Importation of Clinical Trials Materials:

Contracts, Technical Agreements and Qualified Persons

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GMP(医薬品の製造管理および品質管理に関する基準)
有資格者
製薬会社との契約書
輸入
GCP(医薬品の臨床試験の実施に関する基準)

Summary

Since the transposition of the Clinical Trial Directive (2001/210/EC) into national law throughout the EU, the requirements for the importation of medicinal products for clinical trials have changed significantly. The study sponsors, the manufacturers, the importers, the packagers and the Qualified Persons all have their roles to play, and it is becoming more and more important to have written agreements in place to describe these roles. The so-called Technical Agreement is a key document to ensure GMP compliance, and is routinely inspected by the Authorities during GMP inspections. This article describes points to consider when drafting a comprehensive Technical Agreement.

臨床試験に関する新EU指令（2001/210/EC）がEUメンバー各国で法制化されて以来，治験用医薬品の輸入のための要件が大きく変わった。治験依頼者，治験薬製造業者，輸入業者，包装業者，有資格者にはそれぞれ果たすべき役割があり，こうした役割を文書化して契約書を作成しておくことがますます重要になりつつある。「テクニカル契約書」と呼ばれるこの契約書はGMP遵守を保証する上で鍵となる資料であり，GMP査察時に規制当局から定期的点検を受ける。本稿では，包括的なテクニカル契約書を作成する際に考慮すべき点について述べる。

The implementation of the Clinical Trials Directive[1] has in many ways simplified and unified the regulatory environment for sponsors of clinical studies in Europe. In return, however, it has imposed a number of obligations on Sponsors, particularly in ensuring that they are complying with GMP requirements as well as with international norms of GCP. Many Japanese companies wishing to run studies in Europe will manufacture their products in Japan, and then export them to Europe for packaging and labelling under contract. Before the products can be released into the clinical study, they must be certified in Europe by a Qualified Person (QP), that all aspects of their manufacture, and supply comply with European standards of Good Manufacturing Practice (GMP), with the Clinical Trial Authorisation, and with the file of technical data relating to the product submitted to the Regulatory agency, the so-called *Product Specification File*. Thus we have several different people or organisations along the supply chain, all with different, but overlapping responsibilities (Table 1).

Organisation	Role
Sponsor (through Legal representative)	• Applies for and holds the Clinical Trial Authorisation **(CTA)** • Ensures that the study is carried out to GCP • Ensures that manufacture and supply comply with GMP
Manufacturer	• Possesses appropriate authorisations and licences to allow manufacture to take place • Makes product in compliance with the requirements of the Product Specification File and of the Clinical Trial Authorisation
Importer	• Possesses appropriate authorisations and licences to allow importation to take place • Holds product in compliance with the requirements of the Product Specification File
Packager	• Possesses appropriate authorisations and licences to allow packaging to take place • Packs and labels product in compliance with the requirements of the Product Specification File and of the Clinical Trial Authorisation
Qualified Person	• Certifies that the investigational product has been: – made and tested, – imported, – packaged and labelled in compliance with the Product Specification File and the Clinical Trial Application, And in premises that hold appropriate authorisations and licences And in compliance with EU GMP

Table 1: Roles in the Clinical Supply Chain

The QP must be a person named as QP on a relevant manufacturing licence in the EU, so he or she may be employed by the Packager or by the Importer, or indeed may in some cases be employed by the Sponsor, but since there can be only one QP responsible for certifying the product, he or she must have a knowledge of the quality systems operating throughout the supply chain.

If the prime role of the Qualified Person is to *certify* that the investigational product has been

– made and tested,
– imported,
– packaged and labelled

in compliance with the Product Specification File and the Clinical Trial Application, in premises that hold appropriate authorisations and licences and in compliance with EU GMP, then one of the biggest questions for the QP to answer therefore is "How do I ensure all this?"

The Technical Agreement

Most work between companies is carried out under the terms of a contract of some sort. The contract normally describes WHAT the services are that are being provided, prices, delivery and so on. It allocates risk, and the responsibilities for managing risk. It defines guarantees made by the parties and describes dispute resolution processes.

The Technical Agreement, on the other hand is a much more focused document, describing HOW the day-to-day activities are carried out. It defines reporting lines, and it provides the technical details that may be changed or updated throughout the life of the relationship.

The Contract and the Technical Agreement are separate documents, but they are closely linked. It is good practice to ensure that it is clearly stated that where there is a conflict in interpretation between the two documents, the commercial contract will prevail. It is worth noting that the two documents are often handled by quite different groups of people. The contract is negotiated between the lawyers and financial staff, but the terms of a successful Technical Agreement are best agreed by the technical or development experts involved: they are after all the people that have to make the agreement work in practice. Only once they are happy should the document be handed over to the lawyers to be turned into "legal language".

The QP Code of Practice[2] requires clearly-written Technical Agreements between the QP and the Sponsor, and between the various parties in the supply chain. Furthermore, it is clear that the Regulatory Authorities also regard the Technical Agreement as an essential document, and will require sight of a copy of any such agreement during the routine GMP inspections of the licence-holder and any contractors, citing Article 12 of the European GMP Directive[3] as their authority.

What then should go into a Technical Agreement? The guidelines that follow are no more than that: guidelines. Each case is different, and each Technical Agreement should be approached as a new project. Not everything that follows will

apply to all Agreements, but nonetheless there are a number of critical areas that must be considered by study Sponsors when negotiating a set of Technical Agreements with their contractors.

The Contractors

Are they on your Approved Supplier list? If not, carry out any necessary audits before the contract is finalised! Remember there may need to be multiple audits, with the Sponsor auditing the contract storage or packaging sites, but also the Qualified Person responsible for certifying the product may need to audit all the sites in the supply chain. If the QP is an employee of one of the Contractors, and the Sponsor owns the manufacturing site, there may be some delicate discussions to be had!

Description of work

Make sure that the detailed technical arrangements for the activity are described. Verify the location where your contractor will carry out the work (Is it the same site that you audited?). Give an outline description of the process and equipment to be used, the GMP/environmental standards to be applied, and any change control systems that you will require.

Amendments

Ensure that there is a clear mechanism for agreeing amendments to the Technical Agreement, especially for things like specifications.

Approval

Ensure that the Technical Agreement is approved by persons responsible for Quality Assurance in both organisations (and by the QP).

Standards for the work

Make sure you define the appropriate GMPs to be followed (the Contractor must comply with GMP and other relevant legislation, for example Health and Safety, Environmental Protection). You may need to provide information and guidance on this point if it is a new chemical or biological entity.

The Contractor must not sub-contract any work to a third party without your permission, and must agree to refrain from any activity which may adversely affect the quality of the product manufactured and/or analysed (for example work involving penicillins).

Validation work

Define the responsibility for any validation needed. Remember to include assay validation work to support equipment cleaning, and define any technology transfer processes that you want to use. The Directive requires that "Critical" processes should be validated (for example, sterilisation), but remember that some countries want full process validation even for Phase 1 studies. Whatever the validation requirements for the process, it goes without saying that all manufacturing and packaging equipment should be properly qualified.

Regulatory Inspections

The Contractor should notify the Sponsor prior to Regulatory Authority inspections: that gives the Sponsor the opportunity to be present. Remember: an adverse GMP observation may put your study at risk! Similarly, the Sponsor must tell the Contractor that the work is subject to inspection by Regulatory Authorities, particularly if the Contractor does not normally work in the pharmaceutical industry.

Materials Management

Make sure that responsibilities are clearly stated:

– for the purchase and/or supply
– for sampling, testing and release

This covers both the starting or packaging materials supplied by the Contractor and any intermediate bulk product supplied by the Sponsor. Remember to also define the appropriate storage conditions.

A particular point to note here is Transmissible Spongiform Encephalopathy (TSE) Certification: the European Authorities are very sensitive about this issue, and will always want proper certificates[4] in place before the QP certifies the products.

Documentation

Define the documents and records generated for each batch manufactured or packed, and define the responsibility, Sponsor or Contractor.

Ensure that there is a mechanism for Sponsor to keep the QP informed of changes to the technical data relating to the product, e.g. specification, methods of manufacture, stability data.

Record and Sample Retention

Define responsibilities and arrangements for retention and storage of records and samples. Remember that there are legal requirements for record-keeping that may outlast the term of the agreement.

Channels of communication

Good practice in the Technical Agreement is to name key quality and technical people in an appendix that is regularly updated. Give telephone numbers and email addresses as well if necessary.

Remember you need a mechanism for routine communication, as well as a mechanism for handling product or service complaints. It may also be necessary to have a defined mechanism for the resolution of disputes over technical matters including product quality, naming suitable "third-party" analysts.

Recalls

The recall decision and the management of any product recall is clearly the Sponsor's responsibility, but the procedures of both parties must be consistent. All necessary information must be quickly and accurately made available to the persons responsible for the recall, the Qualified Person MUST be involved, and responsibilities of individuals in each organisation need to be stated with contact points in case of emergencies. QPs are deeply involved in recalls and they need to agree the details.

Artwork and Labels

This is probably one of the most critical areas for clinical studies, and is one where things go wrong too often. There must be a mechanism for writing and approving label text, and a mechanism for verifying consistency with Clinical Trial Authorisation. The procedures for randomisation may need to be described, and there should also be a mechanism for the QP to review the label text.

Assembly of Finished Pack

Describe in outline any sampling or in-process inspection of the packaging and pack assembly operation. The quality standards need to be agreed, together with the nature of critical, major and minor defects. Again there must be consistency with the CTA, and a way for the QP to review the information BEFORE packaging takes place.

Deviations

Few projects ever proceed in the manner that was intended, therefore there should be defined procedures to handle deviations, errors, planned changes, out-of-specification analysis results and so on. Normally the contactor should report these to the Sponsor, but the QP responsible for certifying the product must also know about these.

Release of Product

Remember the final release to clinic is the responsibility of the Sponsor, but the QP must certify the product first. Therefore there should be a description of the mechanism for QP certification. Consideration should be given to defining:

- the Mechanisms for review of manufacturing and packaging records
- the Mechanisms for review of quality control results
- the Interactions between different QPs on different European sites[5] in the supply chain.

Conclusion

In conclusion, we can see that the Directive has clarified a number of issues for clinical development within Europe. Unfortunately, the view from outside the European Union is not as clear. A well-written Technical Agreement is a powerful tool for clarifying where responsibilities divide between companies, as well as for demonstrating to the Regulatory Authorities the commitment of the Sponsors to compliance with GMP and GCP.

References

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3. European Union Directive 2003/94/EC
4. Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01): http://www.emea.eu.int/htms/human/tse/tse.htm
5. EU Guide to GMP, Annex 16: http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm

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