AESGP
Association Européenne des Spécialités Pharmaceutiques Grand Public
Association of the European Self-Medication Industry
Europäischer Verband der Arzneimittel-Hersteller

# AESGP comments on the EC Concept Paper on the delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use

AESGP represents manufacturers of non-prescription medicines of either chemical or herbal origin at European level. It counts 29 national associations and 25 associate members. Through its national and associate members, it represents many small and medium-sized companies operating in the self-care sector.

AESGP appreciates the opportunity to take part in this very important consultation.

Overall we would prefer that the Directive is revised in a way to cover finished medicinal products and APIs in two distinct parts, one focusing on finished products, the second one focusing on APIs.

We also think the specific case of atypical/non-traditional actives should be reflected in this revised Directive via a specific article defining this category of substances and referring to a specific annex (as one exists for e.g. herbal medicines in annex 7 or for e.g. ectoparasites in annex 4 for the veterinary sector).

It is also important to ascertain that the revision of the scope of Directive 2003/94/EC will not bear consequences on the GMP Part II and its basic principles including that of increasing GMP requirements (as displayed in table 1). On the same vein, we trust that the revision will not bear any effects on the existing Eudravigilance volume 4 GMP annexes.

**Consultation item No 1 – Proposal to extend the scope of Directive 2003/94/EC to active substances**
***Do you agree with this appraisal and approach? Please comment***

We agree in principle with the objective to bring coherence into the regulatory setting for medicinal products and active substances. However, we have concerns with the approach to extend the scope of Directive 2003/94/EC to active substances without clearly differentiating between the requirements applying to finished medicines and those applying to active pharmaceutical substances. The various differences in interpretation of 'drug product GMPs' vs. 'drug substance GMPs' may give rise to a lot of exemptions which, in total, would then complicate the GMP text and dilute the purpose of having clear rules.

With the aim of having a clear and simple structure of the Directive, we hence suggest reorganising Directive 2003/94/EC into two chapters: one for medicinal products and investigational medicinal products – this part which already exists could be grouped under a heading Chapter 1 *Medicinal product*s – and a second one for active substances – chapter to be created under a heading Chapter 2 *Active substances*.

7, avenue de Tervuren • B-1040 Brussels • Belgium • Tel.: + 32 (0)2 735 51 30 • Fax: + 32 (0)2 735 52 22
E-mail: info@aesgp.be • http://www.aesgp.be

We would agree to the extension of the scope of Directive 2003/94/EC on the condition of having two clear and distinct parts as outlined above. As a last option, if the approach described below is not accepted, a distinct Directive on GMP for APIs may be foreseeable.

The revision of the scope of the Directive should not entail any modification of the existing guidelines on good manufacturing practices for active substances. The part concerning APIs should be fully in line with GMP Part II (i.e. ICH Q7A). It should not add new requirements nor diverge in the requirements. The main principle of 'increasing GMP requirements' should not be put into questions, neither should the existing annexes concerning APIs.

**Consultation item No 2 – Adaptation of regulatory requirements of Directive 2003/94/EC to active substances**
***Are there other aspects which should be considered? Please comment***

We welcome the explicit listing of provisions of Directive 2003/94/EC that would not apply to drug substances. However, as suggested under consultation item 1, we would prefer having two distinct sections in the Directive so as to ensure full clarity.

In addition to the aspects mentioned under 2.1, several other aspects need to be clarified, including, but not limited to, the following examples:
1) document retention times should be the same as those stated in ICH Q7A, 6.13.
2) retention periods should be aligned with those in ICH Q7A, 11.71.

In addition, we propose to also consider the aspect of non-traditional (atypical) active substances. Those are substances which are used in much greater quantities in other industries and for which manufacturers have little incentives to comply with full GMP part II. The following EMA Question and Answer[1] acknowledged the existence of atypical actives and proposed a pragmatic solution concerning GMP compliance. It states that: "*Full compliance with GMP for finished products and active substances is a legal obligation for Manufacturing Authorisation holders. It is recognised that for a small number of medicinal products the primary use of the active substance is not in a medicinal product and the producer may therefore not be aiming to meet the specific requirements of pharmaceutical customers that represent an insignificant volume of business. Alternative sources should normally be sought but in exceptional circumstances the manufacturing authorisation holder should assess and document to which extent GMP is complied with and provide a risk-based justification for the acceptance of any derogation. The declaration provided by the Qualified Person should set out in detail the basis for declaring that the standards applied provide the same level of assurance as GMP. The European Medicines Agency will collect experience with this approach which can be used as a basis for discussion on related amendments to guidelines in the future*."
Some provisions are not applicable as such for these actives and as a consequence, appropriate measures should be foreseen for this type of active substances such as those sourced from nature.

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&jsenabled=true#

For instance, the manufacturer of the active substance could ascertain the appropriate good manufacturing practice on the basis of a formalised risk assessment taking into account compliance with other appropriate quality systems, the source, the intended use and previous instances of quality defects.
In particular the provisions stipulated particularly in Article 3 (Inspections), Article 4 (Conformity with GMP) and Article 6 (QA system) of Directive 2003/94/EC have to reflect the specific situation of these active substances. As a principle, such inspections, manufacturing practices and QA systems must provide confidence that the atypical active in question is fit for purpose and will not negatively affect the safety and efficacy of the medicinal product.

To achieve this aim the necessary measures for qualification of the atypical active manufacturer have to be evaluated on a scientific basis and a risk assessment on product specific basis.

We would propose that the specific situation of atypical actives be reflected in the revised Directive 2003/94/EC and that further guidance is provided later on in a specific annex dedicated to atypical actives including recommendations on the risk-based approach (as it is done in annex 4 for ectoparasites in the veterinary sector).
For example, in this annex, the following elements could be mentioned for consideration and use, as appropriate, by applicants who cannot declare their API as fully GMP-compliant:

1. The dosage form manufacturer or MAH should perform a quality assessment of the atypical actives manufacturer against the requirements of Part II of the GMP Guide in order to identify gaps.
2. These gaps should be subject to a risk assessment of deviations from GMP and the rationale documented for continued acceptance of material from that source.
3. Clear specification for the material being purchased, detailing both product critical chemical and physical attributes, as appropriate. This should be agreed between the supplier and the purchaser.
4. A quality agreement which includes a requirement to notify changes between the atypical active manufacturer and the dosage form manufacturer (and any other intermediaries) or MAH should be striven for.

**Consultation item No 3 – Provisions in Directive 2003/94/EC that would need to be amended: Article 1 ('Scope') and Article 2 ('Definitions').**

***Do you consider this list complete? Please comment***

We refer to our first comment in which we expressed our preference for having two clear and distinct sections in the Directive (or as a last resort, a separate Directive covering GMP for APIs). We would also propose adding a definition for atypical actives.

**Consultation item No 4 – Other provisions on active substances that could be added to Directive 2003/94/EC e.g. provisions specific to active substances, 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.**

***Do you agree with this specific point? Do you consider that other provisions specific to active substances should be added?***

To our point of view, the addition of an obligation on the manufacturer of the active substances to make sure that the starting material is sourced from premises claimed by the manufacturer of the starting material largely exceeds the framework of the GMP for active substances. Indeed, current GMP part II applies to steps following the first introduction of the starting material in the process of the manufacture of the active substance only.

We refer in particular to the increasing uptake of GMP standards in manufacturing. For herbal substances/preparations, it is important to underline that the first steps are covered by GACP and not GMP. This essential nuance should not be jeopardised by the Directive.

**Consultation item No 5 – Other issues (Directive, transposition timeline and date of application of the delegated act)**

***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 consultations items set out above.***

We agree with the points raised under section 3.

*20 April 2012*