Bundesverband der Arzneimittel-Hersteller e.V.
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BAH comments

on the 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

Common part:

The Bundesverband der Arzneimittel-Hersteller e. V. (BAH), the German Medicines Manufacturers' Association, represents the interests of the pharmaceutical industry in Germany comprising international companies as well as local small and medium enterprises (SME). By company membership BAH is the leading trade organisation of the pharmaceutical industry in Germany. BAH covers the entire range of the industrial landscape from self-medication medicines (OTC) through to prescription drugs (Rx) and medical devices.

BAH welcomes the public consultation concerning good manufacturing practices and clinical trials for human medicinal products, opened August 28, 2015. The BAH's Expert Group on GMP for IMPs in Clinical Research would like to comment on the "Commission Delegated Act on Principles and guidelines on good manufacturing practice for investigational medicinal products for human use" by answering the questions within the consultation paper for the Delegated Act.

However, even if the BAH's Expert Group understands the need for a new legal base on GMP for IMPs coming with the EU regulation on Clinical Trials (EU/536/2014), the group feels there is not really a need for drawing apart completely the GMP requirements for IMPs and authorised medicinal products. The actual situation with a common part on GMP for both and additional requirements for IMPs, due to their special situation, worked well for the past decades and was continuously adapted to new knowledge as needed. The Expert Group foresees an increased workload and investments necessary for industry as well as for all authorities involved. Training efforts and expertise for experts at the manufacturing site, for GMP inspectors as well as for surveillance authorities issuing manufacturing licenses will be doubled. Bureaucracy will be more complicated to get the required certificates and supporting documents necessary for regulatory procedures involved.

Therefore the BAH's Expert Group on GMP for IMPs in Clinical Research questions the dimension of the new legal basis with two Delegated Acts in parallel, introducing two parallel areas on GMP requirements for IMPs and for authorised products. The Expert Group proposes to have one Delegated Act for common requirements on GMP instead with additional guidelines on the manufacturing of IMPs and manufacturing of authorised medicinal products.

Special part (Questions)

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?*

Answer:

We believe that a particular product specification file is not necessary or useful for investigational medicinal products. The relevant information including history of development is already laid down in the IMPDs and directly used for the above mentioned processes. The content of an IDMD is more (additional clinical and pre-clinical information) than what is proposed for a PSF so the requirement would only generate an additional file with duplicated information. This would increase the burden on generating, maintaining and archiving documents required for clinical trials in the EU. Additional the data for each individual batch are kept in the batch records, analytical results for CoAs and import and distribution documentation.

Question 1b: *Do product specification files exist for manufacture of all investigational medicinal products in the EU?*

Answer:

Companies seem not to have an explicit particular PSF, but have the above mentioned documentation in place covering the processes with SOPs and internal policies. Some companies have started to prepare SOPs for the future creation of PSFs for IMPs.

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.

Answer:

Option b is preferred.
We think this can be handled easier. A fixed timeline is less complicated than a flexible one. Additionally, "late" requests from trial participants could be answered easier and so the longer period offers a higher level on safety. Also the retention period of batch documentation would correspond with the retention period of the TMF and the essential documentation of IMP and TMF are ensured.

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.*

Answer:

Yes, this should be required, to ensure that any imported IMP, which was ordered according to specifications laid down in a quality agreement, fulfills the defined

specifications. Also if the manufacturer in a third country is not able to perform the analytical tests, contract laboratories should be assigned to perform the tests and to generate a CoA. We think Certificates of Analysis will ensure the quality of the IMP and should accompany each shipment of IMPs or arrives at the importer site at the same time.

Question 4a: *Should retention samples also be required to be retained by the manufacturer?*

Answer:

The QP who releases the IMPs or the API for the IMP has to keep necessary retention samples for a clinical study medication. In fact, in case of export, not only the QP releasing the API/IMP for export should draw retention samples but also the QP of a pharmaceutical company importing IMPs/APIs will draw additional retention samples as this QP will be responsible for the final release in his country. As retention samples are always required for additionally tests in case of doubts, also the manufacturer of the IMPs should hold own retention samples for his own protection.

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.*

Answer:

We think additional photos might be useful, but to have them in addition to physical reference samples should be a case by case decision. In general, this should be an option but not a requirement.

Question 5a: *In how many clinical trials authorised under the Clinical Trials Directive 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 authorised, if available.*

Answer:

No figures can be provided by the Expert Group as per company no study or only about 1% of all studies have been identified as conducted under article 13(3) of directive 2001/20/EC.

Question 5b: *In how many clinical trials authorised under the Clinical Trials Directive, is the comparator product not authorised 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 authorised, if available.*

Answer:

No clinical trial was identified.