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European Medicines Agency (EMA)
7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

**SUBMISSION OF COMMENTS ON BATCH RELEASE CERTIFICATION FOR
INVESTIGATIONAL MEDICINAL PRODUCTS referred to in Art. 13.3 of
Directive 2001/20/EC**

ISPE is pleased to provide comments on the above Guideline which have been compiled by the Regulatory Subcommittee of the EU Investigational Products Group.

We would much appreciate that the comments and issues detailed in the document are addressed.

Yours sincerely,

Robert P. Best
President/CEO, ISPE



European Medicines Agency

SUBMISSION OF COMMENTS ON BATCH RELEASE CERTIFICATION FOR INVESTIGATIONAL MEDICINAL PRODUCTS

COMMENTS FROM: ISPE Investigational Products – Community of Practice- Regulatory Subcommittee (final : 27th July 2007)

GENERAL COMMENTS

ISPE welcomes the opportunity to comment on the EMEA proposals for Batch Release Certificates for Investigational Medicinal Products (IMPs). While it is recognised that there may be advantages in having consistent documentation to facilitate the free movement of IMPs within the EEA we are not convinced of the necessity for a standard format for QP Certification and the current proposals do not meet this need. Some of the information requested is already provided (either in the CT Authorisation for a given trial or in a Manufacturing Authorisation (IMPs). This proposed certificate does not meet the requirements of Article 13.3 (b) of Directive 2001/20/EC, which specifically require that the batch to be manufactured to standards of GMP as least as equivalent to those defined for the EU (not to the GMP requirements of the local Regulatory Authority as stated in item 14 of the proposed certificate). Furthermore, some information required to complete the QP certification in accordance with Article 13.3, specifically reference to the Product Specification File and the information notified to the Competent Authority (i.e. the Clinical Trial Authorisation), is absent from the current form.

This form has been derived from an existing form for Marketed Products. This form is used to distinguish the requirements between Mutual Recognition Agreement (MRA) countries and non MRA countries for Marketed Products. For IMPs, this distinction is unnecessary as the GMP Directive (2003/94/EC) clearly states in Article 11. 2 for IMPs that “when products are imported from third countries, analytical control shall not be mandatory”. Harmonisation and facilitation of free movement of IMPs would be increase if all member states adopted Article 11.2. This compares to the current situation where some member states require some testing to be undertaken on import of the product into the EU.

Some detail on the Certificate for IMPs has the potential to “unblind” studies. This is a cause for concern. Specifically, product or batch details would be inappropriate where packs contain more than one product e.g. active and placebo. In some cases, where product is purchased on the open market for use as a reference (comparator) product in a clinical study, much of the information on the form would not be available. This would result in numerous “Not Applicable” entries on the form. Furthermore, where more than one site, including 3rd parties, may be involved with the overall manufacturing and packaging activities, it may be necessary to transcribe data from one system/document to the single proposed template. This is duplicating work and a potential source of error without adding benefit to the patient. In addition, confusion would arise if different specifications (and hence different results) are reported for the same product if different IMPDs are submitted in a given country.

Finally, there are no comments addressing IMPs from non MRA countries again reflecting the commercial product nature of this form, which is not relevant for IMPs. Also it is also not clear if the form should be used for bulk IMPs, which may be transferred to another site for subsequent packaging or for the final packaged IMP itself. Clarity on this issue is required.

Comment [RS1]: We have received clarification from David Coburn at the EMEA that batch release certificated at site are not required unless the investigator is also the sponsor. Batch certificates can be held at the sponsor.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no¹. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Explanatory note, 3 rd para	<p>The current format has been derived for Marketed Products from MRA countries. This is not considered valid for IMPs and to ensure consistency for IMPs imported from all third countries.</p> <p>It is not clear whether the certificate applies to bulk IMPs or the final packed IMP.</p>	<p>It is suggested that the form be simplified should contain items that do not have the potential to unblind particular clinical studies. For example, items 4, 5, 6, 7 all have the potential to unblind studies if specific product information is provided. Further clarification for product names/details need to be considered to avoid the potential for “unblinding” of some clinical studies.</p> <p>Clarify if the form applies to bulk product, which may be shipped to another site for further processing/packaging. Some of the information on the form may be appropriate to bulk product, e.g. name and strength of product, but not appropriate to the packed product, which, for some studies, may contain several individual products (active, placebo, comparator) depending on the study design.</p>
Explanatory note, 3 rd para, last sentence	<p>Reference should be made to GMP Directive 2003/94/EC, Article 11.2, which states that (for IMPs) “when products are imported from third countries, analytical control shall not be mandatory”. If this approach were to be adopted by all members states this would significantly enhance harmonisation activities and promote facilitation of free movement.</p>	<p>Suggest the last sentence should refer to Article 11.2 of 2003/94/EC and state that harmonisation and facilitation of free movement of IMPs would be significantly increased if this clause was adopted by all member states.</p>
Letterhead of Manufacture	<p>Change this to Letterhead of Organisation issuing the Certificate.</p>	

¹ Where available

Content of Certificate Item 1	The Name of Product had the potential to “unblind” the study, as the product used may be active, placebo or a comparator, depending on the nature of the specific arm of the study.	Further clarification is requested for the naming of the product to avoid the potential for “unblinding”.
Item 2	Product which is released may not be imported into a country	Change to Releasing Country
Item 3	Clarification needed as to whether the form should be re-issued and re-supplied to IMP receiver when the EUDRACT number becomes available.	For simplicity and clarity, rephrase to read “Eudract No(s) to be provided, if available.
Item 4	Detail here may have potential to “unblind” a study, similar to item 1 above	Further clarification is requested for the naming of the product to avoid the potential for “unblinding”.
Item 5	For final packed products, used in blinded studies, the declaration of the pharmaceutical form may unblind studies. For example, capsules and tablets may be both forms used.	Further clarification is requested for the naming of the product to avoid the potential for “unblinding”.
Item 7	Delete reference to batch size. This parameter is of no value as the specific shipment will be secondary packed from a primary packed or bulk batch of IMP. Also the lot batch number may be assigned as a packaging number, particularly where the pack may contain active, placebo and/or comparator products.	More guidance is required how to assign batch numbers for blinded studies
Item 9	Include the option to have Retest Date or Use by Date as stated in Annex 13, section 26, in addition to Expiry Date.	
Item 10	Delete. This information is defined in the CT Authorisation or Manufacturing Authorisation (IMP).	
Item 11	Delete.	
Item 12	Delete this section. For blinded clinical studies, the visibility of the analytical results for the released batch will “unblind” the study. For example, results for doses of active, placebos and comparators where used, will confirm which product has been packed and thereby unblind the shipment. Also, where different IMPDs are submitted for the same product in the same country, different specifications and hence different results may be reported, adding further confusion to the recipient.	

Item 13	Delete this section. If additional items are deemed necessary, they should be mandated. It is also considered that this section may be used for country specific requirements, which would be contrary to a harmonised approach.	The importer should accept the decision of the Qualified Person to release the batch without the need for additional remarks/comments or country specific information.
Item 14.	<p>This clause contains a significant error and is therefore inconsistent with the requirements of 2001/20/EC. The batch should be made to standards of GMP that are at least equivalent to those of the EU (as stated in 13.3 (b) not “in full compliance with GMP requirements of the local Regulatory Authority.”</p> <p>Also, delete last sentence. It is not appropriate to state that the records (for processing, packaging and analysis) are in compliance but that the overall process itself is in compliance.</p>	<p>Modify to reference 13.3 b) and delete reference to local Regulatory Authority.</p> <p>Alternative wording is suggested (where applicable to the final packed IMP only):</p> <p><i>This certificate is a declaration that the product has been manufactured and packaged following Directive 2001/20/EC - Article 13- and Directive 2003/94/EC Requirements and in accordance to current Good Manufacturing Practices, the relevant Product Specification File and the Clinical Trial Applications.</i></p>
Add explanatory note on Page 3	Add a note to page 3 as some items are specific to the EU and would be only known to the European importer.	<p>Add suggested text as explanatory note:</p> <p><i>“Some information may not be available at the manufacturer site in the 3rd country e.g. Eudract number, importing country, and may be added by the importer if known prior to countersignature of the QP of the importer.</i></p>

Please feel free to add more rows if needed.

These comments and the identity of the sender will be published on the EMEA website unless a specific justified objection was received by EMEA.