



Brussels,

IMPORTATION OF ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE

QUESTIONS AND ANSWERS

VERSION 7

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Important notice: The views expressed in this questions and answers document are not legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Union law.

This documents sets out frequently-asked 'questions and answers' regarding the new rules for the importation of active substances for medicinal products for human use.

These rules are contained in Articles 46b and 111b of Directive 2001/83/EC.

The 'written confirmation' is addressed in Article 46b(2)(b) of Directive 2001/83/EC.

¹ http://ec.europa.eu/health/documents/pharmaceutical-committee/index_en.htm

1. QUESTION: WHEN DO THE NEW RULES FOR THE WRITTEN CONFIRMATION APPLY?

Answer: They apply as of 2 July 2013. Any active substance imported into the EU from that date is subject to the rules on the written confirmation.

2. QUESTION: DO THE RULES ON THE WRITTEN CONFIRMATION ALSO APPLY TO ACTIVE SUBSTANCES FOR VETERINARY MEDICINAL PRODUCTS?

Answer: No. The rules apply only to active substances for medicinal products for human use.

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.

3. QUESTION: DO THE RULES ON THE WRITTEN CONFIRMATION APPLY TO ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS INTENDED FOR RESEARCH AND DEVELOPMENT TRIALS?

Answer: Active substances imported to be used in the manufacture of non-authorised medicinal products intended for research and development trials are excluded from the rules.

Active substances imported to be used in the manufacture of authorised medicinal products intended for research and development trials are expected to fulfil the requirements of Directive 2001/83/EC and be accompanied by a written confirmation, unless there is proof that the full amount of the imported API will be used for the manufacture of batches/units of an authorised medicinal product exclusively intended for research and development trials. In the latter case, those batches/units of an authorised medicinal product fall outside the scope of Directive 2001/83/EC and the API used in their manufacture is exempted from the rules on the written confirmation.

4. QUESTION: DO THE RULES ON THE WRITTEN CONFIRMATION APPLY TO ACTIVE SUBSTANCES WHICH ARE BROUGHT INTO THE EU WITHOUT BEING IMPORTED ('INTRODUCED' ACTIVE SUBSTANCES)? AN EXAMPLE IS THE INTRODUCTION OF AN ACTIVE SUBSTANCE WHICH IS SUBSEQUENTLY EXPORTED.

Answer: No. The rules on the written confirmation only apply to the *import* of active substances for medicinal products for human use.

- 5. QUESTION: WHAT IF, AT THE TIME OF EXPORT OF AN ACTIVE SUBSTANCE TO THE EU, IT IS NOT KNOWN WHETHER THE ACTIVE SUBSTANCE IS USED IN A MEDICINAL PRODUCT FOR HUMAN USE OR NOT?**

Answer: If the consignment is not accompanied by a written confirmation, the active substance cannot be used in a medicinal product for human use.

- 6. QUESTION: IS THE WRITTEN CONFIRMATION EXPECTED TO CONFIRM COMPLIANCE WITH EU-RULES?**

Answer: No. The written confirmation has to confirm compliance with GMP rules 'equivalent' to the rules applied in the EU.

- 7. QUESTION: IN MY NON-EU COUNTRY, THE APPLICABLE STANDARDS FOR MANUFACTURING OF ACTIVE SUBSTANCES ARE THE GOOD MANUFACTURING PRACTICES FOR ACTIVE SUBSTANCES OF THE WORLD HEALTH ORGANISATION (WHO) – FORTY-FOURTH TECHNICAL REPORT, No. 957, 2010, ANNEX 2. ARE THESE STANDARDS EQUIVALENT TO THOSE IN THE EU, AS REQUIRED ACCORDING TO EU LEGISLATION?**

Answer: Yes.

- 8. QUESTION: IN MY NON-EU COUNTRY, THE APPLICABLE STANDARDS ARE ICH Q7. ARE THESE STANDARDS EQUIVALENT TO THOSE IN THE EU, AS REQUIRED ACCORDING TO EU LEGISLATION?**

Answer: Yes.

- 9. QUESTION: DOES THE WRITTEN CONFIRMATION HAVE TO BE ISSUED BY A CENTRAL, REGIONAL OR LOCAL AUTHORITY?**

Answer: Each non-EU country decides autonomously which body within that country issues the written confirmation. That non-EU country may decide to issue the written confirmation at central, regional or local level.

- 10. QUESTION: DO THE RULES APPLY ALSO TO ACTIVE SUBSTANCES CONTAINED IN AN IMPORTED FINISHED MEDICINAL PRODUCT?**

Answer: No. Regarding finished medicinal products, the rules for importation of finished medicinal products (importation authorisation and batch release by a qualified person, see Articles 40(3) and 51 of Directive 2001/83/EC) apply. These rules remain unchanged.

10A: QUESTION: IS WRITTEN CONFIRMATION ALSO REQUIRED FOR A STARTING MATERIAL OR AN INTERMEDIATE USED FOR THE PRODUCTION OF AN ACTIVE SUBSTANCE, FOR EXAMPLE BY WAY OF PURIFICATION OR FURTHER SYNTHESIS?

Answer: No. Such starting material or intermediate used for the production of an active substance does not fulfil the definition of Article 1(3a) of Directive 2001/83/EC.

11. QUESTION: IS THE WRITTEN CONFIRMATION ALSO REQUIRED FOR IMPORTED ACTIVE SUBSTANCES WHICH HAVE ALREADY BEEN MIXED WITH EXCIPIENTS, WITHOUT YET BEING THE FINISHED MEDICINAL PRODUCT?

Answer: No. Such partial manufacturing of the finished product is not included in the rules on the written confirmation.

11A. QUESTION: IS THE WRITTEN CONFIRMATION ALSO REQUIRED WHERE THE FINISHED DOSAGE FORM MANUFACTURED IN THE EU IS DESTINED FOR EXPORTATION ONLY?

Answer: Yes.

12. QUESTION: WHO CHECKS THAT THE IMPORTED ACTIVE SUBSTANCE IS ACCOMPANIED BY THE WRITTEN CONFIRMATION?

Answer: This should be checked by the receiving manufacturer of the finished medicinal product. It may also be checked by the importer of the active substance upon its importation.

The verification whether such checks take place depends on the transposing law of the Member State where the active substance is imported. It may be verified

- by the relevant authority upon importation; and/or
- in the context of an inspection of the importer of the active substance, and/or
- in the context of an inspection of the manufacturer of the medicinal product that uses the imported active substance.

13. QUESTION: HOW CAN I CHECK IF THE WRITTEN CONFIRMATION IS AUTHENTIC?

Answer: You should contact the manufacturer of the active substance or the issuing authority in the non-EU country.

14. QUESTION: IS THE WRITTEN CONFIRMATION SENT TO AN EU REGULATORY AGENCY?

Answer: No. The written confirmation accompanies the imported active substance.

15. QUESTION: DOES THE WRITTEN CONFIRMATION HAVE TO BE SUBMITTED WITH A REQUEST FOR AUTHORISATION OF A MARKETING AUTHORISATION OF A MEDICINAL PRODUCT?

Answer: No.

16. QUESTION: IS THE WRITTEN CONFIRMATION TO BE ISSUED FOR EACH BATCH/CONSIGNMENT'?

Answer: No. The written confirmation is issued per manufacturing plant and the active substance(s) manufactured on this site.

17. QUESTION: DOES EACH IMPORTED CONSIGNMENT HAVE TO BE ACCOMPANIED BY THE WRITTEN CONFIRMATION?

Answer: Yes.

18. QUESTION: IS IT ACCEPTABLE THAT THE WRITTEN CONFIRMATION ACCOMPANYING THE IMPORTED CONSIGNMENT OF THE ACTIVE SUBSTANCE IS A COPY?

Answer: Yes, provided that the original written confirmation is still valid.

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. In this case, the written confirmation should indicate which authority has inspected the site.

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'.

19. QUESTION: WHAT IS THE VALIDITY PERIOD OF THE WRITTEN CONFIRMATION?

Answer: The validity of the written confirmation is established by the issuing authority of the non-EU country.

19A. THE WRITTEN CONFIRMATION REFERS TO 'UNANNOUNCED INSPECTIONS'. DOES THIS MEAN THAT AN UNANNOUNCED INSPECTION HAS TO HAVE BEEN CONDUCTED?

Answer: No. Rather, the system of supervision as a whole (including different types of inspections, such as unannounced inspections) has to ensure a protection of public health at least equivalent to that in the EU.

20. QUESTION: IF ACTIVE SUBSTANCES ARE MANUFACTURED IN A NON-EU COUNTRY 'A', BUT IMPORTED IN THE EU VIA THE NON-EU COUNTRY 'B', WHO HAS TO ISSUE THE WRITTEN CONFIRMATION?

Answer: The written confirmation accompanying the imported active substance has to be issued by the non-EU country where the active substance is manufactured (i.e. non-EU country 'A').

21. QUESTION: THE TEMPLATE FOR THE WRITTEN CONFIRMATION REFERS TO A 'CONFIRMATION NUMBER'. DOES THIS NUMBER HAVE TO BE A SEQUENTIAL NUMBER PER COUNTRY?

Answer: No. This number would be attributed by the issuing authority of the non-EU country.

22. QUESTION: THE TEMPLATE FOR THE WRITTEN CONFIRMATION REFERS TO A 'RESPONSIBLE PERSON' IN THE ISSUING AUTHORITY. DOES THIS RESPONSIBLE PERSON HAVE TO HAVE A SPECIFIC QUALIFICATION?

Answer: No. The 'responsible person' in this context is the person responsible within the administration for issuing the written confirmation.

23. QUESTION: ACCORDING TO THE TEMPLATE FOR THE WRITTEN CONFIRMATION, INFORMATION OF FINDINGS RELATING TO NON-COMPLIANCE ARE SUPPLIED TO THE EU. TO WHOM THIS INFORMATION SHOULD BE SENT TO?

Answer: The information should be sent to the European Medicines Agency (qdefect@ema.europa.eu).

24. QUESTION: IS THE WRITTEN CONFIRMATION ALSO REQUIRED WHERE THERE IS A 'MUTUAL RECOGNITION AGREEMENT' BETWEEN A NON-EU COUNTRY AND THE EU?

Answer: Yes. The process of a written confirmation is independent of the existence of 'mutual recognition agreements'.

25. QUESTION: IF A MANUFACTURING PLANT IS LOCATED IN A NON-EU COUNTRY 'A', CAN THE WRITTEN CONFIRMATION BE ISSUED BY AN AUTHORITY IN ANOTHER NON-EU COUNTRY (NON-EU COUNTRY 'B')?

Answer: No.

26. QUESTION: ARE THERE EXCEPTIONS FROM THE REQUIREMENT OF A WRITTEN CONFIRMATION?

Answer: The Commission publishes a list of countries which, following their request, have been assessed and are considered as having equivalent rules for good manufacturing practices to those in the EU. Active substances manufactured in these countries do not require a written confirmation.

See also Questions n° 27 and 28.

27. QUESTION: WHERE CAN I FIND THE LIST OF NON-EU COUNTRIES TO WHICH THE REQUIREMENT OF A WRITTEN CONFIRMATION DOES NOT APPLY?

Answer: The list is published in the *Official Journal of the European Union* and also reproduced here: http://ec.europa.eu/health/human-use/quality/index_en.htm.

28. QUESTION: HOW MANY NON-EU COUNTRIES HAVE SO FAR REQUESTED TO BE LISTED?

Answer: A list of non-EU countries which have so far requested to be listed is available here: http://ec.europa.eu/health/human-use/quality/index_en.htm.

29. QUESTION: WHEN IS THE LIST GOING TO BE PUBLISHED BY THE COMMISSION?

Answer: The Commission is going to publish an additional non-EU country on the list once its equivalence assessment has been finalised. The equivalence-assessment takes several months from the request from the non-EU country.

29: QUESTION: HOW DOES A NON-EU COUNTRY REQUEST TO BE LISTED?

Answer: The request is made by way of a letter to the Director-General of DG SANTE. It should contain the relevant information for conducting the 'equivalence assessment'. More information on the procedure and the documents to be submitted is available here: http://ec.europa.eu/health/human-use/quality/index_en.htm, under the section "Listing of third countries".

The relevant information can also be sent directly to the responsible service within the Commission (sante-pharmaceuticals-b4@ec.europa.eu).

30. QUESTION: DO I NEED A WRITTEN CONFIRMATION, EVEN THOUGH MY MANUFACTURING SITE HAS RECENTLY BEEN INSPECTED BY THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES (EDQM) OF THE COUNCIL OF EUROPE?

Answer: Yes. The process of a written confirmation is independent of such inspection activities. See also Question n° 31.

31. QUESTION: DO I NEED A WRITTEN CONFIRMATION, EVEN THOUGH MY MANUFACTURING SITE HAS RECENTLY BEEN INSPECTED BY AN EU MEMBER STATE?

Answer: Yes. The process of a written confirmation is independent of such inspection activities. However, exceptionally and where necessary to ensure the availability of medicinal products, following inspections by an EU Member State, a Member State may decide to waive the need for a written confirmation for a period not exceeding the validity of the GMP certificate ('waiver').

32. QUESTION: I WOULD LIKE TO BE INSPECTED BY AN EU MEMBER STATE. WHERE DO I 'APPLY' FOR SUCH AN INSPECTION?

Answer: You should address through

- any registered importer of the active substance;
- any holder of a manufacturing authorisation that uses the active substance;
- any holder of a marketing authorisation that lists the active substance manufacturer

to the national competent authority of the EU Member State where they are established.

33. QUESTION: WHAT HAPPENS WHEN AN ACTIVE SUBSTANCE MANUFACTURING SITE COVERED BY A WRITTEN CONFIRMATION IS FOUND GMP NON-COMPLIANT FOLLOWING AN INSPECTION BY AN EU MEMBER STATE?

Answer: A statement of GMP non-compliance issued by a EU Member State for a specific site and API supersedes the corresponding written confirmation until the non-compliance is resolved.

34. QUESTION: WHERE CAN I FIND A LIST OF ACTIVE SUBSTANCE MANUFACTURING SITES THAT RECEIVED STATEMENTS OF GMP NON-COMPLIANCE?

Answer: Statements of GMP non-compliance are stored in the EudraGMDP database (<http://eudragmdp.eudra.org/inspections/displayWelcome.do>) and publicly available.

35. QUESTION: CAN AN API BATCH MANUFACTURED DURING THE PERIOD OF VALIDITY OF A WRITTEN CONFIRMATION BE IMPORTED INTO THE EU ONCE THE WRITTEN CONFIRMATION IS EXPIRED?

Answer: Article 46(b)(2)(b) sets out that active substances can only be imported if manufactured in accordance with EU GMP or equivalent, and accompanied by a written confirmation from the competent authority of the exporting third country certifying, inter alia, that (1) the GMP standards applicable to the manufacturing plant are equivalent to those of the EU, and (2) the supervision of the plant compliance with GMP ensures a protection of public health equivalent to that of the EU.

It is legitimate to consider that the guarantees of equivalence provided by the written confirmation apply to any API batch in the scope of the written confirmation which was released for sale within the period of validity of the written confirmation, even if not exported in that time period.

Against this background, it can therefore be considered that the importation into the EU of an API accompanied by an expired WC is acceptable provided that the paperwork accompanying the consignment (1) unequivocally proves that the whole consignment has been manufactured and released for sale by the quality unit before the expiry date of the written confirmation; and (2) provides a solid justification of why a valid written confirmation is not available.

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