E.I.P.G. - European Industrial Pharmacists Group

Submission of comments on the following consultation documents:

Document A

"Commission Delegated Act on Principles and guidelines on good manufacturing practice for investigational medicinal products for human use and inspection procedures, pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014"

Document B

"Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014"

EIPG Position

General Observations

As specified in the **Consultation Document A** (lines 27-31), this consultation document carries the majority of the principles and guidance set out in Directive 2003/94/EC relating to IMPs for human use.

However, it is to be noted that these principles and guidance are also currently applied to market medicinal products and that many pharmaceutical companies currently manufacture both market medicinal products and IMPs, by applying the same GMP principles, though following the specific additional requirements of Annex 13 of EudraLex Vo. 4 Part I.

We agree on the development of specific GMP principles and guidance for IMPs, containing more appropriate requirements, focusing on the specific activities which are required in IMPs manufacture and

control. We expect that this new guidance will be the result of an evolution of Annex 13 (which will be delated)

However, we observed that a few requirements which are today present in Annex 13 are missing in the **Consultation Document B**, which should represent the future guidelines on GMPs for IMPs.

In particular, we think that in order to improve the specificity of these guidelines, the following points should be taken into due consideration:

a) A more extensive emphasis should be reported about the co-operation (interaction) between the manufacturer and the sponsor. This is in relation to, at least, the following activities:

- Outsourcing of operations
- Storage of samples
- Shipping operations
- Supporting on auxiliary materials

b) A better emphasis should be made on the presence of a Technical Quality Agreement between sponsor and manufacturer, covering their interacting activities. The simple reference to EudraLex Vo. 4, Part I, Chapter 7 seems to be not sufficient, taking into account the specificity of GMPs as applied to IMPs.

c) The two step procedure - certification by the QP and release by the sponsor for use in a clinical trial – (as reported in Annex 13 at points 43-47) should be kept as a key requirement for a better management of shipping operation.

d) A better emphasis should be made on the application of the principles of Quality Risk Management, taking into account the degree of complexity of the manufacture of IMPs and the progressive increase of product and process knowledge. This approach would be essential when considering, at least, the following GMP activities, as mentioned in **Consultation Document B**:

- Qualification of supplier of starting materials (line 132)
- Control of cross contamination risk (line 168)
- Validation of manufacturing process (line 289)

e) The glossary of **Consultation Document B** should be completed by adding a few definitions which are missing, such as: blinding, clinical trial, investigator, randomization, randomization code, sponsor (which are present in Annex 13)

f) Some minor points about the text are made on **Consultation Document B**:

- Line 338-339: *stability studies* should be mentioned for determining the expiry date
- Line 352: clarification about "*and/or* "should be added
- Line 363-364: is this requirement also applicable to on-site re-labelling?

g) We also expect there will be no change to current practice for inspection of manufacturers located in third countries.

Response/Comments to Questions

Responses to Questions, contained in Consultation Document A, are here below reported.

Question 1a:

Would a requirement for a product specification file (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) be useful to be introduced?

Response/comment

The compliance of the batch with the Product Specification File should be assessed prior to releasing the batch. Based on this, a special requirement seems unnecessary.

Question 1b:

Do product specification files exist for manufacture of all investigational medicinal products in the EU?

The product specification file should exist for any IMP which is manufactured according to Annex 13

Question 2:

Different options exist for the retention period of batch documentation:
a) Retention for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever is the longer period
b) Retention for at least 25 years after the end of the clinical trial in line with the retention period of the clinical trial master file.
Please indicate the preferred option with justification.

It seems irrelevant to store the batch documentation for 25 years in line with the clinical trial master file, unless batch documentation is included in the clinical trial master file.

Storing batch documentation for such a long time even though the clinical trial is already discontinued or complete is unnecessary. Therefore, Option a) is preferred.

Question 3:

Would it be feasible to require that Certificates of Analysis should accompany each shipment of imported investigational medicinal products as a means to ensure that analytical control had been carried out in the third country? Please, elaborate your answer to this question.

The CoA may list information that should be undisclosed or it may contain technical information that is not understandable to non-technical staff. For these reasons, it is not necessary to include

the CoA in shipping documentation. Imported products are already subject to local and GMP arrangements, as a full analytical control is required for a product imported from a third country.

Question 4a

Should retention samples also be required to be retained by the manufacturer?

Since retention samples are stored for identification purposes, they should be stored by the manufacturer responsible for the packaging operations.

The meaning of "manufacturer" in the question needs to be clarified (manufacture in multiple sites)

Where the manufacturer is not responsible for the packaging operations, it is not necessary for the manufacturer to store retention samples.

In case the manufacturer is also responsible for the batch certification and final release, it should be defined in the Quality Agreement where the retention samples should be stored.

Question 4b

If only reference samples are required, would a requirement for photos of the investigational medicinal product, the packaging and the labelling to supplement the reference sample be useful? Please justify.

Since reference samples are stored for the purpose of being analysed, photos are not relevant for the scope. However, photos and other relevant material – packaging, labelling – could even be taken and stored when retention samples are not stored.

The decision on how to proceed should be part of the Technical Quality Agreement between sponsor and manufacturer.

Question 5a

In how many clinical trials authorized under the Clinical Trials Directive[3] has Article 13(3)(c) of that Directive been used? Please provide figures both as actual number of trials and as a percentage of the trials authorized, if available

No figures have been collected.

Question 5b

In how many clinical trials authorized under the Clinical Trials Directive, is the comparator product not authorized in an ICH country (EU, US, Japan, Canada and Switzerland)? Please provide figures both as actual number of trials and as a percentage of the trials authorized, if available

We have no figures available but are unclear why the numbers are relevant.

E.I.P.G. __24.11.15_____