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 implementing act on the requirements for the assessment of the regulatory framework applicable to the manufacturing of active substances of 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.

We first think that it is important to restate the primary goal of the Directive: to combat falsification of medicinal products and to impede potential falsified medicines to reach patients via the licit or illicit supply chains. Hence the licit supply chain was also strengthened. We believe this important goal needs to be translated into measures which fulfil the primary objective of the legislation in a targeted and proportionate way so as not to drive genuine medicines and their components out of the market. Shortages of medicines or disappearing of medicines as consequences of too strict measures should be avoided at all cost as this would be equally against public health.

Hence, to avoid serious problems in the availability of medicinal products in the EU market, it is critical that the list (Article 111b) of countries with equivalent GMP rules be as broad as possible. It is also important that the completion of the list is not delayed. We also fear that the set up of the process around the written confirmation in third countries for import of APIs will take some time. In the meantime, temporary measures should be thought of.

An essential pre-condition to the establishment of the list of countries with a GMP system equivalent to the EU's is that third countries be aware of the new system as they need to ask the EU to be on the list. We also deem important that the requirements for equivalence assessment should be prepared in co-operation with the Competent Authorities of these third countries so as to ensure that the Competent Authorities are fully aware of the new rules (including the written confirmation), of the requirements that being on the list entail and can in turn inform EU authorities about their legislation, scope, enforcement system and alert them in case of non-compliance issue.

For specific categories of APIs, we can foresee additional issues, namely the difficulty to have the increased stringency 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 fall outside the medicinal products legislation. This may be the case for herbal substances and preparations which, in many countries, are regulated as 'food' and will as such 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 extremely concerned that such situation means that such substances can no longer be exported to the EU. Many of those substances have no other growing habitat and can even only be collected from the wild, and hence no alternative sourcing would be able to be found. This would lead to very important consequences both in the third country where indigenous populations would be deprived from their sometimes unique source of revenue, and in Europe where medicinal

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products containing those substances would disappear from the market. It should also be borne in mind that the development of small rural local communities in third countries is a very important political agenda in the EU where EU fundings were heavily invested.

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 legislation of the exporting country.

In light of the above, we believe an exemption of the 3rd countries import requirements for herbal substances, preparations and atypical actives would be justified.

Given the nature of those substances, the low volume used and their usually low price, the risk of falsification is quite low. The manufacturing authorisation holder is responsible for ensuring 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 preparation would lead to the detection of falsified substances (e.g. different specie used or different source than that mentioned).

Consultation item No 1 – Equivalence assessment of the rules for GMP

We generally agree that the EU rules to be taken into account are those laid down in GMP Part II of Eudralex Volume 4. However, this document makes reference to a table 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 detail the requirements per product categories. Annex 7 addresses herbal medicines and makes it clear that for herbal-derived APIs (i.e. 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 critical that not only the general GMP part II requirements be taken into account but also the specificities of some APIs categories. This is vital for natural substances which are collected in the wild 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 and preparations 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 import requirements from third countries should exempt herbal substances, preparations and atypical actives.

Consultation item No 2 – Equivalence assessment of the regularity of inspection to verify compliance with GMP and the effectiveness of enforcement of GMP

We generally agree with the appraisal; however effectiveness of GMP enforcement appears difficult to assess based on the current annex. It would be beneficial to have more precise measures.

With reference to our above comments, the specificities of herbal-based, mineral-based and atypical actives should be taken into account. As the scope of what is subject to GMP requirements may differ from one country to another, we wonder how verification of enforcement may be done in such a case. For example at the EU-China bilateral meeting in May 2011, the SFDA said that not all APIs are under their control and hence it is highly unlikely that written confirmation be delivered for such APIs by the Authorities.

We believe that against the background that plants producing herbal substances and preparations would not be inspected as falling outside the pharmaceutical legislation in many countries the most pragmatic option would be to exempt those substances from the import requirements.

Consultation item No 3 – Regularity and rapidity of information provided by the third country relating to non-compliant producers of active substances

We generally agree with this appraisal. It is important that a solid network is established between EU authorities, the Commission, the EMA and 3rd countries authorities. As a prerequisite the Commission needs to have clear contact points/responsible persons in each exporting country outside the EU. The EU rapid alert system should be preferably used or a link to the PIC/S rapid alert and recall system may be established to enable PIC/S countries to only notify once.

If the principle of equivalency is applied, would this mean that third countries would have access to EudraGMP? If so, specific confidentiality agreements should be put in place.

Consultation item No 4 – Other issues including form of assessment, interface with existing mechanisms, regular verification, date of application

4.1 Form of assessment

The choice of the 3rd country's manufacturing site to be inspected should be decided by the EU Authorities in order to avoid bias.

4.2 Interface with existing mechanisms

With regard to the assessment of equivalency, we fully support the fact that existing framework such as PIC/S should be taken advantage of in order to avoid duplication. The EU and the PIC/S GMP guide are practically identical and PIC/S has adopted the ICH Q7A guideline which in the EU became GMP Part II. PIC/S is open to any Authority having a comparable GMP inspection system and PIC/S members have been subject to an evaluation process before being formally accepted as member. Hence PIC/S member should already be considered as candidates for the list of 3rd countries referred to in Article 111b.

Third countries, which have a Mutual Recognition Agreement in relation to conformity assessment of regulated products including Sectoral Annexes on Good Manufacturing Practice for Human and Veterinary Medicinal Products with the EU, may also provide a good basis for the evaluation of equivalency. However the scope of many MRAs with the EU only covered finished medicinal products and it may need to be updated to cover APIs as well.

The GMP inspections performed by the EDQM and national inspectors in the framework of CEPs may be added to the list.

4.4 Date of application

Given that the application date is only a year from now, we make the urgent plea to the Commission to think about transitional measures.

The two main 3rd countries supplying APIs are India and China: would they be ready to issue written confirmation of GMP compliance by this date? It seems important to focus on these countries as a priority.

Consultation item No 5 – Any other issues not raised above

Other areas which need to be considered are the following:

- How to ensure that suppliers from 3rd countries where EU GMP equivalence has been established continue to accept audit from the manufacturing authorisation holder?
- What happens in the case of a 3rd country getting a negative result post GMP equivalence assessment? Could they appeal? Could they still produce written confirmation of GMP compliance?
- What happens in case a country is on the list but audits or a GMP inspection have shown that a plant in that country is not GMP compliant?
- What will happen in case a country has not yet transposed the falsified medicines legislation into its national law by July 2013?

We believe that there are at the moment too many uncertainties as to the functioning in practice of the written confirmation when importing an API. The following aspects (non-exhaustive list) should be clarified:

- Harmonised format and content of the written confirmation
- Legal power of the document – will it be attesting of the GMP compliance of the manufacturing plant?
- Process of issue by third countries

- Role of customs
- How would the shipment for use in human medicines be differentiated from those used in veterinary medicines given that they are not subject to the falsified medicines legislation?
- Means to ensure that this document cannot be falsified; we believe its content should be made available in a database easily accessible by customs around the world which could check it against the written confirmation accompanying the API shipment.

We believe the written confirmation document and the process should give rise to a document which would be subject to consultation. A meeting dedicated to import of APIs organised by the Commission with stakeholders, Member States and possibly third countries' representatives would be highly beneficial to clarify the situation and dissipate fears and uncertainties. We would ask the Commission to urgently consider such a request.

It also seems critical to clarify the interpretation of the wording 'exceptionally and where necessary to ensure availability of medicinal products'.

23 March 2012