9 January 2009

European Medicines Agency (EMEA)
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SUBMISSION OF COMMENTS ON NEW PROPOSED REVISIONS TO ANNEX 13 OF VOLUME 4 EU GUIDELINES TO GOOD MANUFACTURING PRACTICE

ISPE is pleased to provide revised comments on the above Guidelines, compiled by the Investigational Products Community of Practice within ISPE. These revised comments are based on the new revision to the Annex published by the EMEA in October 2008. While there are some minor changes to our previous comments, our main observation remain. These observations are as follows:

1. In general the changes are welcome and give additional clarity to the existing Annex.

2. Some sections need clarification to avoid different interpretation in the different member states, and local laws or regulations need to take these revisions into account, in order for the benefits to be achieved, and to avoid problems during inspections.

3. The new sections describe conditions where the sponsor and manufacturer are different, emphasizing the need for a Technical Agreement. Due consideration needs to be made where sponsor and manufacturer are the same, hence responsibilities for activities may be defined in a standard operating procedure without the need for a Technical Agreement.

4. Retention period needs to be modified and sampling requirements need to be clarified in particular for sample size and definition of retention samples

5. The current proposed revision does not contain any reference for the necessity to minimize the risk of the application of counterfeited comparator products. A recommendation concerning the prevention should be included.

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

Yours sincerely,

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European Medicines Agency

SUBMISSION OF COMMENTS ON REVISION OF ANNEX 13

COMMENTS FROM: ISPE Investigational Products – Community of Practice- Regulatory Subcommittee

GENERAL COMMENTS

ISPE welcomes the opportunity to comment on the proposed changes to Annex 13. In general the changes are welcome and give additional clarity to the existing Annex.
However, there are some general comments and clarification required, as indicated below:

1. There should be an invitation to “companies” and “sponsors” to utilize the appropriate wording and distinctions between the term “certification” and “release”.

2. References to 91/356 should be replaced by 2003/94

3. Some sections need clarification to avoid different interpretation in the different member states

4. The new sections describe conditions where the sponsor and manufacturer are different, emphasising the need for a Technical Agreement. Due consideration needs to be made where sponsor and manufacturer are the same, hence responsibilities for activities may be defined in a standard operating procedure without the need for a Technical Agreement.

5. Retention period needs to be modified and sampling requirements need to be clarified in particular for sample size and definition of retention samples

6. Annex 13 doesn’t contain any reference for the necessity to minimise the risk of the application of counterfeited comparator products. A recommendation concerning the prevention should be included. Precluding the possibility of the application of counterfeit comparator products, special attention should be paid to the control on the genuineness of comparator products.

7. Finally, the revised annex is no help, if local drug laws do not take these revisions of the annex into account. For example, the German drug law which not allow samples to be stored in an MRA-country. If this law is not updated to include the modified requirement in the Annex to allow sample storage in 3rd countries, then this will create again problems during inspections

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SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Note to Principle of Annex 13	This section refers to the fact that other product, apart from Investigational Medicinal Products may be supplied to patients. However, no reference is made to the Guidance from the EMEA entitled “Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials”	It is recommended that reference to the document is added into this section of the annex.
Glossary	The Product Specification File should contain the information about the documents and information actually used for manufacture, testing and release of a batch of IMP. Thus the PSF would reflect the information filed in the IMPD/CTA and would support the QP release.	A reference file containing, or referring to files containing~~,~~ all the information ~~necessary to draft the detailed written instructions~~ on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

[1] Where available

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Glossary	The additional note on Reconstitution brings additional clarity, however, some elements in terms of definition of Manufacture and Packaging in the context of IMPs are still missing and subject to national authorities interpretation: • The note on Reconstitution and/or the definition of Manufacture should be revised to clearly state that such operations are not to be regulated by Annex 13 • In addition to the note on reconstitution activities, what about dispensing activities (*including dispensing of IMPs into blinded individual patient containers according to a randomization list provided by the Sponsor)*? It should also be allowed that such operations be done by a pharmacist/doctor without involvement of the QP registered for the study?	Amend Definitions as of the glossary in Eudralex Volume 4 (GMP) specifically for Annex 13. MANUFACTURE All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls. *Note: Reconstitution steps performed by a medical doctor / nurse are not considered as a manufacturing operation to be regulated by Annex 13 and are therefore excluded from this definition.* PACKAGING All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product. Note Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers. *Note: Dispensing of investigational medicinal product (including dispensing of IMPs into blinded individual patient containers according to a randomization list provided by the Sponsor) by a pharmacist or a medical doctor / nurse for use on short term is not considered as a packaging operation to be regulated by Annex 13 and therefore excluded from this definition.*
Glossary	Definition on the terms “use by date”, “expiry date”, “re-test date” in the area of IMPs should be given (§ 26), as they are not included in the glossary of Eudralex Volume 4.	▪ “retest date” or “use by date” : May be extended when new stability data are available ▪ “expiry date”: Only for commercial products with a corresponding marketing authorization

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2	Not only the "product specifications and manufacturing instructions may be changed" and not only the phase of „development" may be important. The annex also includes guidance on ordering, shipping, and returning clinical supplies, therefore the meaning of full control and traceability regarding the lifecycle of IMP should be emphasized.	The product specifications and manufacturing instructions may be changed during development but full control and traceability of <u>any critical changes</u> should be maintained.
3 (2nd para)	Not sure the suggested change brings greater clarity, and the requirement applies for all kind of staff size. Thus, the section should be reworded as proposed.	Even if the number of staff involved is small and there is no separate production and quality control department, there should be, for each batch, different people responsible for production and quality control.
4	GMP as a basic document has to be referred instead of Annex 13.	The Qualified Person should in particular be responsible for ensuring that there are systems in place that meet the requirements of <u>GMP</u> and should therefore have a broad knowledge of pharmaceutical development and clinical trial processes.
5	To minimise all risks of cross-contamination is a GMP requirement. There is no need to emphasize this relating to the missing knowledge on toxicity, potency and sensitising potential of the IMPs.	Delete the sentence: "~~The toxicity, potency and sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross contamination.~~" The design of equipment and premises, inspection / test methods and acceptance limits to be used after cleaning should reflect <u>the need to minimise all risks of cross-contamination.</u>
7	The EU guideline on the quality requirements of IMPs should be involved as a reference.	Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and documented <u>in accordance with the Guideline on the requirement to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials.</u>

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
14	Directive 91/356/EEC is repealed.	Batch manufacturing records should be retained at least for the periods specified in Directive 2003/94/EC.
17	Premises and equipment are expected to be qualified. Change the wording.	Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified.
26	The current text includes the sentence: 'The following information should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system: However: - this is not recognised by many EU authorities, and - it should be clarified which information could be absent because of the use of an electronic randomisation system Thus this section should be reworded to strengthen in anyway that flexibility offered by the use of an IVRS	The following information should be included on labels, unless its absence can be justified. ~~e.g. use of a centralised electronic randomisation system:~~ [Expiry date/re-test date,…*(list all the other items that can be can be excluded)*] can be excluded if using an IVR/IWR system that is validated and controls this information.
26	Directive 91/356/EEC is repealed.	Labelling should comply with the requirements of Directive 2003/94/EC.
26 (point(a))	Clarify if the "," (comma) between "….of the sponsor, contract research org…" has to be interpreted as an "and" or a "or" This because some countries such as Germany have different interpretation from other member states in their local regulations.	

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Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
28	Storage conditions and period of use should be included on the label of outer packaging only, since these dates are subject to frequent revisions in the context of a development process. Re-labelling of the immediate containers of IMPs includes re-packaging operations which are of high risk for potential errors. Re-labelling operations should therefore be limited to the outer packaging.	Particulars listed in Article 26 *with the exception of storage conditions and period of use*, should appear on the immediate container. *However, all particulars listed in article 26 should appear on the outer packaging*. *Exceptions for i*mmediate containers are described in articles 29 and 30".
30	Due to technical reason, especially for sterile product in single packaging presentation, it could be practically impossible to comply with section 30	Add: in very special circumstances, e.g. for sterile mono-dose products in single packaging presentation, the immediate container labelling requirements could be fulfilled in a different language (e g. English). A complete and full justification should be present in the IMPD section of the CTA.

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Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
33	In §33 the requirement is described that "If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date **and repeat the batch number**." The highlighted part of the requirement does only make sense for open labelled studies. For blinded studies to follow the requirement means to accept the risk of unblinding: If, in a first shipment, a site received active and placebo medication but patients get, by chance resp. according to randomization, only placebo then re-supply of material will become necessary when the placebo part of the first shipment has been consumed. The re-supply will, may be, have another batch No. than the first shipment. The placebo patients will consequently receive medication from the second shipment (different batch No.) only, since, as already mentioned, the placebo portion of the first shipment has already been consumed. So it becomes obvious that the remaining portion of the first shipment (batch 1) is different from what the patients get. If then a later recruited patient gets material from shipment 1 (batch 1) partial unblinding has definitely happened. For this reason we don't print the batch No. on labels for blinded studies.	Therefore we propose neither to require labelling of batch numbers on original labels nor on use-by date extension labels for blinded studies**.**

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
36 (Quantity of reference and retention samples)	Annex 19 specifies the size of the stored reference samples of finished products, but Annex 13 doesn't contain any definition regarding the quantity to be retained for IMPs reference samples. It also should be specified in Annex 13 and be consistent with Annex 19. However, due to limited supply of the investigational product, it may not always be possible to have a retention sample that is an exact replica sample of the finished product. In such circumstances, there need to be flexibility to be able to re-create a sample of the finished pack using packaging components from the packaging run and product taken from the reference samples or flexibility to reduce the quantity of product in the retain sample. For example, the finished pack may contain 25 vials but the retain pack would only contain 2 vials.	Add the following to paragraph 36: The reference sample should be of sufficient size to permit the carrying out, on at least two occasions, the full analytical controls on the batch. At a minimum, the retention sample should contain sufficient product to perform 2 x identity testing of the investigational product and contain representative samples of all packaging materials used to manufacture the product. Where there is insufficient investigational product, due to limited supply, then sufficient samples of the packaging materials must be kept so that a retention sample can be created using these sample packaging materials and product reference samples. The packaging sample must be coded with the batch/random code information used to pack the product.
36 (2nd paragraph)	As the definition of reference sample is taken from Annex 19 which is not valid for IMPs, the sentence on reference samples of intermediate stages should not be part of the annex on investigational products, as this covers more a business risk than a quality risk.	Delete the sentence: "~~Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates that are transported outside of the manufacturer's control should be kept~~".

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36 (3rd paragraph – retention samples)	This definition does not take into account the specificities of clinical trials: 1) In the case of blinded studies, the individual pack is unique and hence the labelling is also unique and cannot be used for identification purposes as defined (i.e. the word labelling should be removed), 2) Considering secondary packaging / assembly of patient packs a packaging run, this definition requires IMP manufacturers to retain samples of patient packs. This leads to high volumes of samples which need lots of storage space. Consequently, it is proposed to allow sampling for retention samples at the step of primary packaging incl. labelling, instead of the step of patient pack assembly. The link between labelled primary packaged material and the patient pack is given by appropriate documentation in the batch records of patient packaging runs (as allowed by the last paragraph of section 37).	**Change the definition of retention sample by the following:** "… ~~a sample of a packaged unit from a batch of finished product for each packaging run/trial period~~. *A sample of a primary packaged unit from a batch of finished product for each packaging run, provided batch records on final packaging in written or electronic form provide sufficient information.* It is stored for identification purposes. For example, packaging, ~~labelling, leaflet,~~ batch number, expiry date should the need arise" **Alternatively the definition could be replaced by the following:** "… ~~a sample of a packaged unit from a batch of finished product for each packaging run/trial period~~. *In cases where secondary packaging runs only differ because of the language used on the label one* sample of a packaged unit from a batch of finished product for ~~each~~ one packaging run/trial period, *provided batch records on final packaging in written or electronic form provide sufficient information.* For example, packaging, ~~labelling, leaflet,~~ batch number, expiry date should the need arise" This includes §37,last paragraph allowing that no retention samples of the final patient packs are taken, provided batch records provide sufficient information.

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Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
36 (4th and 5th paragraph)	The retention period of reference and retention samples is not appropriate for the following reasons: 1) The duration of storage is not in accordance with Annex 19. Thus, this can cause some serious issues both for commercially available products used in Phase IV and for comparators, whose reference samples are thus supposed to be stored according to both Annex 19 and Annex 13 requirements, which can lead to inconsistencies and the multiplication of reserve samples for a same batch of commercial products. Also, knowing that we often use a plethora of batches to have enough material, we would not be in the physical position to store samples for each batch as reference samples. 2) It does not make sense to retain reference samples 2 years after completion of study/or discontinuation, as the product has expired and the purpose of reference sample is re-analysis. 3) There are clinical trials e.g. in the oncology area that may last over periods of several years, depending on the evaluation criteria of the trial. A clinical report may then be finalized only years after the expiry of such reference and retention samples. Allowing the destruction of retention samples only once the clinical trial report is finalized or with the approval of the corresponding regulatory filing only, would require complex logistics and validated procedures in place. 4) Inconsistent clinical trial results should be investigated earlier, e.g. upon interim analysis in studies where such analysis are foreseen. Consequently, it is proposed to set a maximum retention period of 1 year after the maximum retest period of the IMP.	Proposed to change as follows: "Reference and retention samples of IMPs , incl. blinded product should be kept for at least one year after ~~completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer~~ *the maximum retest period of the IMP*". And delete: ~~"Considerations should be given to keeping retention samples until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results~~".

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37 (1st paragraph)	1) There is an inconsistency between the requirements contained in EU Directive 2001/20/EC and the requirements here in terms of the way to ensure compliance with EU GMPs. Directive 2001/20 (art. 13 3b) states that it is the QP responsibility to ensure that a batch manufactured in a third country has been manufactured to a standard at least equivalent to EU GMPs. However, this section means that we could rely only on MRA, and not on the QP certification, to determine where reference samples could be stored. Thus, this means that a QP could certify that a batch has been manufactured according to EU GMPs, but could not determine if a reference samples could be stored in a site in a third country, where he could only rely on a MRA. 2) A Technical Agreement is not required if the sponsor and manufacturer are the same. In that case the storage location of retained and reference samples may be defined in a procedure/policy of the sponsor. 3) "In exceptional circumstances" should be removed from the sentence. The reference samples may be stored in the third country if documented in a technical agreement between the sponsor, importer and manufacturer and should not be subject to "exceptional circumstances". Moreover, having the reference samples stored in a third country should not be "justified" when clearly documented in the technical agreement. 4) In addition, "Exceptional circumstances" and “justified" may be subject to different interpretations between inspectors end Competent Authorities leading to significant discrepancies in expectations across EU countries and regions. 5) "Normally" is creating ambiguity in the requirement and should not be used in a GMP guideline. Alternatively, a definition for "normally" should be provided	Change section 37 to the following: *“Reference samples* of finished product should normally be stored within the EEA. In the case where the reference samples are stored in a third country, the Qualified Person of the importer is responsible for ensuring that the reference samples will be stored at the third country manufacturer in accordance with standards of good manufacturing practices at least equivalent to those laid down in EU Directive 2003/94/EC. The storage location of Reference and Retention samples should be documented in a Technical Agreement between the sponsor and manufacturer (if different) and should allow timely access by the competent authorities. “

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Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
39 (paragraph c)	This paragraph does not mention the guidance document CHMP/QWP/185401/2004. In section 3 of this document, it allows for quality to be confirmed by demonstration that the product has a manufacturing authorisation in an ICH country and identity testing of the product.	Change paragraph c) as follows: "Where an imported comparator is purchased from an ICH region, then certification of the product can be achieved by confirming the identity of the product and demonstrating that the product has a marketing authorisation in the ICH region. For an imported comparator product, from a Non ICH region, where adequate assurance……."
40	Assessment also may include the qualifications on API.	Assessment of each batch for certification prior to release may include as appropriate: • evaluation on the appropriate quality of API manufactured in accordance with the requirements of GMP
40	"qualification" is the correct wording instead of "validation" regarding the status of facilities, processes and methods	• the qualification status of facilities, processes and methods;
42	"Where, permitted in accordance with local regulations, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other health care professional as allowed in those regulations, the Qualified Person is not required to certify the activity in question. " We feel that especially for early clinical studies involving few patients, this approach should be acceptable as a rule, even if performed by a pharmacist or other health care professional not located at the investigator's site.	Add: "For (re)packaging or labelling activities performed by or under the supervision of a licensed pharmacist, the sponsors Qualified Person is not required to certify the activity in question. "

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Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
44	The last sentence of this paragraph should be deleted. Chapter 7 of EU Guide only requires a Technical Agreement when contract manufacturing or analysis takes place. There will be many circumstances where the QP works for the sponsor company and therefore no Technical Agreement will be required. Management of the Product Specification File through a change control process should be managed through the Quality Management System which is clearly defined in §1 of this annex	In practical terms, this can best be achieved through a change control process for the Product Specification File and defined in a Technical Agreement between the QP and the Sponsor (if different).
Table 2 (Batch release of products)	Neither the directive 2001/20 nor the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial" require a Certification of the Qualified Person (QP) that the analysis and tests are carried out in compliance with GMP at least equivalent to EU GMP. Thus, this leads to different interpretation from different countries (i.e. some competent authorities are requiring such certificates as part of the CTA)	Delete last paragraph of section e) "~~Where these analyses and tests are not performed in the EU, this should be justified and the QP must certify that they have been carried out in accordance with GMP standards at least equivalent to those laid down in Directive 91/356/EEC~~."

Please feel free to add more rows if needed.

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