Bundesverband der Pharmazeutischen Industrie e.V.
BPI
Leben ist Vielfalt

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

GENERAL COMMENTS

The German Pharmaceutical Industry Association wishes to express 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. In this light the legal supply chain has to be 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 availability of medicinal products in the EU market it is critical that the list (Article 111b) of countries with equivalent GMP rules will be as broad and the creation of the list should be done as quickly as possible. It is also important that this list will be updated on a regular basis.

On the whole, we would appreciate if the implementing act would be discussed with representatives of several 3rd countries beforehand, as the production of several APIs does not take place in Europe anymore and the Pharmaceutical Industries strongly depends on the unobstructed circulation of these goods. Therefore, an essential pre-condition to the establishment of the list of countries with equivalent GMP system 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 see the importance that the requirements for equivalence assessment should be prepared in co-operation with the Competent Authorities of these 3rd countries so as to ensure that the competent Authorities are fully aware of the new rules (including the written confirmation), 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 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 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 be only 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 population would be deprived from their sometimes unique source of revenue and in Europe where medicinal products containing those substances would disappear from the market.

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 preparation would lead to the detection of falsified substances (e.g. different specie used or different source than that mentioned).

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, if they are being manufactured under regulations that provide the same quality and, therefore, the same level of protection for EU-citizens.

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GUIDELINE SECTION TITLE	
Line no. + paragraph no.	**Comment and Rationale**
Introduction	The German Pharmaceutical Industry Association 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 this products..
Consultation item No 1 - Equivalence assessment of the rules for GMP	The German Pharmaceutical Industry Association agrees in principle that the EU rules to be taken into account are those laid out in GMP Part II of Eudralex volume 4. Considering the principle approach of the suggested Implementing act, we strongly suggest that other regulations that are in accordance with those laid down in the documents of ICH Q7 should be acceptable as 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 GMP for active substances (cf. Art. 47(3) Directive 2001/83/EC and Concept paper Sanco.ddg1.d.6(2012)73176)), does 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. This mechanism should also apply for future changes in the European legal framework in the years to come. 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 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 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 supersedes its own rules to comply with the rules of a foreign

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	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 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	The German Pharmaceutical Industry Association agrees with the assessment in principle; 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 country to country, we wonder how verification of enforcement may be done in such 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 plant producing herbal substances 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. We strongly suggest considering the existing PIC/S documents on this matter.
Consultation item No 3 - Regularity and rapidity of information provided by the third country relating to non-compliant producers of active substances	The German Pharmaceutical Industry Association agrees with this assessment in principle. It is important that a solid network is established between EU authorities, the Commission, the EMA and 3rd countries authorities. As a prerequisite, the European Commission needs to have clear contact points/ responsibilities 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. It may seem advisable to establish a system of Confidentiality agreements with authorities from 3rd countries to protect sensible data.
Consultation item No 4 – Other issues including form of assessment, interface with existing	*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*

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mechanisms, regular verification, date of application	With regard to the assessment of equivalency, we fully agree 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 it 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 hence 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 include 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 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	In the context of the interface with existing mechanisms the Commission states that “it is intended to take into consideration, where available and appropriate”, Mutual Recognition Agreements (MRA) on GMP of active substances, regulatory alignment with applicable guidance of the ICH and other existing assessments. We welcome this approach that the use of existing knowledge and experience should be used wherever possible. We also believe that – in parallel to the provision laid down in Art. 111b(1) (3) of Directive 2001/83/EC – existing MRAs on GMP, which may include active substances, should not just be taken to consideration, but there should be a certain automatism inherent to it that leads to a positive assessment result. As another point which is closely linked to the “third country list” (Art. 111b of Directive 2001/83/EC) the requirement of a written confirmation of Art. 46b (2) (b) should be addressed as well. We believe the development of a template for the “written confirmation” (including language requirements) could help officials and companies in the EU as well as in third countries in their daily work and could eliminate the danger of various interpretations of the necessary content and format. The publication of a regularly updated list of the competent local authorities for the issuance of the confirmation by the Commission or the EMA would be helpful as well.