Regulation of clinical trials in Europe

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Pharmaceutical companies spend billions of dollars every year on carrying out clinical trials for their potential products. Many other trials are funded by charities, government research councils and other bodies. However, within Europe, national differences in approval procedures and the law relating to clinical trials can lead to increased costs and delays, particularly where trials are conducted in different countries. New European legislation is currently under review that is designed to ensure a common level of patient protection and scientific standards whilst reducing the costs and delays that can occur before trials can commence

Ethical guidelines

Immediately after the end of the Second World War, it was widely recognized that there was a strong necessity to have a common set of principles to control medical research involving human subjects. Following one of the Nuremberg trials, a set of ten principles was developed in connection with experimentation using human subjects, known as the Nuremberg Code[1]. Subsequently, these principles were developed into the Declaration of Helsinki[2], a document adopted by the World Medical Association in 1964, and which has since been amended several times. In broad terms, the Declaration of Helsinki sets out the following principles:

- Research on human subjects should conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
- The potential benefits of the research should outweigh the predicted risks, i.e. the research should not be carried out unless the risks involved are believed to be predictable.
- Concern for the interests of the subject should always prevail over the interests of society.
- Before commencement, the planned research should be reviewed for its ethical acceptability by an independent ethics committee.
- Each subject of the research should be fully informed of, and understand, the purpose and nature of the research or trial and its anticipated benefits and risks and give their free consent to participate. This consent can be freely withdrawn at any time. In certain cases and with appropriate safeguards, the legal guardian can give such consent.
- Every precaution should be taken to safeguard the privacy of the subject and minimize the impact of the research on their physical and mental integrity and on their personality.

In 1997, the Council of Europe issued a Convention for the protection of human rights and the dignity of the human subject with regard to the application of biology and medicine (Convention on Human Rights and Biomedicine)[3]. A chapter of this Convention deals specifically with scientific research on human subjects and human embryos. However, not all the Member States have ratified the Convention.

Several other ethical guidelines have also been developed, mainly on a national basis, that have been published by medical associations, national bodies, patient groups and industry associations[4]. These vary in their comprehensiveness, and might only apply to certain types of clinical

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trials or those involving certain diseases or patient groups, or to specific aspects of conduct such as the payment of compensation to organizations, staff and subjects taking part in the trial.

The Declaration of Helsinki is an internationally recognized statement of ethical principles to be observed in all clinical trials. It has no direct legal force but, in practice, its contravention would have serious consequences for those involved in conducting the trial. Essentially, any physician who conducts a clinical trial and does not follow the principles laid down in the Declaration of Helsinki would, at the very least, be committing a serious breach of professional conduct and could, therefore, be open to professional sanctions. In addition, under this Declaration, all clinical trials should be subject to the review of an independent ethics committee. Because of the respect and independence that most countries accord to members of the medical profession, and the involvement of an independent ethics committee, it is perhaps not surprising that European countries differ considerably in their legislative attitude towards the regulation of clinical trials, as will now be discussed.

Regulatory guidelines

A set of official guidelines has been issued in Europe that cover many aspects of clinical trials. Compliance with these guidelines is not mandatory, but their contravention could result in a refusal to grant the relevant marketing approval. As a result, trials that are sponsored by pharmaceutical companies usually do follow these guidelines. However, this is not necessarily true for other trials.

The most important of these guidelines is the Note for Guidance on Good Clinical Practice (GCP)[5]. This describes the responsibilities of, and modes of interaction between, the independent ethics committee, the staff taking part in the trial, and the sponsor of the trial (usually a pharmaceutical company). It also sets out the basic requirements on matters such as the protection of trial subjects, the design of procedures to be used in the trial, the recording and reporting of results, the documentation that is required, and the monitoring and audit of the trial to ensure that these requirements are being met.

Since 1990, there has also been an international process, known as the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which involves representatives of the regulatory authorities and industry associations of Europe, Japan and the US. The objective of the ICH is to harmonize pharmaceutical regulatory requirements on an international basis to minimize the possibility that tests and trials on new medicinal products have to be repeated for the purposes of obtaining regulatory approval in different countries. Such repetition not only increases the costs of obtaining such approvals, but also requires the use of humans and animals in research that might otherwise be considered scientifically and medically unnecessary.

One aspect of the ICH process is the harmonization of many of the regulatory requirements relating to clinical trials. So far, this process has generally been considered successful, and there has been a major step forward in the harmonization of the guideline on GCP. This guideline was finalized in 1996, and this has now been adopted by the European, the US and Japanese regulatory authorities. Several other harmonized guidelines on specific aspects of clinical trials have also been finalized or are in draft form.

Existing legislation

Within Europe, clinical trials have to satisfy certain common criteria where the results of such trials are used to support an application for marketing approval of a new medicinal product. However, so far as European law is concerned, there is generally no sanction for contravention of these requirements, other than refusing to grant a marketing authorization.

In broad terms, the European law[6] states that, where an applicant wishes to obtain marketing approval for a new medicinal product:

- Clinical trials must be designed, implemented and reported in accordance with 'good clinical practice' (compliance with GCP and other regulatory guidelines will normally satisfy this requirement).
- All clinical trials should be carried out in accordance with the Declaration of Helsinki and, in principle, the freely given informed consent of each trial subject should be obtained and documented.
- The trial should not begin before the opinion of an ethics committee has been obtained.
- All aspects of conduct of the trial should be documented in pre-established, written procedures (e.g. written protocols) and documentation and records of the trial should be archived for specified minimum periods of time.

As contravention of these requirements could lead to the rejection of an application for marketing approval of a new medicinal product, this is a powerful incentive for commercial sponsors of trials to follow them. However, compliance with these requirements is not mandatory and, although in practice there is universal adherence to the principles contained in the Declaration of Helsinki, the law relating to the conduct of clinical trials differs considerably across Europe.

Differences in national laws become most significant in planning and conducting trials that are carried out at more than one site (multicentre trials), particularly those conducted in more than one country. Often, such trials are necessary to recruit sufficient patients to make the trial statistically valid. However, to ensure validity, it is virtually essential to ensure that these trials are conducted according to the same protocol at each centre, but this can be problematic because of each country's different procedures for initiating and monitoring clinical trials. For instance:

- Some countries have central or regional ethics committees, some have local ethics committees, and some have both.
- For multicentre trials, some countries require an opinion from the ethics committee at each site, whereas other countries require only one opinion in relation to the whole trial.
- Countries vary considerably in the quantity of information concerning the proposed clinical trial required for submission to the regulatory authorities prior to the start of the trial.
- Some countries require that an approval to commence the clinical trial must be obtained from the relevant regulatory authorities; other countries merely require notification to the regulatory authorities of an intent to commence the trial, together with a waiting period before the trial can begin so that the regulatory authorities can object to the trial if they wish.
- Although according to GCP, clinical trials should be open to inspection by regulatory authorities, procedures for such inspections have not been established in all EU countries.
- The time taken to obtain an ethics committee opinion and, where applicable, approval from the regulatory authorities varies between countries.

These differences in requirements have several consequences. Firstly, the preparation of all the necessary documentation can be very complicated. Secondly, commencement of trials can be further delayed while all the necessary opinions and approvals are sought. Finally, modification of the original trial design might be required to gain approvals at every site.

The Clinical Trials Directive

History of the Directive

The European Commission issued papers in 1991 (Ref. 7) and 1995 (Ref. 8) discussing the need for European legislation on clinical trials and, in 1997, it adopted a formal proposal for a Clinical Trials Directive[9]. Following examination by the European Parliament in November 1998, an amended proposal was issued in April 1999 (Ref. 10). Reportedly, the need for European legislation was accepted by all member states of the EU and it should have been approved at a meeting of national government ministers in November 1999, but there still appears to be one major outstanding area of disagreement. If this disagreement cannot be resolved in the near future, the Directive might still be taken forward, but without the contentious sections.

Scope of the Directive and compliance with Good Clinical Practice and Good Manufacturing Practice

With certain exceptions, the Directive is intended to regulate all clinical trials (from Phase I to Phase IV), designed to develop medicinal products. This would suggest that most industry-sponsored trials would be covered, although purely academic or observational studies might be exempt from the provisions of the Directive.

A central provision envisages the adoption of further legislation containing 'the principles and guidelines of good clinical practice', which should essentially follow the existing GCP guideline. The Directive then goes on to state that all clinical trials within the scope of the Directive must be designed, conducted and reported in accordance with good clinical practice. Thus, compliance with GCP will become a mandatory European requirement for all clinical trials covered by the Directive, regardless of whether they will be submitted in an application for marketing approval.

In addition to compliance with good clinical practice, the Directive envisages that the manufacture of medicinal products to be used in clinical trials should comply with good manufacturing practice, the standards of which are already generally laid down in European law. Products for use in clinical trials would also have to be labelled in accordance with guidelines to be published by the Commission. However, these new guidelines are expected to follow existing regulatory guidance in these areas.

Protection of trial subjects

The Directive lays down a minimum standard of protection for trial subjects. Basically, this reflects a standard that should already be in place in all member states, given that the need to comply with the Declaration of Helsinki is well established in all member states and that most industry-sponsored trials comply with the existing guidelines on GCP. Even so, it was felt important that the Directive did not overlook the paramount importance of protecting patients and volunteers who take part in clinical trials.

Briefly, the Directive confirms that the risks to the trial

subject must not be disproportionate to the expected benefits for human health and that the rights of the subject to physical and mental integrity and privacy must be safeguarded. In addition, the subject must give their informed consent to participation in the trial and can withdraw from the trial at any time without any resulting detriment. Finally, the medical care of the subject must be the responsibility of an appropriately qualified healthcare professional and the subject should be provided with an independent contact point for the purposes of obtaining further information.

Ethics committees

The Directive stipulates that the ethics committee must be an independent body of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and health of human subjects involved in the trial. This opinion of the committee should be delivered before the trial commences and should cover various aspects of the trial including:

- The design and procedures of the trial
- The suitability of the staff and facilities involved in the trial
- The methods and documents used to inform trial subjects and obtain their informed consent
- The compensation available to trial subjects in the event of a trial-associated injury or death
- Any insurance or indemnities available to cover the liability of the staff involved in the trial and its sponsor, and any arrangements for rewarding or compensating the staff and subjects for participation in the trial.

The Directive is also intended to streamline the process of obtaining an ethics committee opinion. First, the Directive envisages that the Commission will give detailed guidance on the application format and documentation that should be submitted to the ethics committee. Secondly, there is stipulated a maximum length of time by which an ethics committee can take before issuing an opinion. Thirdly, for multicentre trials, each country must establish a procedure whereby one ethics committee issues a 'lead' opinion and, if that country requires opinions to be obtained in relation to each site, these opinions can only relate to the suitability of that site to conduct the trial and not to the trial itself.

Notifications to, and approvals by, regulatory authorities

As already stated, the involvement of national regulatory authorities before the commencement of a clinical trial varies considerably within Europe. The amended Directive clearly favours a notification rather than an approval procedure, except in the case of biotechnological products. Under the proposed notification procedure, the clinical trial could begin, assuming the ethics committee had issued a favourable opinion, 30 days after the notification had been made, unless the relevant authorities had notified the sponsor that they objected to the trial. Where an approval is required, the Directive restricts the time in which the authorities must make a decision.

Reportedly, this was the most contentious part of the amended Directive when discussed by government ministers in November 1999. Certain national governments would apparently prefer an approval procedure for all applications to commence clinical trials, rather than the simpler notification procedure that would apply in most instances. However, the pharmaceutical industry fears that this would lead to delays given that, in the past, certain countries have often found it difficult to comply with time limits imposed by European legislation.

Surveillance and inspection

Finally, the Directive would introduce an obligation on member states to appoint inspectors to verify compliance with the provisions of good clinical practice and specify procedures whereby sponsors should report unexpected serious adverse reactions in trial subjects to the relevant regulatory authorities. Member states would have the right to suspend or prohibit any trial where any of the conditions had not been met or where there were doubts about the safety or science of the trial.

Conclusion

The Directive has generally been welcomed in that it seeks to lay down substantive requirements for the conduct of clinical trials. However, in practice, it basically gives a firmer legal basis to the regulatory guidance that was already in place and that was being adhered to in the majority of industry-sponsored clinical trials. Furthermore, the introduction of streamlined procedures for obtaining ethics committee opinions and the use of a regulatory procedure based on notification for most clinical trials would reduce the time taken for their commencement.

However, the pharmaceutical industry would be concerned if the current proposal were amended to oblige the regulatory authorities to issue formal approvals in all instances before the commencement of clinical trials. Regardless of whether the Directive lays down maximum time periods for the authorities to come to a decision, the industry fears that this could cause considerable delays

before trials could be commenced. In addition, the Directive envisages the issue of several supporting guidelines, and any definitive analysis of the impact of the Directive cannot be made until these guidelines have been published and considered.

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Collaborations in Japan…

Fujisawa Pharmaceutical Co. Ltd (Osaka, Japan) has entered into a collaboration with **Arena Pharmaceuticals** (San Diego, CA, USA). Under the terms of this agreement, the companies will jointly validate selected orphan G protein-coupled receptors as drug screening targets. Arena will then be responsible for receptor identification, together with the discovery of receptor localization and regulation, as well as validation of screening assays. Meanwhile, Fujisawa will be responsible for screening its chemical compound library using selected CART™ receptor assays, identification of chemical leads and pre-clinical and clinical development of these leads.

SmithKline Beecham (SB; Philadelphia, PA, USA) has signed a license and development agreement with **Asahi Chemical Industry Co.** (Tokyo, Japan) for Asahi's β_3-receptor agonist, AZ40140, and related compounds for the potential treatment of diabetes and obesity. Current preclinical studies have shown a good toxicological profile for the drug. Under the terms of the agreement, SB will be responsible for the worldwide development of the compound, except in China, Taiwan, Korea and Japan, where development will be the joint responsibility of both companies. The two companies have also entered into a co-distribution agreement for Asahi's type 2 diabetes therapy, rosiglitazone maleate (Avandia).

Fujisawa Pharmaceutical Co. Ltd (Osaka, Japan) has also signed an agreement with **Protein Design Laboratories** (PDL; Fremont, CA, USA) for PDL to humanize an antibody for the potential treatment of inflammatory and immunologically mediated diseases. PDL will receive a non-refundable $1.5 million, followed by milestone payments and royalties on any product sales. This agreement follows successful results of a funded research program in July 1999. Robert L. Kirkman, PDL's Vice-President said, 'Through our initial collaboration, we modified certain Fujisawa antibodies…We are now taking the next logical step, which is to humanize the antibody selected by Fujisawa.' Masanobu Kohsaka, Managing Director of the Research Division at Fujisawa said, 'We have already demonstrated in preclinical testing the potential for this antibody and look forward to having a humanized antibody available for clinical trials'.