ASSOCIAZIONE ITALIANA COMMERCIO CHIMICO
AssICC
ITALIAN ASSOCIATION OF CHEMICAL TRADE

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Subject matter: AssICC comments to European commission draft paper, released for public consultation, with a view to preparing the "Delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use"

Dear Sirs,

In my quality of Secretary General of the Italian association of wholesale distributors of chemicals, I am please to provide you with our comments to the European Commission draft paper on the "Delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use" (see annex attached further below).

I remain at disposal should you need any additional information and/or clarifications on that respect.

Kind regards

AssICC
Secretary General

Dr. Rinaldo Canofari

Rinaldo Canofari

Unione CONFCOMMERCIO IMPRESE PER L'ITALIA MILANO · MONZA E BRIANZA

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Annex

AssICC comments to European commission paper released on "Delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use"

Preamble

AssICC is the Italian association of wholesale distributors of chemicals and includes, *inter alia*, wholesale distributors of active principles.

AssICC was funded on 1946 and since then it regularly assists and provides to its members a vast range of services, including legal and economic support.

AssICC groups together about 300 companies, representing 70% of Italian chemical distributors, equal to over 90% of total market turnover.

AssICC belongs to FECC, the European Association of Chemical Distributors, representing the chemical distribution industry in Europe. With a growing membership of companies and national associations, FECC represents around 1.400 companies of which many are also small and medium sized enterprises.

Please note that AssICC does not object that its contribution is made publicly available on the "Europa website" on pharmaceuticals once the consultation period is over.

Comments

1. EC TOPIC

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.
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 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. 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.

ASSICC
ITALIAN ASSOCIATION OF CHEMICAL TRADE

1. EC Consultation item

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

1. AssICC comment to Consultation item No 1

We agree with the approach of extending the scope of Directive 2003/94/EC to active substances and, as a consequence, the application of certain provisions of Directive 2003/94/EC, adequately modified, to the manufacturing of active substances.

We also agree the recalled approach might (i) 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; (ii) allow relatively swift adoption of GMP for active substances, thus giving legal clarity to Member States and stakeholders.

It should be noted, however, that by proceeding so, careful attention should be paid to the actual activity performed by each of the actors of the supply chain and to the definition of "manufacturer of active principles" provided by the legislation (see also further below).

In particular, the principles and guidelines for GMP applicable to manufacturing of medicinal products should also be applicable for the manufacturing of active substances, but the manufacturing of active substances should be clearly distinguished by activities that nothing have to do with manufacturing such as, for example, importation and wholesale distribution of active principles.

In case of medicinal products, indeed, "importation" is compared to "manufacturing" because once a medicinal product is imported in the EU it can be then administered to patients with not need to perform further additional analysis and/or controls. In case of active principles, on the contrary, "importation" should not be compared to "manufacturing" because once an active principle is imported in the EU it can not be administered to patients before further additional analysis and/or controls are performed (typically by the manufacturer of the finished medicinal product).

2. EC TOPIC

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 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 authorisation10).
• Provisions addressing investigational medicinal products (these products are outside the scope of Directive 2001/83/EC11 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;
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.

2. EC Consultation item

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

2. AssICC comment to Consultation item No 2

We agree with the approach of adapting “in principle” regulatory requirements of Directive 2003/94/EC to active substances.

However, the type of provisions currently applicable to manufacturing of medicinal products to be possibly applied also to the manufacturing of active substances and the extent of such application should be duly considered. In particular, clear distinction should be made between manufacturing activities and activities that not foreseen any intervention of the active principle commercialised. Moreover, the compliance with GMP of manufacturers of active principles may be advisable, although different rules should apply to manufacturers compared with distributor (see above).

We also agree that some of the current **provisions** in Directive 2003/94/EC **cannot apply** to active substances (see point 2.1 above).

As to it, in particular, we communicate as follows.

We fully agreed that the provisions above mentioned should not apply to active substances. Their application, indeed, would be not necessary (i.e. these tasks and obligation are already covered by other actors of the supply chain – e.g. manufacturers of the finished product) and not proportioned vis-à-vis to the activities performed and the objectives pursued by the Directive 2011/62/EU and by European legislation as a whole.

In light of the above and in order to ensure an harmonised implementation throughout the EU, however, we believe that European Commission Delegated act should clearly and adequately defined the reasons why these provisions should not be applicable to active principles and why different interpretation at national level should be avoided as contrary to a common European market.

In particular, we believe that it should be made clear in the Delegated act that obligations concerning qualified person, batch analysis and audits should not be applicable to active principles and, in particular (*a fortiori*), to all activities not involving manufacturing. The decision to exclude the application of said requirements should be motivated, in our opinion, by referring to the fact that the above requirements are (i) already complied with by manufacturers of finished medicinal products and (ii) clearly not applicable in case of import/wholesale of active principle that nothing has in common with manufacturing activities.

3.EC TOPIC

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.

3. EC Consultation item

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

3. AssICC comment to Consultation item No 3

We also agree that **some of the current provisions in Directive 2003/94/EC will have to be amended** (see point 2.2 of the Concept paper).

As to it, in particular, we communicate as follows:

- We agree with the extension to active substances of the scope of 2003/94/EC.

- We agree the definition of “active substance” contained in Article 1(3a) of Directive 2001/83/EC should be added to Directive 2003/94/EC.

- We only partially agree that the definition of "manufacturer" contained in Article 46a(1) of Directive 2001/83/EC[1] should be simply added to Directive 2003/94/EC for the following reasons.

  Manufacturers of active principles clearly perform manufacturing activities.

  Importers/wholesalers of active principles clearly do not perform manufacturing activities[2].

  It derives from the above, that manufacturers of active principles on one hands and importers/wholesalers of active principles on the other hands, have extremely different roles and that they can not be regarded, defined and treated in the same way.

  As to it, it should be noted, in particular, that Directive 2011/62/EU acknowledges the existence of many actors in the distribution chain of medicinal products, who are not necessarily manufacturers or wholesale distributors as referred to in Directive 2001/83/EC (see, *inter alia*, recital 6), and provides that an *ad hoc* discipline should be introduced for each of these players in compliance with the well known principle of proportionality. A confirmation on that respect (i.e. clear distinction between the different role of the actors of the chain) can also be found on a number of provisions of the Directive 2011/62/EU (see, *inter alia*, Recital 9: "[i]*n order to facilitate enforcement of and control of compliance with Union rules relating to active substances, the manufacturers, importers or distributors of those substances should notify the competent authorities concerned of their activities*.")

  In view of the profound differences between manufacturing activities on one side and importation and distribution activities on the other side, we believe essential to make clear in the definition of "manufacturer of active principles" that importation of active principles does not fall within said definition, because it does not concern and/or imply any intervention by the importer on the active principle commercialised (i.e. importers of active principles, indeed, only temporarily stock the product before delivering them to manufacturer and do not perform any additional activity such as production, packaging, repackaging, labelling, relabeling, quality control, release etc).

  Alternatively to the above, in case a definition of "manufacturer of active principles" encompassing also import and distribution of active principles is deemed preferable, we would strongly advice to make then extremely clear that requirements imposed for manufacturing of active principles should differ according to the activities actually performed by each of the actor of the supply chain (e.g. import importation of active principles).

  In particular, as to the difference between these two type of activities it should be remembered that all active principles imported in the EU and duly controlled before use

[1] See article Article 46a(1) of Directive 2001/83/EC "1. For the purposes of this Directive, manufacture of active substances used as starting materials shall include both total and partial manufacture or import of an active substance used as a starting material as defined in Part I, point 3.2.1.1 (b) Annex I, and the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labelling, such as are carried out by a distributor of starting materials."

[2] Please note that when we refer to the difference between manufacturing and importation of active principle we refer, of course, to cases where the importer (as typically happens) does not intervene upon the active principles commercialised by it, being understood that where any intervention on the active principles is made, this – according to the cases - might fall within the definition of manufacturing. Mere stock of active principles should therefore by excluded by the discipline applicable to manufacturing of active principles.

by manufacturers of the finished medicinal products and that any different approach will have as consequence the application of rules concerning manufacturing activities to activities that are clearly fall within wholesale distribution activities.

- In general, we would advice amending, to the extent needed, all those provisions that, as a result of the introduction of the definition of "manufacturer of active principles" - as per the expert opinion of the European Commission - might be interpreted as imposing to all actors of the supply chain obligations that are clearly not applicable to them. In other words, we would advice ensuring that where an actor of the supply chain is not involved in manufacturing activities (e.g. importers/wholesalers) this is duly reflected on the rules applicable.

4. EC TOPIC

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 is sourced from the premises claimed by the manufacturer of the starting material.

4. EC Consultation item

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

4. AssICC comment to Consultation item No 4

We agree that some further **provisions** specific to active substances could be **added** (see point 2.3 of the Concept paper).

As to it, in particular, we communicate as follows:

- We agree with the obligation for the manufacturer of the active substances to make ensure that the starting material is sourced from the premises claimed by the manufacturer of the starting material**.**

- Further provisions might be added necessary and/or suitable to differentiate import and distribution of active principles from manufacturing activities, including *ad hoc* obligations on information to be collected, archived and provided (upon request or proactively) to national competent authorities in order to ensure traceability of all products commercialised.

- We would add also a number of provisions specifically referable to importers/distributor of active principles, in order to ensure that, in the silence of community law, national implementation does not hinder harmonisation throughout the EU and the effective functioning of the common market.

5.EC TOPIC

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.

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.

5. EC Consultation item

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.

5. AssICC comment to Consultation item No 5

Ideally, it would be preferable that the delegated act make clear take that significant differences in the transposition into national law of the Member States might be avoided in order to ensure a harmonised application and approach throughout the entire European Union. In particular, differences possibly affecting EU Treaties fundamental freedoms should be excluded.

As to the timing of both "the transposition into national law of the delegated act" and "the application of the delegated act and the national laws transposing it", we agree with the approach proposed. As to it, it would be advisable, however, to encourage member states, pending the transposition period into national law of the delegated act, to non-apply national legislations that are in contrast with what provided by both Directive 2011/62/EU and the following relevant delegated act.

Moreover, it is advisable that the delegated act makes clear that member states freedom is limited to what is strictly necessary in order to put into practice the precise principles and rules set out at European level. National law, in other words, should not introduce additional burdens and/or obstacle to companies that are not justified by the protection of public health as indicate at European level (see also Recital 33 further below – cfr. "principle of proportionality" and need to not "go beyond" what is necessary in order to achieve the objective).

As to it (i.e. need to set out principles and rules at European level for the purpose of ensuring harmonisation throughout the EU) it should be noted, *inter alia*, what provided by Recital 33 of Directive 2011/62/EU that reads as follows: "*Since the objective of this Directive, namely to safeguard the functioning of the internal market for medicinal products, whilst ensuring a high level of protection of public health against falsified medicinal products, cannot be sufficiently achieved by the Member States, and can, by*

reason of the scale of the measure, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Directive does not go beyond what is necessary in order to achieve that objective."

As already stated above, we agree, in principle, that active substances are regulated in a consistent manner with principles, definitions, criteria, and relevant requirements, provided for by Guidelines GMP ICH Q7 (Eudralex Volume 4 – Part II).

We believe, however, essential that a clear distinction is made amongst all different actors of the supply chain – in terms of different roles, tasks and obligations (e.g. clear distinction between manufacturers, importers/wholesalers performing or not performing stock activities etc.).

It is paramount, indeed, that actors of the supply chain never involved in manufacturing activities (i.e. importers/wholesalers) are neither treated nor asked to comply with rules and requirements clearly not applicable to them.

In view of this, we would also recommend clearly specifying, to the extent reasonable/possible, the type of obligations applicable to each of the actors of the supply chain (e.g. either in terms of procedure and information to be provided to competent authorities).

In particular, obligations imposed to each of the actors should be functional and proportioned to the objective pursued by European legislation and, in particular, by Directive 2011/62/EU (i.e. to safeguard the functioning of the internal market for medicinal products, whilst ensuring a high level of protection of public health against falsified medicinal products).

In line with all the above (cfr. measures proportioned and sufficient vis-à-vis to the objective pursued), we believe that importers/wholesalers obligations should focus on the type and amount of information to be provided to competent authorities in order to ensure full traceability of all active principles commercialised by them.