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Public consultation on the

DELEGATED ACT ON THE PRINCIPLES AND GUIDELINES OF GOOD MANUFACTURING PRACTICE FOR ACTIVE SUBSTANCES IN MEDICINAL PRODUCTS FOR HUMAN USE

Comments of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE, www.eucope.org) was founded to promote companies and associations active in research, development, production and distribution of pharmaceutical products and enhance their scientific, technical, economic and legal objectives. Via the member associations (the German Pharmaceutical Industry Association (BPI), the Ethical Medicines Industry Group (EMIG) of the UK, the German Biotech association BioDeutschland as well as the Swedish association of mid-sized innovative companies IML as well as SwedenBIO), EUCOPE represents more than 900 mid-sized innovative member companies, many of them SMEs. In addition, many innovative companies from Sweden, UK, France, Bulgaria, Italy, Greece, Germany, the Netherlands and Austria are represented on the board of the association.

I. General findings

EUCOPE appreciates the efforts of the European Commission to involve the experiences of the stakeholders to find suitable solutions for the delegation act concerning GMP for APIs. EUCOPE considers that the establishment of a sound and appropriate binding framework for GMP for APIs

is important to ensure the protection of public health. As the Commission pointed out in the impact assessment regarding the Directive 2011/62/EU (SEC(2008) 2674, p. 20 f.): "*GMP compliance of API play an important role in the context of counterfeit. Therefore, compliance and its scrutiny is crucial."* In the corresponding footnote n° 39 it is stated that: "*Currently, the Community GMP for API are guidelines, i.e. non-binding. One could consider turning them into binding provisions. This, however, would be merely a question of legal* technique *and not change the substance.*" EUCOPE agrees with this position of the Commission and urges the Commission at the same time not to use the adoption of the delegated act to add further requirements. Not only against the background of the new rules on import of APIs from third countries (cf. Art. 46b(2) of Directive 2001/83/EC and Concept paper SANCO/D3/(2011)ddg1.d3. 1438409), we regard it as crucial to focus the resources on achieving better results in compliance with the rules on GMP already existing.

The delegated act should in particular take into account the situation of specific categories of APIs. For such substances difficulties might arise from an increased inflexibility in the application of the GMP principles laid out in the EU GMP Part II being respected and the fact that those substances may not be considered "APIs" in those countries and hence fall outside of the medicinal products' legislation.

This may be the case for **herbal substances** and preparations which in many countries are regulated as 'food' and as such will be subject to very different manufacturing standards. As a consequence the third country health authority would have no supervisory control over those substances and would have no legal duty to enforce new measures to "comply" with the requirements of the EU legislation. We are thus concerned that such situation means that such substances can no longer be exported to the EU.

In the case of **atypical actives** which are substances used in much greater quantities in other industries and for which manufacturers have little incentives to comply with the full GMP, the application of the import requirements would be extremely difficult not to say impossible due to the very nature of these substances and the fact that many of them would fall completely outside the scope of the pharmaceutical countries of the exporting country. Given the nature of those substances, the low volume used in Pharmaceutical Industry and their usually low price, the risk of falsification appears to be low. The manufacturing authorisation holder is responsible to ensure that those substances when used in a medicinal product are fit for purpose and that appropriate standards have been applied for their manufacturing; regular audits have to be conducted and those manufacturing plants remain subject to inspections.

In addition the pharmaceutical requirements concerning the characterisation of herbal substances and preparations would lead to the detection of falsified substances (e.g. different species or different sources used than the mentioned ones).

EUCOPE suggests the exclusion of all tissue-engineering products from this regulation. These products are already addressed in

- Directive 2004/23/EC of the European Parliament and of the Council of the 31. March 2004 (On setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells),
- Commission Directive 2006/17/EC of 8 February 2006 (Implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements of the donation, procurement and testing human tissues and cells) and
- Commission Directive 2006/86/EC of 24 October 2006 (Implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for coding, processing, preservation, storage and distribution of human tissue and cells).

We therefore do not see the need for further regulation in this area and ask for the exemption of these products.

II. Consultation topics

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

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

EUCOPE welcomes the Commission's approach to set out a coherent framework for GMP for APIs as this is set out as an obligation in Directive 2011/62/EU. We would point to the specificities of certain substances as mentioned above, e.g. herbal substances or tissue ingeneering which would require specific exemptions. Considering the approach to extend the provisions of the Directive on GMP to APIs, it should be recognized that not all countries have yet implemented ICH Q 7.

We agree with the Commission that the equivalence assessment in regard to the country's rules for GMP should take into account the rules of Part II of the good manufacturing practice guideline of the EU (EudraLex Volume 4). At the same time the Commission has to ensure that future

changes in the EU rules on API GMP, which is e.g. coming up with the adoption of a delegated act regarding import for active substances (cf. Art. 47(3) Directive 2001/83/EC and Concept paper Sanco.ddg1.d.6(2012)73176)), do not affect the legal certainty for importing pharmaceutical companies. It would have to be ensured that the list position of the third country would remain valid for a certain period allowing the third country to align their rules to the changed EU framework.

The document also refers to a table in Annex 7 of the EU-GMP-Guideline and explains that "*the stringency of GMP in active substance manufacturing should increase as the process proceeds from early steps to final steps, purification, and packaging*" and that the "*guidance would normally be applied to the steps shown in grey in table 1*". It is further complemented by a series of annexes which details the requirements per products categories. Annex 7 addresses herbal medicines and makes clear that for herbal derived APIs, the particularity herbal extracts used as API, API consisting of comminuted or powdered herbs, the initial steps taking place in the field e.g. collection of plants and cutting and comminuting or initial extractions are subject to GACP but not to GMP requirements.

It is hence crucial that not only the general GMP part II requirements are taken into account but also the specificities of some API categories. This is vital for natural substances which are collected in the nature with a special permit. For some of these APIs, third countries may be the only suppliers (for example in the case of tropical plant-based or mineral-based APIs). In addition, herbal substances are regulated very differently in various countries and in some countries they may not fall under the medicinal products' legislation. In practice this would mean that the EU requirements will not be able to be met as understandingly a country will not supersede its own rules to comply with the rules of a foreign country.

There is also the issue of the so-called 'atypical actives' for which suppliers have no economic interest or no possibility to produce them according to GMPs. The problem caused by such actives was acknowledged in the EMA Q&A but in the absence of any other acknowledgement or reference in the legislation, their cases is taken care on a case by case basis in the EU at the moment.

In light of the above we believe the intended extension of the scope should exempt herbal substances and atypical actives.

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

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

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

EUCOPE welcomes and supports the decision to extend the scope of Directive 2003/94/EC to active substances if the adequate adjustments will be made.

However, two important points should be addressed here:

- Manufacturing of atypical actives is instead by GMP covered by accepted QA Systems (e.g. ISO 9000 series)
- Manufacturing of early steps and early intermediates in herbal medicinal products should not be subject of the directive

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

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

The Commission proposes the following specific obligation:

- Obligation for 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

  In this context we would like to point out that it would be helpful to clarify that the manufacturers of APIs have to provide the MAHs with the information needed to perform their inspections and oversight. This would be helpful especially in regard to manufacturers of APIs in third countries.

EUCOPE agrees with the Commission assessment in principle. It would, however, seem appropriate to define the term "atypical actives" here. We suggest the following wording:

"Atypical actives are substances which are registered as API in a medicinal product but whose primary industrial use is not as a pharmaceutical active substance. Therefore, other adequate rules and regulations for the description of their quality may apply."

Concerning homeopathic medicinal products we recommend to clarify – as it is already foreseen e.g. in the respective German GMP law in § 1 (3) AMWHV[1] – the scope by adding the following sentence into the Preamble or under Art. 1 of Directive 2003/94/EC:

"Raw materials used as starting materials for homeopathic medicinal products as defined in Art. 1 (5) Directive 2001/83/EC and in the European Pharmacopoeia are not subject to this Directive before being entered into the process of manufacture of mother tinctures or triturations".

Justification: According to the European Pharmacopeia (7th edition, page 1275 et seqq.)[2] raw materials are either processed to mother tinctures or glycerol macerates (in the case of materials of botanical, zoological or human origin) or triturated or dissolved to a lowest producible potency (in case of materials of chemical or mineral origin) as active ingredients for homeopathic medicinal products or as starting materials for being potentised to higher potencies as active ingredients. In this case the starting materials itself therefore does not become an active ingredient of the homeopathic medicinal product and therefore does not fall under the definition of an active substance pursuant to Art. 3a Directive 2011/62/EU. As the inclusion of § 1 (3) AMWHV into German law shows such a clarification is necessary because the agencies dealing with manufacturing and distribution of active substances are often not aware of the particular characteristics of the manufacturing processes of homeopathic medicinal products.

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[1] Verordnung über die Anwendung der Guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft, http://www.gesetze-im-internet.de/amwhv/index.html. § 1(3) reads: "(3) Die Anforderungen dieser Verordnung gelten nicht für

1. Stoffe gemäß Homöopathischem Arzneibuch, die zur Herstellung von Homöopathischen Zubereitungen als Ausgangsstoffe eingesetzt werden, […]

Im Falle des Satzes 1 ist durch die Einhaltung vergleichbarer Standards und Verfahren sicherzustellen, dass die Qualität der Herstellung und Prüfung gleichwertig zu den in den Abschnitten 2 bis 4 festgelegten Anforderungen ist."

[2] http://online6.edqm.eu/ep705/#info.

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

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

EUCOPE agrees with this assessment in principle.

However, for starting materials a risk based approach should be applied and the requirements should be limited to **critical** starting materials.

In accordance with such a risk based approach the addition of the obligation for the active substance manufacturer to ensure that the starting material is sourced from the premises claimed by the manufacturer of the starting material exceeds the framework of EU GMP Part II. The requirements laid down in EU GMP Part II apply from the point at which the active substance starting material is introduced into the active substance manufacturing process. Production of the active substance starting material is generally not covered by EU GMP Part II. In this context also the requirements for starting herbal materials and initial processing steps should be set to the extent possible (e.g. GACP).

3. Other issues (Date of transposition / application 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.

Finally, we would like to stress that it is essential that manufactures of APIs have enough time to prepare for the upcoming changes in the regulatory framework. Therefore, adequate periods for transposition are necessary. We urge the Commission to extend the proposed periods of 6 months and 9 months to at least two years since for most Member States the application fo GMP to APIs is a new requirement. The proposed periods are not foreseen by Directive 2011/62/EU or Directive 2003/94/EC.