European Industrial Pharmacist Group

Concept Paper on a Guideline on Chemical and Pharmaceutical Quality Documentation concerning Biological Investigational Medicinal Products in Clinical Trials

The European Industrial Pharmacists Group representing the views of the member associations in the 27 member states of Europe welcomes the provisions stated in the consultation paer on Chemical and Pharmaceutical Quality documentation concerning Biological Investigational Medicinal Products in Clinical trails.

On behalf of EIPG, below please find comments to the above mentioned concept paper.

This new guideline is welcomed as the provisions stated with in it are related as long overdue.

In general it is desirable that the guideline has the same template structure as the "Guideline on the requirements to the chemical and pharmaceutical documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004)". If possible, with a table overview of the different requirements and expectations for phase I to III and post phase III, i.e. activities that are not essential until a marketing authorisation application is filed.

It is hoped that the guideline will state the minimum essential requirements that should be met but indicate that a certain degree of flexibility can be acceptable on a case by case basis, dependant on the product type, potential unmet clinical need and clinical development phase. Ideally, the sponsor should be able to present arguments and justifications for the suitability of the development work performed for a particular product at a particular clinical development phase. Sound arguments would be necessary for any exceptions that could impact on critical product quality parameters. Patient safety is of the utmost importance; exceptions could only be allowed if supported by convincing rationales and risk-benefit assessments.

It is requested that the new guideline can function as a one point of reference for biotechnological/biological IMPs, i.e. that as far as possible

guidance is contained in this guideline rather than referring to existing guidance. If existing guidance is referenced directly or used in the authoring process it is requested that a summary/ reference list is included. It is recommended that the "Guideline on strategies to identify and migrate risks for first-in human clinical trials with investigational medicinal products (CHMP/SWP/28367/07)" and all other relevant guidelines are considered when authoring the new guideline.

It is requested that the scope also addresses requirements for adjuvants (both commercially available and investigational adjuvants) and media that may be administered with biotechnological/biological IMPs.

It is requested that the new guideline outline the minimum essential requirements and clarification of the extent of information and detail necessary in relation to:

1) the structure of a molecule and the quality characteristics of the drug substance

2) cell banks - expression vector, host cell, recombinant production organism, MCB/WCB production and characterisation expected for phase I, II, III up to registration.
The level of detail and extent of documentation for raw material of human or animal origin used during cell line development before establishment of the master cell bank should be outlined.

3) characterisation of process and product related impurities, outlining minimum essential requirements. Ideally the extent of impurity characterisation expected for phase I, II, III up to registration should be outlined.

4) the manufacturing process and control of critical steps and in-process controls
It is expected that only critical in-process controls which are known to ensure product quality and patient safety should be stated, to give an indication that controls are in place during manufacture and if applicable to give assurance that the final specifications will be met.

5) the extent of development and/or validation of the manufacturing process that is required prior to and during clinical development with expectations for phase I, II, III and addressing the fact that the process will change in development and scale-up, what information and rationales are necessary when process changes are made.
It is expected that only validation of critical manufacturing steps which can impact patient safety are validated during clinical development e.g. the sterilisation process, virus validation reduction steps. Process changes due to process development between clinical phase to the critical steps that can impact patient safety will require re-validation/verification. It should be

possible to perform full process validation on e.g. consistency batches produced in conjunction with submission of the final registration file.

6) the extent of development and qualification/validation required for the analytical procedures with distinction between the analytical procedures used for Drug Substance/Drug Product release, in-process, characterisation and stability analysis. In particular basic requirements for safety relevant analysis i.e. purity/impurity endotoxin, DNA, HCP and sterility analysis) and non-safety analysis including expectations for phase I, II, III.

7) setting and justification of preliminary specifications with distinction between specifications for safety relevant analysis i.e. purity/impurity - endotoxin, DNA, HCP, sterility and aggregate analysis and non-safety analysis
-include expectations for phase I, II, III and extent of information /rationale needed when changing a DS/DP specification
-In general the specification limits for impurities should be based on the levels qualified in toxicological studies, or based on existing safety limits. Batch release data and stability data should not be the only basis for setting specification limits as such data is normally limited during clinical development.
Allow the opportunity for industry to present risk based justifications of specifications and perhaps even challenge existing safety limits e.g. process related impurities specifications – it could be argued that DNA from an E. coli cell line is less of a risk to patient than DNA from a mammalian cell line.

8) the requirements for stability data,
-addressing the need for justification that the analytical methods are stability indicating
-state acceptable examples of real time/accelerated stability data necessary to allow a IMP shelf-life of X months
-allow as per CHMP/QWP/185401/2004 the possibility to inform the authorities at the time of CTA filing the intentions of stability extension during the study based on acceptable data from ongoing stability studies.
-studies of compatability of the IMP with its immediate packaging, between all components for multi antigen products, with an adjuvant, reconstitution medium, diluent or any medium and the syringe/infusion system used when administering the IMP
- in-use stability requirements
- extractable/leakage data requirements
- possibility to repeat a container closure challenge at the final time point of a stability study rather than repeating a sterility test

9) changes that require a substantial amendment to a clinical trial application
-with examples of changes that require substantial amendments.

The above 9 points come from the concept paper, requests for specific detail to these points are in italics. In addition to these points it is requested that the topics below are also addressed.

Drug Product:
- The extent of information needed on the formulation development and justification of the formulation
- The formulation will often change during development. Extent of information /rational required when changing the formulation
- Data needed on drug compatibility with container closure system and syringe/infusion system (drug absorption and extractable/leakage studies)

Comparability:
Highlight the requirements and expectations of data necessary to show comparability between batches. This is of course highly dependant on the complexity of the product, but general guidance would be beneficial, potentially with examples of what can be acceptable for a specific type of product and clinical phase. The extent of validation of the process to allow comparability conclusions should be addressed.

Reference material:
Data needed / characterisation requirements for analytical reference material

Facilities and Equipment
In general IMPs are required to be manufactured according to GMP at approved facilities. As such, it should not be required to provide information on facilities and equipment in the IMPD in detail until submission of the registration file. Ideally, it should be possible to state that the sponsor is responsible for the manufacture and analysis regardless of whether manufacture or analysis are performed at the sponsor's facilities or outsourced.

Please address any queries to;
John DR Jolley
The Chase
Badgers Ridge
Newbury
Berks RG20 0LQ
johndrjolley@aol.com