

What Every CRA Should Know About GMP (and was afraid to ask)

Even though the deadline for implementation has passed, there is still much confusion among clinical research professionals about how the European Clinical Trials Directive 2001/20/EC (CTD) will affect the way in which we work. Despite the numerous guidance and discussion documents that exist and the training courses and seminars that have taken place, I have yet to meet a person who feels that they are fully prepared for the changes that will be enforced on 1st May 2004.

We know that sponsor companies, contract research organisations (CROs) and sites are all trying desperately to be ready for the transition, but what about the individuals at the coal face of clinical research? The clinical research associate (CRA) is in the sometimes unenviable position of being the primary contact between the clinical research site and the sponsor, and it is their knowledge and understanding of the new requirements that will help smooth the path for studies taking place under the CTD. Although the majority of CRAs will have received training or information regarding the good clinical practice (GCP) aspects of the new directive, how many are aware that the implementation of Good Manufacturing Practice (GMP) requirements will also affect them?

Before being able to decide what aspects of GMP are pertinent to the CRA, the role of the CRA must be clear. This job can vary considerably across companies and although some CRAs will find themselves fulfilling only the monitoring aspects of the role, others will also be responsible for other project management tasks. As such, the importance of certain areas of GMP will change for the individual concerned. In this article I will try to explain the purpose of GMP and some of the details that might be pertinent to a CRA with regards to fulfilling their monitoring responsibilities under the CTD.

A (Very) Brief History of GMP

Principles governing GMP have been present in the pharmaceutical industry since the 1930's. However, despite the FDA having regulatory control over GMP since then, it was not until the 1970s when the Medicines Control Agency (MCA) released the first version of the "Rules and Guidance for Pharmaceutical Manufacturers and Distributors" otherwise known as the "Orange Guide". This was followed by the European directive 91/356/EEC in 1991, which meant that such standards became commonplace throughout Europe.

GMP was introduced to ensure that "*...products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification*". It is clear from this statement that the primary consideration was for the quality of marketed products and not those used in clinical trials. Although aspects of GMP have been followed in the production of investigational medicinal products (IMP) at many manufacturing and packaging facilities it is only with the introduction of the CTD that such measures have been made mandatory.

Articles 13, 14 & 15 of the CTD contain requirements for the quality standards and labelling that must be met for medicinal products used in clinical trials from the 1st of May 2004. In addition the need for inspection procedures for ensuring compliance to GCP and GMP requirements are also covered. The primary purpose of this part of the directive is to ensure that the same standards are applied in the manufacture of medicinal products used in clinical trials, as are already accepted for medicines manufactured for marketing. On reading the wording of the directive itself, one could be forgiven for not understanding the extent of the impact that these requirements will have for the CRA; one might think that only the manufacturing facilities would be affected; however if one takes the time to wade through the related GMP documentation for example Volume IV Good Manufacturing Practices, Annex 13 Manufacture of Investigational Medicinal Products July 2003 (Annex 13), one might get an altogether different impression.

Personnel

Section 3 of Annex 13 pertains to the personnel requirements for people involved in handling IMP. It states "*All personnel involved with IMP should be appropriately trained in the requirements specific to these types of products*". Not only does this statement mean that

CRAs themselves must be trained in relevant aspects such as handling and storage conditions, but also that staff involved at the investigative site must receive adequate training to enable them to dispense IMP, instruct study subjects on how it should be used, relabel supplies with new expiry dates (when applicable) and in some cases even administer the IMP themselves. As the CRA is the primary contact with the investigative site, and commonly the person present at the site initiation visit, this means that the CRA must be well versed in all these aspects of the IMP requirements in order to provide adequate training and information to the study site team.

Blinding

It is a requirement of GMP that systems should be in place to “[allow] for identification of ‘blinded products’ when necessary, including batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency”. Although the majority of such systems will be required to be put in place by personnel at the manufacturing/packaging facility, it is imperative that there are procedures in place that allow for not only study subjects to be unblinded, when necessary, but also that a process exists to allow for a batch recall to be performed and accounted for by the CRA.

Code-Breaks

Randomisation codes should be controlled via documented procedures that describe “...the generation, security, distribution, handling and retention of any randomisation code used for packaging IMP, and code-break mechanisms. Appropriate records should be maintained.”⁴. Although ICH GCP requires that “Documentation of investigational product and trial related materials shipment”⁵ be present both at the investigator site and sponsor, it does not specifically mention what documentation is required with regard to randomisation procedures and code-break information. It must be considered what records should be maintained at site to ensure that the requirements of both ICH GCP and GMP are met, and what role the CRA should play in this aspect of the study. If not already covered in a documented procedure, a CRA must consider how they will account for, and document, the presence of all required code-breaks, and ensure that they remain unopened, but accessible, to the investigator throughout the study.

Labelling

Although most IMP packaging will take place prior to the involvement of the CRA, it is possible that throughout the course of the study there will be a need for IMP expiry date relabelling to be performed at the investigative site. Annex 13 section 24 requires that “precautions against mis-labelling such as label reconciliation [and] in-process control checks by appropriately trained staff should be intensified”⁶. As such, the CRA must ensure that any relabelling of IMP that takes place at the site should be controlled, and allow for continued accountability of the IMP. The labels used to perform this procedure must also meet GMP standards. In my experience, labels are usually provided to the monitoring group by the manufacturing or packaging facility. However, the CRA should know the requirements of such labels to ensure that they can be confident that all such requirements have been met in the label content - especially if part of their role happens to include the sign-off or translation of IMP labels.

The fortunate CRAs out there will be working for companies with comprehensive Standard Operating Procedures (SOPs) that will cover all the aspects of monitoring for which a CRA is responsible. It may come as a surprise to some that these requirements are new, as they may have been performing these tasks for a while. What the CRA must now be aware of is the increased likelihood that compliance with the requirements, and therefore the SOPs, will be subject to audit or inspection either by the internal QA group or by the regulatory authorities such as the MHRA. CRAs may have experienced a number of investigator site audits whilst working in the industry, but the focus of the audits and inspections will now include the GMP requirements of the directive and as such, an in-depth knowledge of SOPs is not sufficient; CRAs will also be expected to know the regulations.

This might sound obvious as one would always expect a CRA to have a good understanding of ICH GCP guidelines as well as knowing what their internal SOPs require, but unfortunately it is not common for CRAs to be provided with training or information in guidelines such as

GMP that are considered by many not to be directly relevant to them; At a recent training session a colleague of mine was surprised to discover that in a room full of experienced CRAs, not one of them had heard of Annex 13, or knew to what it pertained. It seems that it has often been considered sufficient to include requirements in the company SOPs without explaining the reasoning behind them, and without providing specific regulatory training. One risk of doing this is that your CRAs will not be aware of which study related tasks are legally mandatory and which they might be able to deviate from. In addition, they are not being provided with adequate knowledge to ensure that staff at investigator sites are meeting regulatory requirements; site staff have no obligation to follow company SOPs, but they do have to adhere to the law. By informing CRAs of what is required under the directive, they are empowered to educate the site staff and ensure that the study is being conducted appropriately.

If you are not so fortunate as to have such comprehensive SOPs then you are at even more of a disadvantage. By being aware of the requirements of GMP that affect your job function, you will hopefully be able to influence and inform those people responsible for writing the company SOPs and ensure that procedures are updated or introduced as soon as possible and in the mean time, you are at least aware of what should be done.

Although the majority of the Orange Guide and Annex 13 are not applicable to the CRA or Investigator role, it is reasonable to expect an individual to be aware of the regulations that are followed by their colleagues and where the regulations apply across job functions. Inspectors will not only want to be convinced that each individual involved in a clinical trial is appropriately qualified "*by training and experience*", they will expect this to be demonstrated via the completion of documentation such as IMP accountability and storage records and evidence of study specific training both for the CRA and the site staff. Of course you must work to your SOPs but you must also know why your SOPs require you to perform certain tasks. This knowledge will help you to work with your study sites to achieve a high standard of documentation - and will certainly prove useful should you ever be present during an audit or inspection - but it will also aid you in your relationships with colleagues who will appreciate your understanding of their needs.

We all know that the ultimate goal of a clinical trial is to get a marketing authorisation for your IMP, having produced good quality data collected whilst protecting the safety and well being of study subjects. It is the responsibility of each company and individual involved in the trials process to be aware of the regulations that allow this goal to be met in a scientifically sound and ethical manner.

References

1. Page 3, Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002. MCA
2. Section 3 Personnel - Volume 4, Good Manufacturing Practices, Annex 13 Manufacture of Investigational Medicinal Product, July 2003 Revision 1
3. Section 21 Blinding Operations - Volume 4, Good Manufacturing Practices, Annex 13 Manufacture of Investigational Medicinal Product, July 2003 Revision 1
4. Section 22 Randomisation Code - Volume 4, Good Manufacturing Practices, Annex 13 Manufacture of Investigational Medicinal Product, July 2003 Revision 1
5. Section 8.3.8 ICH Harmonised Tripartite Guideline for Good Clinical Practice
6. Section 24 Packaging - Volume 4, Good Manufacturing Practices, Annex 13 Manufacture of Investigational Medicinal Product, July 2003 Revision 1
7. Section 2.8 ICH Harmonised Tripartite Guideline for Good Clinical Practice