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

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DELEGATED ACT ON THE PRINCIPLES AND GUIDELINES OF GOOD MANUFACTURING PRACTICE FOR ACTIVE SUBSTANCES IN 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 places an obligation on Member States to take appropriate measures to ensure that manufacturers of active substances on their territory comply with good manufacturing practice ('GMP') for active substances.[3]

3. It also places an obligation on the Commission to adopt, by means of delegated acts,[4] the principles and guidelines of good manufacturing practice for active substances.[5]

4. This concept paper is being released for public consultation with a view to preparing the delegated act.

5. The adoption of the delegated act is planned for 2013.

Stakeholders are invited to comment on this consultation paper, and especially on the boxed text, by 20 April 2012 at the latest. Responses should be sent preferably by e-mail to sanco-pharmaceuticals-d6@ec.europa.eu, or by post to Unit SANCO/D/6, DM24/028, 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 (patients, manufacturers, wholesale distributors, 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.

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1 OJ L 174, 1.7.2011, p. 74.

2 OJ L 311, 28.11.2001, p. 67. A consolidated version of Directive 2001/83/EC including the amendments made by Directive 2011/62/EU is available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20110721:EN:PDF.

3 Article 46b(1) of Directive 2001/83/EC.

4 The measures may be contained in one delegated act or several delegated acts. For the purpose of this document reference is made to 'delegated act'.

5 Third paragraph of Article 47 of Directive 2001/83/EC.

1. Extension of the Directive on GMP for medicinal products to active substances

6. The Commission has adopted, on 8 October 2003, Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.[6]

7. Directive 2003/94/EC lays down the principles and guidelines in a comparatively broad manner. The interpretation of these principles and guidelines provided in the detailed guidelines published by the Commission[7] in EudraLex - Volume 4, Part I.[8]

8. Similarly, detailed guidelines on good manufacturing practices for active substances (ICH Q7) have been published by the Commission in EudraLex – Volume 4, Part II.[9]

9. Against this background it is therefore currently envisaged to **extend the scope of Directive 2003/94/EC to active substances**. Consequently, subject to certain modifications (see below), the provisions of Directive 2003/94/EC would also apply to the manufacturing of active substances.

10. This approach would bring coherence:

- in terms of the regulatory setting (Commission Directive plus detailed Commission guidelines) for both medicinal products and active substances; and

- in terms of substance: the principles and guidelines for GMP would be the same during the manufacturing of active substances as well as medicinal products.

Moreover, this approach would allow relatively swift adoption of GMP for active substances, thus giving legal clarity to Member States and stakeholders.

Consultation item No 1: Do you agree with this appraisal and approach? Please comment.

2. Adaptation of regulatory requirements of Directive 2003/94/EC to active substances

11. In line with the approach to extend the scope of Directive 2003/94/EC to active substances, **all provisions in that Directive which currently address the manufacturing or manufacturer of medicinal products would also apply to the manufacturing and manufacturer of active substances**. However, it is acknowledged that some of the current provisions in Directive 2003/94/EC either

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[6] OJ L 262, 14.10.2003, p. 22. The text is available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32003L0094:EN:NOT.

[7] Second subparagraph of Article 47 of Directive 2001/83/EC, Article 3(2) of Directive 2003/94/EC.

[8] http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm.

[9] http://ec.europa.eu/health/files/eudralex/vol-4/2007_09_gmp_part2_en.pdf.

cannot apply to active substances (see point 2.1) or will have to be amended (see point 2.2). Moreover, some further provisions specific to active substances could be added (see point 2.3).

2.1. Provisions in Directive 2003/94/EC that would not apply to active substances

12. As a general rule, the following provisions in Directive 2003/94/EC would not apply to active substances:

- Provisions reflecting specific rules for medicinal products contained in Directive 2001/83/EC. This includes the rules in Directive 2003/94/EC that build on the following:
  - Marketing authorisations for medicinal products (the placing on the market of active substances per se is not subject to a marketing authorisation);
  - Qualified persons (the concept of 'qualified person' does not apply to active substances); and
  - Manufacturing authorisations for the manufacturing of medicinal products (the manufacturing of active substances is not subject to a manufacturing authorisation[10]).
- Provisions addressing investigational medicinal products (these products are outside the scope of Directive 2001/83/EC[11] and thus outside the scope of its rules on active substances).

13. Consequently, the following provisions in Directive 2003/94/EC would not apply to active substances:

- Article 4(1) ('Conformity with good manufacturing practice') – insofar as it relates to the manufacturing authorisation: The manufacturing of active substances is not subject to an authorisation.
- Article 4(2) ('Conformity with good manufacturing practice'): Regarding importation, Directive 2001/83/EC contains specific rules in Article 46b(2) to (4);
- Article 7(2) ('Personnel') – insofar as it relates to the qualified person: The concept of 'qualified person' does not apply to active substances;
- Article 9(1) second sub-paragraph ('Documentation') – insofar as it relates to Article 51(3) of Directive 2001/83/EC: The obligation in Article 51(3) of Directive 2001/83/EC does not apply to active substances;
- Article 11(2) first sub-paragraph ('Quality control') – Article 20(b) of Directive 2001/83/EC does not apply to active substances;

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[10] Article 52a of Directive 2001/83/EC.

[11] Article 3(3) of Directive 2001/83/EC.

- Article 12(2) ('Work contracted out') – insofar as it relates to the qualified person: The concept of 'qualified person' does not apply to active substances;

- Article 13(1) second sub-paragraph ('Recalls'): Article 123 of Directive 2001/83/EC does not apply to active substances;

- All provisions relating to investigational medicinal products, including the provision on unblinding and labelling of investigational medicinal products.

Consultation item No 2: Are there other aspects which should be considered? Please comment.

2.2. Provisions in Directive 2003/94/EC that would need to be amended

14. In addition, the following provisions in Directive 2003/94/EC would need to be amended:

- Article 1 ('Scope'): The scope would be extended to active substances;

- Article 2 ('Definitions'):

  – The definition of 'active substance' contained in Article 1(3a) of Directive 2001/83/EC would be added;

  – The definition of 'manufacturer' contained in Article 46a(1) of Directive 2001/83/EC would be added.

Consultation item No 3: Do you consider this list complete? Please comment.

2.3. Other provisions on active substances that could be added to Directive 2003/94/EC

15. Another point which could be considered is whether to add to Directive 2003/94/EC provisions specific for active substances.

16. In particular, an obligation could be placed on the manufacturer of the active substance to make ensure that the starting material[12] is sourced from the premises claimed by the manufacturer of the starting material.

Consultation item No 4: Do you agree with this specific point? Do you consider that other provisions specific to active substances should be added?

3. Other issues

3.1. Date of transposition of the delegated act

17. The delegated act would take the form of a Directive, which requires transposition into the national law of the Member States.

18. In line with the transposition timeline in Directive 2003/94/EC, the time limit for transposition would be 6 months after publication of the delegated act at the latest.[13]

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[12] In this context the definition of 'starting material' as contained in Part I, Section 3.2.11.b of Annex I to Directive 2001/83/EC would be used.

3.2. Date of application of the delegated act

19. The date of *application* of the delegated act and the national laws transposing it would be set later than the date of transposition at nine months after publication of the delegated act.

Consultation item No 5: Please comment on section 3. Please raise any other issues or add any other comments you wish to make which have not been addressed in the consultation items set out above.

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[13] The delegated act is published after the right of opposition by the co-legislators in accordance with Article 121c of Directive 2001/83/EC has expired. For details on the procedural aspects for delegated acts see Commission Communication COM(2009) 673 – 'Implementation of Article 290 of the Treaty on the Functioning of the European Union' at http://eur-lex.europa.eu/Result.do?checktexts=checkbox&TypeAffichage=sort_key&page=1&idReq=1&Submit22=GO.