GMP REQUIREMENTS FOR CLINICAL TRIAL MATERIAL / INVESTIGATIONAL MEDICINAL PRODUCT MANUFACTURING

Clinical Trial Materials (CTM) or Investigational Medicinal Products (IMP) are medicinal products used to confirm the efficacy and safety of the drug, which is in the trial stage, on human population. This means, clinical trial material is destined to be used by some of the most vulnerable patient populations (including the terminally ill).

The most important element about CTM is that there is very limited information available on the safety and efficacy of the medicinal product. Hence lot of care and attention is necessary for the manufacture and supply of clinical trial material as Quality Assurance of experimental material going into human beings for the first time is much more critical. This serves a dual purpose of eliminating risks to clinical trial volunteers (estimated at more than 40,000 annually and still growing) the organization.

Are there any regulations / guidance documents available to understand the exact GMP requirements for such products ? Are GMP applied consistently for them ? Well the answer is yes and no too!. Why is this contradiction ? There appear to be two reasons for this.

One, the personnel involved in the development efforts always carry a feeling that drug discovery is a creative science and there should not be any limitations placed on this process. If one tries to bind or limit them in some systems, the expanse is lost and it stems the thinking and application process. This may also further delay the already lengthy drug discovery process. The activities of drug development are carried out at R&D centers, by highly qualified technical scientists who many times fulfill the joint activities, for instance, of analytical development and material release. The former encompasses trial and error aspect while the later is a confirmatory process. What is therefore critical is the thorough understanding of tasks, clear requirements of quality and responsibilities involved in the project, particularly in the absence of formal QA.

The other aspect involved in this process, apart from manufacturing and testing, is the distribution of clinical trial material. When the supplies are small in number (i.e. not as voluminous as commercial supplies), the aspect of good distribution practice poses a different risk altogether depending upon the distribution channel used. However, it should be remembered that the storage, handling, and distribution of temperature sensitive drugs represent an increasingly important component of the global pharmaceutical supply chain. Clinical trial material or investigational medicinal products are an important part of the earliest stages of the life science supply chain. Hence the pharmaceutical supply chain

should ensure product quality and protect patient safety for CTMs/IMPs in a manner similar to that of commercial products.

The second reason on the division in quality is due to the different approach of regulatory agencies, for instance, the EU and US FDA. The EU GMP requires that all clinical material must be manufactured in accordance with the requirements of Annexure 13 (which has been further amended / upgraded in 2010). There is no much difference in the various GMP requirements for commercial products and CTMs as per this document and it also refers to ditto the provisions mentioned in the basic EU GMP guide for medicinal products part 1. However, it is surprising to note that despite all discussions and unfavourable comments from the experts, US FDA issued a final rule exempting most phase 1 clinical material from GMP regulations.

The September 15, 2008 clarification issued by US FDA states that if the compound is already in use in a phase 2 or phase 3 trial, or if the compound is already marketed, the clinical material must be manufactured following the GMP regulations, but for phase 1 trial, for the first time, the organization does not need to follow the GMP regulations, although they must follow some standard of GMP in that manufacture. This requirement of some GMP standard particularly is because all drugs must be manufactured per the GMPs, per the U.S. Federal Food, Drug and Cosmetic Act. (FD&C Act section 501(a)(2)(B), GMP compliance needed for all drugs, No distinction made clinical/commercial. 21 CFR 210.3 (definitions), (4) Drug product: Applies to all drugs, including placebos. 21 CFR 211 (reference 211.1(a)) Scope- for all drugs administered to humans or animals).

This means, the US FDA removed an enforceable standard (the regulation) in favor of using a guidance document (non binding recommendation) for CTM GMP. Further to this is an interesting account in the excerpt from FDA guideline on Preparation of Investigational New Drug Products, “When drug development reaches the stage where the drug products are produced for clinical trials in human or animals, then compliance with cGMP is required. FDA, while recognizing the differences between the manufacture of investigational products and commercial products, believes that it is nonetheless vital that investigational products be made in conformance with current good manufacturing practice.” Let us look at some differences between the manufacture of clinical trial material and commercial products as mentioned in the table on next page:

ASPECT	CLINICAL	COMMERCIAL
Information	Limited, as the stage and state is exploratory.	Adequate, detailed as stage and state is established.
Use / Application	For volunteers of clinical trial or limited patients, most of them known, identified, traceable.	Unlimited users, not known to the manufacturers, difficult to trace individual users.
Scale of manufacturing	Small scale	Full scale
Toxicity	Limited data	Toxicity qualified
Process	Starts, first time, may be unique non-repetitive, critical parameters not fully known	Proven acceptable ranges and critical parameters established, consistent
Production	Lack of fixed routines, package designs	Planned routine production, fixed packages and designs
Labelling	Blinding is an necessary aspect, Marking and information differs	Always open, marking and information consistent
Validation	More emphasis on verification	All aspects of validation covered
Material Requirements and attributes	Limited data and knowledge in terms of API as single batch may be used	Better data base as multiple API batches are used.
Other Material requirements	Placebos are almost essential	Placebos are not used
GMP requirements	Applicable – the scope and extent may vary, no uniform common regulations, change agency wise, clear guidelines missing in certain areas, applied at appropriate stages	Applicable – scope and extent detailed, uniform common requirements principally, each agency advocates common minimum requirements and applied at all the stages

With few aspects of the differences discussed in the table above, let us look at the commonalities involved :

- Both finished commercial dosage forms and CTM must be produced and controlled according to GMP and Good quality control lab practices and sometimes GLP.
- They should be produced in accordance with principles / requirements / commitments of Marketing authorization.
- There should be a quality management system in place that covers every aspect from procurement to distribution and quality evaluation.
- Material used in the manufacturing of CTM should be in accordance with approved specifications with approved methods / procedures for manufacture and control operations.
- Approval for release of the batch by QA.
- The facilities in which CTMs are manufactured must be qualified.
- Equipment and instruments used in the manufacturing and testing of CTMs should be qualified for use.
- Recruitment, selection, training and medical fitness of personnel engaged in the manufacturing of CTM.
- Appropriate change management system.
- System of failure investigation and market complaint review and dispositions.
- Appropriate contamination control and containment measures necessary.
- Maintaining of the GMP continuum is essential.

Through the above discussion, we realize that in clinical trial material there may be added risk to participating subjects compared to patients treated with marketed products. The whole objective therefore is to adopt a risk based approach from the volunteers view point and successful outcome of clinical trials. There should not be nay hindrance in the path of development from unsatisfactory manufacture.

Adequate and appropriate QMS (keeping in mind the requirements of Pharmaceutical Quality Systems, ICH Q10) for clinical supply manufacturing is therefore a challenging area. Careful attention to sound science, as GMP regulations / requirements is essential to assure a successful molecule to market place journey. The GMP compliance levels for certain phases of development may require careful interpretation, but a scientifically based, conservative approach may be the best way to maintain an appropriate balance.