MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

DIRECCIÓN DE LA
AGENCIA ESPAÑOLA
DE MEDICAMENTOS Y
PRODUCTOS SANITARIOS

COMMENTS TO THE CONCEPT PAPER ON THE DELEGATED ACT ON THE PRINCIPLES AND GUIDELINES OF GOOD MANUFACTURING PRACTICE FOR ACTIVE SUBSTANCES IN MEDICINAL PRODUCTS FOR HUMAN USE
FROM: AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

Consultation item No. 1:
We agree on the aims pursued with the extension of the Directive of good manufacturing practice (GMP) for medicinal products to active substances.

Consultation item No. 2:
Some of the exclusions listed under point 13 of the document should be revised or further refined:

- Concerning the first bullet point, the manufacturing of certain active substances, such as biological or sterile active substances, may be subject to the holding of an authorization. This is acknowledged by the Community format of manufacturing authorization published in Agreement with the European Commission (see Annex 1, Part 1, sections 1.4.1.3 and 1.4.2). Thus this general statement needs clarification.
- In the second bullet point, importation of active substances is considered as manufacture as per the definition in the Article 46a(1) of the Directive 2001/83/EC. However, obligations of active substance importers are not defined in current legislation or guidelines. We think that a clarification of the concept of 'importation of active substances' and the applicable requirements for this activity is needed. Moreover, it is necessary to clarify whether the 'importation of biological or sterile active substances' is to be considered differently to other active substances or if this activity should be subject to the holding of an authorization (MIA).
- Concerning the fourth bullet point, requirements set out in Article 51(3) of the Directive 2001/83/EC (existence of a register or equivalent document, kept for a period) are flexible and not incompatible with requirements of GMP – Part II. The existence of this document would be within inspector's expectations.
- In the seventh bullet point, a reference to recalls should be kept in the first sub-paragraph (although we agree that the reference to Article 123 of Directive 2001/83/EC in the second sub-paragraph would not apply), as active substances manufacturers are required to have a system in place for recalls as per ICH-Q7A detailed guidelines published by the Commission.

Consultation item No. 3:
In addition to the Articles mentioned in point 14, the following provisions in Directive 2003/94/EC should be amended:

- Article 3.1 should be amended to include a reference to paragraph 1b of Article 111 of Directive 2001/83/EC. In Article 3.2, a reference to the third paragraph of article 47 of Directive 2001/83/EC should be added.

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- Article 52 a of Directive 2001/83/EC, as amended by Directive 2011/62/EU, establishes the obligation for importers, manufacturers and distributors of active substances to register their activity with the competent authority of the Member State in which they are established. A reference to this registration should be made.
- Article 46b of Directive 2001/83/EC, inserted by Directive 2011/62/EU, sets out that the distribution of active substances, performed either by manufacturers or by distributors, shall comply with good distribution practices for active substances. Compliance with good distribution practices is also a requirement for manufacturers of active substances when distribution is concerned, so a reference to the need to comply with good distribution practices for active substances should be included. As there is no similar reference on Directive 2003/94/EC about the need to comply with good distribution practices of medicinal products for the manufacturers of medicinal products when distributing their products we suggest that it is also included.

We anticipate a revision of other elements of the Directive (e.g. recitals) as well.

Consultation item No. 4:
A reference to the obligation of the active substance manufacturer to comply with the information in the ASMF and to update it accordingly should be included.
This would include the obligation to ensure that starting materials for the manufacture of active substance are sourced from the right sources.

Consultation item No. 5:
The transposition time-limit of Directive 2003/94/EC was of 6 months, but this period is too short considering the process for amending regulations at a national level. A minimum timeframe of 1 year (12 months) should be considered. In this regard, guidelines for good manufacturing practices for active substances are already well established and enforced by Member States, and resources are shared among other activities stemming from Directive 2011/62/EU.

One last comment: Directive 2011/62/EU establishes the need to comply with good distribution practice for active substances for their distributors. For these entities there are no requirements in the mentioned Directive regarding its personnel, premises, quality system, only a generic obligation to comply with the mentioned good practices. Distributors of medicinal products have their requirements established in Title VII of Directive 2001/83. It should be considered the possibility to include some provisions for these entities in this Directive as the principles of good distribution practice are going to be adopted only as a Commission guidelines that could rise problems in their enforcement.

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