

#### PDA Europe

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and Technology: Lee Kirsch, PhD University of Iowa 31 August 2007

Mr. David Cockburn European Medicines Evaluation Agency 7 Westferry Circus London E14 4HB United Kingdom

Ref: Content of the Batch Release Certificate Referred to in Art.13.3 of Directive 2001/20/EC (EMEA/INS/280218/2006)

Dear Mr. Cockburn:

PDA is pleased to have the opportunity to provide comments on the draft "Content of the Batch Release Certificate Referred to in Art.13.3 of Directive 2001/20/EC". Our comments were prepared by a group of member experts in this field. Our comments are attached in specific detail in the requested EMEA format. These comments are based on the broader issues outlined below.

The intended scope of the certificate may not fully address problems related to patient specific packaging and issues arising from preparation of supplies for blinded clinical trial studies:

1. Comparator products should be generally excluded from the scope of this guidance. It is almost impossible to get sufficient information to prepare a meaningful certificate on a competitor product. There is also the recognition that marketed products are authorized for marketing in a large part due to evidence demonstrating satisfactory GMP compliance and manufacturing controls.

2. Placebos can also be difficult to cover with a meaningful certificate especially when imported from outside the EEA or from countries where no mutual recognition has been stipulated; so certain adjustments must be considered.

3. The integrity of blinding must be preserved. The batch release certificate must therefore be designed to maintain the blinding of the study. The current guidance may possibly result in a certificate that risks revealing the blinding at the study center.

We believe the EMEA has great discretion to adopt our proposed changes, as the wording of Article 13.3 of the directive, and the wording of Annex 13 are somewhat general.

If I can be of further assistance, please feel free to contact me, or our Director of Regulatory Affairs, Jim Lyda at: *lyda@pda.org.* 

With very best regards,

Georg Roessling, PhD Senior Vice President PDA Europe

Attachment

Cc: PDA staff, PDA RAQC



## SUBMISSION OF COMMENTS ON

# Content of the Batch Release certificate referred to in Art. 13.3 of Directive 2001/20/EC

### Doc. Ref. EMEA/INS/280218/2006

## COMMENTS FROM: Parenteral Drug Association (PDA). Contact – James C. Lyda (lyda@pda.org)

#### **GENERAL COMMENTS**

1) The guidance on the content of the batch release certificate does not address the problems related to individual, patient specific packaging, particularly in the case of supplies for **blinded clinical trial studies**. Several of the aspects to be certified for a drug/medicinal product are not feasible to comply with in this situation.

**RECOMMENDATION**: Several specific changes are suggested below and general exclusions and case by case waivers should be provided. One possibility is to have batch specific release certificates for each of the products/batches involved (e.g. IMP batch and placebo) and to include a general waiver for the blinded material, requiring only provision of such data as is actually available at the time of batch record review and release by the QP. Maintenance of blinding is paramount and therefore all issues associated with this, must be fully considered when requesting information on a batch release certificate. The certificate should not provide any unblinding information.

2) The draft guide does not address the problem of <u>comparators</u>, especially those imported from outside the EEA or countries where no Mutual Recognition Agreement has been stipulated. It is often impossible to receive a certificate of any kind from a competitor.

**RECOMMENDATION**: It is suggested that a general exclusion be granted, exempting marketed product comparators from the requirements for certification, recognizing that such products have been authorised for marketing under in part due to evidence of satisfactory GMP and manufacturing controls. This should include modifications to the comparator where such modifications have been performed in accordance with the requirements of Annex 13.

3) The draft guide does not address the problem of **placebos**, especially those imported from outside the EEA or countries where no Mutual Recognition Agreement has been stipulated.

**RECOMMENDATION**: It should be sufficient to have certified evidence that these have been produced according to and in compliance with GMP rules.

4) Manufacturing runs for packaging of clinical trials can be very small, occasionally one or only few units. The additional workload associated with issuing certificates for each of these operations should be taken into consideration.

**RECOMMENDATION:** As listed below, it is recommended to reduce the items to be certified to the essential, scientific and technical meaningful information necessary to assure the quality of the supplies.

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## SPECIFIC COMMENTS ON TEXT

#### **GUIDELINE SECTION TITLE**

Line no <sup>1</sup> . + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Page 3, No. 1	Name of product: in cases of blinded clinical trials this should be extended to the name of the comparator and/or the placebo used.	Replace by: Name of product.As referred to in the clinical trial(s) in the importing country includingwhere applicable, the names of the comparators and/or the placebosused.
Page 3, No. 3	Eudract No(s): Should not be mandatory when there is no specific clinical trial processing. For material already processed for a specific clinical trial, the identification code of the study should be put as mentioned in point 1 since this is the driver for the process. If the Eudract # is not available, another identification code of the study should be allowed to be used (Study Code, Protocol Number, etc.).	<b>Replace by: Eudract No(s)</b> To be provided if available <b>and applicable. Where the Eudract number is</b> <b>not relevant, other identifiers as stated in the IMPD may be used.</b>
Page 3, No. 4	Points 4,5, 6 should be replaced by the description of the product and the manufacturing step that is the scope of the release as this will better describe the nature of the drug/medicinal product(s) used in the clinical trial.	Replace by: Strength/Potency.If applicable, identity (name) and amount per unit dose required for all active ingredients/constituents. Otherwise, a description of the drug/medicinal product as given in the IMPD should suffice.
Page 3, No. 5	See comment above	Replace by: Dosage form (pharmaceutical form).If not applicable, a description of the drug/medicinal product as given in the IMPD should suffice.
Page 3, No. 6	See comments above	<b>Replace by: Package size</b> (contents of container) and <b>type</b> (e.g. vials, bottles, blisters) <b>should be given, if applicable. Otherwise, a description of the drug/medicinal product as given in the IMPD should suffice.</b>
Page 3, No. 7	In clinical trial supplies like those for blinded clinical studies, this should be the/a unique identifier code, e.g. of the last operation	Replace by: Unique identifier code for the last operation carried out and batch size, where batch size refers to the number of units, e.g. patient

Where available

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	carried out (i.e. packaging, encapsulation of comparator etc.) and the batch size should refer to the number of units produced in this production run. It should be possible to replace the lot/batch number by the identification code of the last operation carried out. The "batch size" should refer to the number of patient kits/boxes prepared during this operation.	kits or boxes prepared during this operation.
Page 3, No. 8	For clinical trial drug/medicinal products, the date of manufacture is not of any special importance with respect to batch release. If any date is required, it would be the date of the performance of the last relevant operation, rather than the date of manufacture of the bulk product. It might be impossible to give the manufacturing date of a comparator, as competitors might not be willing to disclose this particular information.	Either delete completely or Replace by: Date of performance of the last manufacturing operation of the finished product used in the clinical trial, if available.
Page 3, No. 9	Expiry date: Should be deleted or replaced by period of use as per Annex 13, Art. 26 j. Usually, concurrent stability studies are ongoing during the development of an investigational medicinal product. Therefore, it would be more appropriate to give a period of use date on the certificate acknowledging that the ongoing stability studies might justify extension of the period for safe use of the product.	Replace By: Period of use
Page 3, No. 10	Name and address of manufacturer(s) - manufacturing site(s): It should be noted, that the requirement does not extend to manufacturers of ingredients of the drug/medicinal product (drug substance, excipients etc.).Likewise, in the case of comparator product the exact site of manufacture may not be readily available.	Insert: All sites involved in the manufacture of the drug/medicinal product including packaging and quality control of the batch should be listed with name and address where such information is available. The name and address must correspond to information provided on the Manufacturing Authorisation/Establishment Licence. If no such Manufacturing Authorisation/ Establishment License is requested by the local Competent Authorities, the compliance with cGMP requirements should be verified by the sponsor of the clinical trial study and referenced here.
Page 3, No. 11	Number of Manufacturing Authorisation / Licence or Certificate of GMP Compliance of the manufacturer/fabricator: if there was no notion to exclude the manufacturers of ingredients to the drug/medicinal product in the preceding item 10, it should be made here.	Replace "Number should be given for each site listed under item 10." by Number should be given for all sites involved in the manufacture of the drug/medicinal product including packaging and quality control of the batch should be listed with name and address, if available. The name and address must correspond to information provided on the Manufacturing Authorisation/Establishment Licence. If no such Manufacturing Authorisation/ Establishment License is requested by the

		local Competent Authorities, the compliance with cGMP requirements should be verified by the sponsor of the clinical trial study and referenced here.
Page 3,	Results of analysis: The Guideline on IMPD states, that there is	Replace: "Should include the specifications, all results obtained and refer to
No. 12	no need for a specification in early development stages and results as found can be provided. Therefore, the requirement here should be adjusted to cover this situation. If a certificate of analysis is attached, the signature on this should be by the person under whose responsibility the analyses have been performed.	the methods used (may refer to a separate certificate of analysis which must be dated, signed and attached)." by "Should include all results obtained and refer to the methods used (may refer to a separate certificate of analysis which must be dated, signed by the responsible person and attached). Specifications may be referred to where appropriate."
Page 3, No. 14	Certification statement: The certification statement should acknowledge the fact that Quality Systems may be in place that might be able to better assure safety, quality and efficacy of a given drug/medicinal product. Therefore, the release of a batch could be performed on the basis of a satisfactory Quality System.	Replace "I hereby certify that the above information is authentic and accurate. This batch of product has been manufactured, including packaging and quality control at the above-mentioned site(s) in full compliance with the GMP requirements of the local Regulatory Authority and with the product specification file for Investigational Medicinal Products. The batch processing, packaging and analysis records were reviewed and found to be in compliance with GMP." by <b>"I hereby certify that the above information is authentic and accurate. This batch of product has been manufactured, including packaging and quality control at the above-mentioned site(s) in compliance with the GMP requirements of the local Regulatory Authority and with the product specification file for Investigational Medicinal Products. The batch processing, packaging and analysis was performed under governance of a Pharmaceutical Quality System which has been evaluated and found to be in compliance with GMP requirements for clinical trial use."</b>

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

Draft PDA Comments on Content of IMP Batch Release Certificate, 7-27-07