



Proposed Regulation/Guidance Document: EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use - Annex 16 - Certification by a Qualified Person and Batch Release

Comments submitted by: International Society for Pharmaceutical Engineering (ISPE)

GENERAL COMMENTS ON THE DOCUMENT
<p><u>Alignment with other guidance and reflecting the reasons for changes to this Annex</u></p> <p>The ICH Q-IWG Points to Consider document for ICH Q8/Q9/Q10 Implementation provides a harmonised overview of the elements needed for batch release. This document should be referenced in the 'principle' section 2.2</p> <p>Document EMA/INS/MRA/387218/2011 Rev5 describes the internationally harmonised requirements for batch certification. A template is described which lists the product particulars to be mentioned on the batch certificate and the template also contains a "certification statement". This may be used also for "intermediates, bulk or partially packed products, APIs and investigational medicinal products".</p> <p>Consideration should be given to aligning the content of this template with the statement in the appendix to Annex 16.</p>
<p><u>Alignment between Member States</u></p> <p>When implemented in the law of a member state, the provisions described in this Annex should be maintained.</p> <p>As currently written section 2.2 could be interpreted that member states may add or delete requirements.</p>
<p><u>National Legislation</u></p> <p>Point 3.5.2 needs to be clarified as to whether it refers to the local national regulations in the country of certification or the destination countries national legislation or both.</p>
<p><u>Approach to "Equivalent"</u></p> <p>'Equivalent' GMP is the standard recognised by health authorities and inspectorates where a Mutual Recognition Agreement (MRA) is in place or where the inspectorate is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S).</p> <p>The concept of compliance with EU GMP "or equivalent" is mentioned in 2.4.2, as a basis for certifying batches.</p> <p>This contradicts 2.3.2 which states that the batch must be in compliance with EU GMP (no equivalence qualification).</p> <p>The concept of standards considered to be "equivalent" to EU GMP should be defined in the Glossary and used consistently throughout the document.</p>

Additional Testing on importation requirements

Concerning the import testing of batches originating from the same bulk product batch, it is stated (in sections 3.4.8) that QC testing from another imported finished batch originating from the same bulk may be used for certification provided that the ID and assay testing are conducted on each occasion within the EEA.

The requirement to test ID and assay on each occasion is an additional requirement which is unlikely to increase public health protection and may delay availability for patients. Furthermore, additional measures are currently being put in place to assure the quality and integrity of products on receipt in EEA e.g. EU GMP Chapter 5 – controls on supply chain traceability – section 5.27

Specific Comments on the Text

ISPE indicates text proposed for deletion with strikethrough formatting and text proposed for addition with bold and underlining.

Section Number	Current Text	Proposed Change	Rationale and Comment
1.1	"The relevant legislative requirements are contained in Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC."	"The relevant legislative requirements are contained in Article 51 of Directive 2001/83/EC, Article 55 of Directive 2001/82/EC <u>and in Article 13.3 of Directive 2001/20/EC.</u> "	Include a reference to material made for human clinical trials for completeness (recognizing also that the Directive <u>is</u> referred in section 3.4.2).
2.2	"...in compliance with the laws in force in the member state..."	.. with the laws <u>reflecting the provisions of this Annex</u> in force in the member state...	When implemented in the law of a member state, the provisions described in this Annex should be maintained. As currently written (e.g. in section 2.2) it could be interpreted that the member state may add or delete requirements.
2.2, 2.4.3, 3.2	"...of the destination country..." "...e.g. of the destination country..." "...or in the destination country."	Delete the term "destination country" or define and use only when strictly applicable.	The term "destination country" of the medicinal product has been introduced in Annex 16 in e.g. sections 2.2, 2.4.3, 3.2 and the template for confirmation. This term can be applied to the finished medicinal product only and to the initial destination. The QP responsible for batch release will not necessarily be aware of the ultimate product destination e.g. in the case of parallel importation and cannot be held accountable for ensuring compliance with local requirements in all cases. It is very difficult for any QP to know the laws in all countries where a pharmaceutical company may export products, This is especially important for QPs who release products for many non-EU countries. In such cases the MAH should be responsible and should notify the QP of the requirements in order that the QP can ensure the product is in compliance with relevant legislation/legal requirements.

Section Number	Current Text	Proposed Change	Rationale and Comment
2.4.2.	The batch has been manufactured and checked in accordance with the principles and guidelines of EU Good Manufacturing Practice, or equivalent;	The batch has been manufactured and checked in accordance with the principles and guidelines of EU Good Manufacturing Practice; or equivalent;	The word “equivalent” creates more confusion than actually helps. The authority to state that the GMP followed in a plant in a third country is EU-GMP compliant lies at the moment with EU Authorities (exception is written confirmation for APIs). In any case, if the principles followed are equivalent to EU-GMP, they are essentially EU-GMP, so, no reason for using this wording.
2.4.3.	Any other relevant legal requirements, e.g. of the destination country, are taken into account;	Any other relevant legal requirements, e.g. of the destination country, are taken into account;	Removal of this still allows the legal requirements of the destination country to be taken into account if necessary.
7. para. 3	Q.P.	<u>QP</u>	Consistency in form for acronyms is desirable.
Glossary	Qualified Person (QP): the person defined in Article 48 of Directive 2001/83/EC and Article 52 of Directive 2001/82/EC.	Qualified Person (QP): the person defined in Article 48 of Directive 2001/83/EC and Article 52, of Directive 2001/82/EC <u>and Article 13 of 2001/20/EC.</u>	QP defined under Article 13 of 2001/20/EC