	36	Option 1; then 2	Situation under control. Listing had to be refused for the time being. Israel has issued written confirmation.
Mexico	35	Option 1, then 2	Situation under control. MEX has confirmed in writing that it would issue written confirmation and later apply for listing.
Brazil	23	Option 1, then 2	Situation under control. BRA has applied for listing. However, documentation has not been received yet. As soon as COM receives the information, COM starts the 'equivalence assessment'. In the interim, BRA will have to issue written confirmation.
Canada	17	Option 1	Situation under control. CAN has informed COM in writing that it would issue written confirmation.
Taiwan	16	Option 1	Situation under control. TWN has sent informally a copy of the written confirmation it intends to issue.

¹ These 20 countries account for 97% of all non-EU API manufacturing sites supplying the EU.

² Survey of the 'Heads of Medicines Agencies' amongst medicines manufacturers in the EU. Duplicates have been removed by MHRA. However, this figure does not take account of the possibility of manufacturers to substitute one API source by another one.

³ <http://www.cdsc.nic.in/api%20wc2013.htm>

⁴ Translation: *SFDA Will Issue Written Confirmation for Enterprises Exporting APIs to the EU, Published on 20 Feb 2013 at 17:15 by CCCMHPIE. On 20 February 2013, chaired by Mr. LI Guoqing (Director General, Department of Drug Safety & Inspection, SFDA), SFDA held the Seminar on Issuing Written Confirmation for Enterprises Exporting APIs to the EU in Beijing. SFDA Deputy Commissioner Mr. WU Zhen attended the Seminar and made important instruction. Vice present of CCCMHPIE Mr. XU Ming also attended the meeting and reported to the Seminar the problems that Chinese APIs exporting enterprises are facing and presented the operational suggestions of issuing Written Confirmation. Representatives from MoFCOM (Department for Foreign Trade, Department for European Affairs), other relevant SFDA departments, local food and drug administrations, and enterprises also attended the meeting. The seminar made it clear that SFDA will issue Written Confirmation for Enterprises exporting APIs to the EU. Relevant notice and detailed implement ru will be published soon. Mr. CAO Gang and Mrs HE Chunhong from CCCMHPIE also attended the Seminar.*

⁵ Translation: *Notice on SFDA's intention to carry out thorough investigation on the basic information of Chinese APIs exporters - According to the EU Directive 2011/62/EU, the Department of Drug Safety & Inspection of SFDA hereby publish the notice on the initiative of carry out thorough investigation on the basic information of Chinese APIs exporters (Reference No.: [2013] No. 14) in order to investigate thoroughly the basic information of APIs producers and to improve the bilingual (EN/CN) SFDA database of APIs. The investigation form can be downloaded from here: [form attached]. 18 January 2013. Department of Drug Safety & Inspection SFDA.*

⁶ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ImportsandExportsCompliance/ucm336570.htm>

Argentina	12	Option 1	More work needed – in particular by industry stakeholders. In addition, COM is in contact with ARG authorities.
Turkey	12	Option 1	Situation under control. TUR has informed COM that it would issue written confirmation.
Malaysia	7	Option 1	More work needed – in particular by industry stakeholders. In addition, COM is in contact with MYS authorities.
Singapore	7	Option 1, then 2	Situation under control. Listing had to be refused for the time being. SGP has confirmed in writing that it would issue written confirmation until issue is solved.
Thailand	6		More work needed – in particular by industry stakeholders. In addition, COM is in contact with THA authorities.
Australia	5	Option 2	Situation under control. The equivalence assessment for AUS is almost concluded.
Russia	5	Option 1	More work needed – in particular by industry stakeholders. RUS has informed COM in a meeting that they are going to issue written confirmation.
Ukraine	4	Option 1	Situation under control. UKR has issued written confirmation.
South Africa	2	Option 1	Situation under control. ZAF has issued written confirmation.

Annex 2: Additional "Q&A" of the Commission Questions and Answers Document

Q&A 2a: Question: Do the rules on the written confirmation also apply to blood plasma?

Answer: No. However, processed derivatives of plasma having a pharmacological, immunological or metabolic action are considered as active substance and written confirmation is thus required.

Q&A 10a: Question: Is written confirmation also required for starting material used for the production of an active substance, for example by way of purification or further synthesis?

Answer: No. Such starting material does not fulfil the definition of Article 1(3a) of Directive 2001/83/EC.

Q&A 11b: Question: Is written confirmation also required for "atypical active substances"?

Answer:

"Atypical active substances" are those substances which primary use is not in a medicinal product, and the producer may therefore not be aiming to meet the specific requirements of pharmaceutical customers that represent an insignificant volume of business. They are addressed in the "questions and answers document" of the European Medicines Agency on good manufacturing practice⁷ (section "EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances", point 6).

It is recognised that the situation described under point 6 of that document also applies in the context of 'written confirmation'. The approach and reasoning set out in that document also applies to the requirement for written confirmation.

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca#section2