Simon Bryson
is Director of European Biopharmaceutical Development Quality Assurance for GlaxoSmithKline R&D. He has a number of years experience in the development, manufacture and supply of licensed biopharmaceuticals and biopharmaceutical clinical trials supplies.

The European Clinical Trials Directive: What does this mean for the biopharmaceutical industry?

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Simon Bryson

Abstract 1st May, 2001, saw the final publication of the long-anticipated European Union Directive relating to *Good clinical practice in the conduct of clinical trials on medicinal products for human use* (2001/20/EC). The Directive consolidates, for the first time, aspects relating to the manufacture and provision of clinical material, clinical trial regulatory approval, and the protection of trial subjects, which encompass the conduct of clinical trials in the European Union.

There are certain aspects of the directive which sow the seed of change within the pharmaceutical industry. For the first time, a qualified person will be required to perform the release of the investigational medicinal product (IMP) for use in a clinical trial. Good manufacturing practice in the manufacture of IMPs will be a legal requirement universally across the EU. This was previously dependent on member states instituting controls voluntarily. There are also changes in the pre-approval process for some biopharmaceutical products prior to trial commencement. In this paper we will explore the contents of the Directive and consider how this will impact the biopharmaceutical industry.

Keywords: clinical trials, European Directive, good manufacturing practice, investigational medicinal product, qualified person

Simon Bryson
Director, European Biopharmaceutical Development QA, GlaxoSmithKline, South Eden Park Road, Beckenham, Kent BR3 3BS, UK

Tel: +44 (0)20 8639 6406
Fax: +44 (0)20 8639 6702
E-mail: sb78567@gsk.com

Introduction

The European Commission Directive 65/65/EEC requires that medicinal products have marketing authorisation prior to marketing in the EU, with the criteria of quality, safety and efficacy used to assess the acceptability of the medicinal product for approval.

The European Union is a complex regulatory environment, containing a number of individual member states, each of which may currently have its own particular requirements relating to the manufacture of clinical trial material and conduct of the clinical study. With considerable reliance placed on clinical studies in human subjects in the quest of proving the safety and efficacy of the medicinal product concerned, understanding the different member state requirements can be complicated.

Added to this complexity is the need to conduct clinical studies involving, in some

cases, thousands of subjects, which may involve studies conducted in universities or clinics. They may involve multi-centre trials conducted across a number of member states in the EU. The conduct of these multi-centre, multi-member state trials must therefore comply with the various member state national provisions. The complexity that has ensued has led to some delays in gaining approval prior to the commencement of multi-centre trials, with cases where one site may have completed its trial prior to trial commencement at another site.

Through this new Directive, the European Commission has built on the experience within the EU member states, ensuring the same level of patient protection and scientific standards are maintained. The requirements for the conduct of clinical trials in Europe have been simplified and provide some degree of harmonisation. Since the Directive leaves a certain amount of flexibility to the member states however, it falls short of complete harmonisation, with the potential for retaining some differences in member state regulations.

Nonetheless, the simplification of the processes goes some way towards reducing the regulatory burden for small biotechnology companies, as the multi-national regulations make multi-states trials extremely difficult. This having been said, there are changes within the legislation that do provide an increased regulatory burden in the manufacture and import of IMPs, and the verification of compliance with good clinical practice (GCP) and good manufacturing practice (GMP) which will be expanded on later in this paper.

Background

The concept of a clinical trial directive was initiated ten years ago when a white paper was published, proposing the need for a directive relating to the conduct of clinical trials in Europe. It was not until late 1995 that the EU issued the first concept paper, which was followed some six months later by the first draft directive in early 1996.

This was amended in a EU Parliament vote in 1998 and has undergone a number of changes since, with considerable input by industry, particularly EFPIA (European Federation of Pharmaceutical Industry Associations). May 2000 saw the European Council reach a common position, which was revised moderately in February 2001, with the final version published in the *Official Journal* of the European Community on 1st May, 2001.

Contents of the Directive

The Directive[1] comprises 24 articles, which can be broadly categorised as:

- scope and definitions;
- protection of the trial subjects;
- ethics committee;
- commencement of a clinical trial;
- good manufacturing practice;
- verification of compliance;
- clinical trial conduct and pharmacovigilance.

The specific provisions relate to the conduct of all clinical trials on human subjects involving medicinal products, Phases I, II and III, bioavailability and bioequivalence studies, but exclude Non-interventional trials, studies where the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation. The Directive brings together for the first time the GCP and GMP regulations.

The aim of the Directive is to ensure that the rights, safety and well-being of the human subject are protected, and hence delivers credible clinical trial results upon which the safety and efficacy of the medicinal product may be assessed.

Protection of the trial subjects

A clinical trial may be undertaken only if certain conditions are fulfilled. The benefits of the trial must outweigh the risks, the subject's participation in the trial should remain confidential, and as the data may be available to third parties they should be anonymous. Written or oral witnessed consent must be obtained from the patient

or legal representative, after they have received all relevant information in order to understand the risks and patients' rights, which include the ability to withdraw from the trial at any point. There must also be adequate insurance to cover investigator and sponsor liability, the patient should be provided with a contact point for further information, and the medical care of the subjects should be the responsibility of an appropriately qualified medical doctor or dentist.

Of particular relevance is the need for member states, if they have not already done so, to adopt detailed rules to protect from abuse individuals who are incapable of giving their informed consent. In addition to the general provisions laid out in the directive, there are specific requirements relating to the conduct of clinical trials on minors and incapacitated adults.

The directive's raporteur is a German paediatrician, Peter Liese, who has taken a keen interest in the text with respect to clinical trials on children. There is clearly a need to consider clinical trials on children in an attempt to improve, in many cases, the treatment available to them. Of particular significance to the vaccine industry, the text states

> Medicinal products, including vaccines, for children need to be tested significantly before widespread use. This can only be achieved by ensuring that medicinal products, which are likely to be of significant value for children, are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protect from the subjects.

An earlier draft of the Directive appeared to indicate that vaccine trials on children would be unacceptable.

This is a positive move within Europe, however, it is unlikely that the pharmaceutical industry in Europe will see immediate incentives comparable to those offered as a result of the US Food and Drug Administration Modernisation Act (FDAMA), which offers companies a patent extension of six months with paediatric exclusivity.

Ethics committee

Within the EU there exists considerable diversity of cultures, traditions and religious beliefs, which, in combination leads to differing expectations and practices in both legal and ethical form. The progression towards a united Europe gives the opportunity to create a basis upon which ethical standards and principles should be considered, without legislating on the basis of cultural differences.

The ethical principles that should be considered in medical research involving human subjects have their foundation in the Declaration of Helsinki (World Medical Association (WMA) General Assembly, Finland, June 1964), which has been subsequently amended through a series of WMA General Assemblies. The latest revision was at the 52nd WMA General Assembly held in Edinburgh, Scotland, October 2000.

Within the Clinical Trial Directive, member states are required to take the necessary measures for the establishment and operation of ethics committees. For multi-centre clinical trials, the member state must establish the necessary procedures for providing a single opinion for the member state. Thus, instead of potentially different opinions from each trial centre, there would be a single opinion, hence reducing complexity for the trial sponsor.

The ethics committee is required to give an opinion prior to the commencement of a clinical trial, in particular on the clinical trial design, protocol, personnel managing the trial, risk : benefit scenario, investigator's brochure, the informed consent process and recruitment of trial subjects. This is to ensure that there is adequate liability/compensation cover for the trial subject and sponsors in the event of injury or death attributable to the trial, and to review the adequacy of any reward or compensation arrangements in place.

The ethics committee has a maximum of 60 days to reach its opinion; however, member states may lay down a shorter period than this. The ethics committee may submit one request for supplementary

information, and at this point the clock is stopped, and restarted only once the supplementary information has been received. Unfortunately it is not quite so simple for biotechnology products. The directive enables an extension period of 30 days for trials involving gene therapy, somatic cell therapy and medicinal products containing genetically modified organisms (GMOs). In addition, a further 90 days is permissible for these products. For xenogenic cell therapy there is no time limit for review.

Commencement of a clinical trial

Before commencing a clinical trial, the trial sponsor must first submit a valid request to the competent authority. The sponsor can submit to both the ethics committee and the competent authority in parallel, which speeds up the process of trial commencement. Earlier drafts of the directive suggested that this would not be permissible.

The sponsor may not start a clinical trial with any medicinal product until the ethics committee has given a favourable opinion, and no rejection has been received from the member state competent authority within 60 days. The member states competent authority may lay down a shorter period than this, if this is in compliance with current practice, eg the UK currently has shorter timelines; however, it remains to be seen whether the UK will implement the 60 day period.

As is the case with the ethics committee's permissible review period, the competent authority may extend the 30 day review period by a further 30 days for trials involving gene therapy, somatic cell therapy, and medicinal products containing GMOs. In addition, a further 90 days is permissible for these products. For xenogenic cell therapy there is no time limit for review.

Further to the extended review period for trials involving gene therapy, somatic cell therapy, xenogenic cell therapy and medicinal products containing GMOs, these trials require written authorisation prior to trial commencement. This is a change to the current practice in many European member states; for example, in the Netherlands there is no prior approval route for trial commencement. Additionally, there is no suggestion in the directive that prior approval will be required for other biotechnology products.

The directive also prevents gene therapy trials being carried out which result in modifications to the subject's germ line genetic identity.

Good manufacturing practice

Medicinal products intended for use in clinical trials do not currently require a marketing authorisation. Nonetheless, member states did agree, at the time when the EU legislation 91/356/EEC on GMP for medicinal products for human use was adopted, that the principles of GMP should be applied to the manufacture of material intended for use in clinical trials. It was also suggested in a 1991 EU discussion paper[2] that it is illogical for experimental products not to be subject to the controls which would apply to the formulations of which they are the prototypes (Annex 13[3]). Member states may implement GMP controls voluntarily, and where they choose to do so they may use Annex 13 as a guide.

With the adoption of the Clinical Trial Directive, the manufacture and importation of investigational medicinal products will be subject to the holding of an authorisation. Associated with this is the requirement for the authorisation holder to have at their disposal, a 'qualified person' (QP). A QP is an individual who is appropriately qualified and certified by the relevant member state authority to release batches of medicinal product for human use within the EC, or European Economic Area (EEA).

QPs are in increasingly short supply, which is already an identified issue facing manufacturers of medicinal products licensed for sale in Europe. With the additional need for QPs in the release of investigational products, the issue is potentially set to worsen. Recognising this, the Directive does allow persons carrying out the activities of a QP at the time the

Directive is applied in the member state to continue to conduct those activities. This does appear to be similar to the 'grandfathering' clause that was used when the QP requirement was introduced for licensed medicinal products, in that companies are able to submit the name of persons whom they wish to be certified. It remains to be seen how the transition criteria develop. This may be member state specific; however, detailed guidance should be forthcoming on adoption of the directive.

The application of European GMP standards to the manufacture of medicinal products to be used in clinical trials in Europe is not restricted to those products manufactured within the EU. Products from a third country, and comparator products must comply with equivalent standards. This assurance will be the responsibility of the sponsor.

In the absence of a mutual recognition agreement (MRA) between the third country and Europe, a practical approach to how industry may assure compliance with European GMP requirements needs consideration. Detailed guidance from European regulators with input from industry representative bodies is required.

Verification of compliance

A number of member states, including the UK, have not until now been subject to compliance inspections. It is a mandatory requirement of the directive that inspections be conducted to verify compliance with the appropriate GCP and GMP standards.

Member states must appoint inspectors to verify GCP and GMP compliance of sponsors premises used in the manufacture and preparation of investigational material and clinical sites.

Member states will also have the ability to request inspection outside the EU, where the site is part of the supply chain for the material used in a particular clinical trial within the EU. The inspection will be conducted by appropriately qualified Community inspectors.

Clinical trial conduct, pharmacovigilance

The Directive provides detailed rules on the process to be followed for protocol amendment, and this requires approval prior to implementation of the revised trial protocol.

There is clearly a need to employ the same standards of safety monitoring in the use of investigational medicinal products (IMPs) as with licensed pharmaceuticals. The Directive contains detailed rules regarding safety monitoring and reporting of adverse events. The detailed provisions cover suspension of the trial or infringements and the route for reporting adverse events.

Exchange of information

Member states in whose territory the trial takes place are responsible for entering information into a European database which is accessible only to the competent authorities, the EMEA and the Commission. The data will include extracts from the clinical trial request, amendments made, ethics committee favourable opinion, declaration of the end of the clinical trial, reference to GCP inspections.

The precise purpose of the database is unclear other than easing the exchange of information on trials taking place within the EU.

Next steps/general comments

Member states will have until 1st May, 2003, to establish the directive into national law, and until 1st May, 2004, in implement these provisions into practice.

Member states will have the flexibility to implement the directive sooner, with the resultant lack of harmony within the EU, potentially for the next three years. This is, however, still a positive step towards harmonisation in the longer term. Providing the detailed rules and guidance which are expected to follow the directive's adoption are drawn up as EC-wide guidance documents, then we can expect to see

further simplification in the conduct of clinical trials in the EU.

References

1. Directive 2001/20/EC of the European Parliament and of the Council of 4th April, 2001, on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
2. 1991 European Commision discussion paper (III/3044/91).
3. Rules Governing Medicinal Products in the European Community, Good Manufacturing Practice for Medicinal Products.