



## Clinical Drug Development in Europe and North America – Present Patterns and Future Trends

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**Abstract** – *The past thirty years have seen important evolutionary changes in the pattern of industrial drug development in the Western World. The rate of these changes has varied depending on whether the stimulus is acute – as, for example, in the case of the thalidomide tragedy, or progressive – as we are seeing in association with the steady development of the European Economic Community (EEC) in political, economic and drug regulatory terms.*

*Much of the regulatory activity during this period of change has been focussed on pre-clinical activities and has been codified through the introduction of measures such as Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP).*

*Similar control of the clinical aspects of drug development has been slower to evolve. The first major steps in this direction were taken with the proposals put forward by the United States Food and Drug Administration in 1977 and 1978. These were refined in the following years, culminating in the publication of the so-called New Drug Application (NDA) and Investigational New Drug (IND) – ‘re-writes’ in 1985 and 1987, respectively.*

*These clinical controls are now being echoed in Europe with the publication of both national (member state) and supra-national (EEC) guidelines relating to what is now commonly referred to as Good Clinical Practice (GCP).*

*The emergence of these broadly similar clinical research guidelines on both sides of the Atlantic is now leading to the important goal of reciprocal acceptance of clinical (as well as pre-clinical) data between the United States and the various European Community (EC) member states. The implications of this for clinical drug development in other countries will be debated.*

**A** major feature of drug development over the past 30 years has been the progressive increase in the volume of government regulations covering the investigation and marketing of new drugs.

This process has been given added impetus by the scientific and political pressures associated with such events as the thalidomide and practolol disasters.

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These regulations were applied at first in those developed countries having major pharmaceutical research and development capacity. With the passage of time, however, virtually every country in the world has adopted similar standards of drug regulation. In the majority of cases these are based, to a greater or lesser degree, on the requirements of the U.S. Food and Drug Administration, – the 'FDA'.

The process of developing new drugs to meet this mass of regulatory controls is becoming increasingly expensive. Estimates for the cost of bringing a new drug from the test tube to the market, today, range conservatively from 50 to 150 million U.S. dollars.

These high costs have caused changes in the way that drugs are developed. In earlier times drug companies could operate economically by producing and marketing a new drug in perhaps only one or two countries. Indeed, the domestic market alone was often big enough to meet and cover development costs.

Today's high development costs can only be recovered by successfully marketing new drugs on an international scale. This means that the drug companies must file applications to market their new drugs in many countries worldwide. The government health authorities in these countries are, of course, particularly interested in the clinical data sections of these applications. Increasingly, they look for evidence that the clinical studies reported have been conducted to certain generally accepted standards; this in turn enables them to assess the significance of the clinical data more readily.

Before 1975 data from clinical studies conducted outside the United States were accepted by the FDA only as supporting data. After 1975 the position changed somewhat in that, foreign studies could now be used as primary evidence for FDA submissions, though only in cases where there was a major health gain, or for diseases that were uncommon in the U.S.A. or where there was a very favourable risk/benefit ratio. In 1978 Dr. Richard Crout, then of FDA, enunciated the Crout policy which stated that the credibility of the data, not the country of origin, should be the determining factor in acceptance by FDA (Table 1).

TABLE 1. FDA Acceptance of Data from Overseas Studies

Pre- 1975	As supportive evidence only
1975	As primary evidence but must be for: <ul style="list-style-type: none"> <li>• Major Health Gain</li> <li>• Disease Uncommon in U.S</li> <li>• Very favourable Risk/Benefit ratio</li> </ul>
1978	'Group Policy' Credibility of data, not country of origin is determining factor
1980	First 'Foreign' Inspections – Mexico and Canada

The Federal Regulations governing the conduct of clinical studies recognise the fact that there may be different approaches to the generation of clinical data outside the States, as opposed to inside, where studies must be done according to the rules governing the IND (the Investigational New Drug Evaluation). These regulations provide criteria for acceptance by FDA of foreign clinical studies not conducted under an IND. These are: that the studies should be well designed, well conducted, performed by qualified investigators, and that the ethical conduct should be to standards acceptable to the world community. These latter are defined as the standards laid down in the Declaration of Helsinki, or of the country concerned, whichever offers the greater protection to the subject.

From 1980 onwards FDA began to conduct overseas inspections in which FDA personnel went to visit studies in other countries to assess the acceptability of the clinical data being produced.

Meanwhile it became clear that work meeting requirements laid down in the FDA regulations would also be acceptable internationally. The FDA has thus set the 'gold standard' for conducting work to meet international registration needs. Good Clinical Practice – 'GCP' – has evolved as a series of measures aimed at meeting these FDA standards as fully as local laws and customs will permit.

Put simply, Good Clinical Practice is about establishing procedures for conducting clinical research to the best international scientific and ethical standards.

Implementation of GCP can be achieved through the following basic measures:

- Provision of an Investigator's Brochure. This should be updated at intervals appropriate to the progress of the trial. Information on potential or actual adverse reactions requires particular attention.
- An approved protocol and case report form. The latter should, as far as possible, be designed to facilitate the full recording of trial data by the investigator.
- Choice of appropriately qualified and trained investigators and study monitors.
- Ethical Committee approval of the study, with informed consent obtained from each patient.
- Adequate physical study facilities.
- An appropriate level of monitoring activity.
- Adequate test drug accountability procedures.
- Full documentation of study conduct (sponsor and investigator)
- Data validity checks (audit)
- Written Operating Procedures for key activities.

The above list can certainly be expanded, according to need; it can, however, be regarded as providing an adequate minimum.

In conducting studies to GCP standards it is important to consider the role of the clinical investigator, who is the spear-head of pharmaceutical clinical research. His obligations can be summarised in a reasonably short form. He should certainly understand the protocol. This is important with today's protocols which are often very lengthy, more particularly if the investigator has not been involved in the creation of the protocol. Having agreed to the protocol, he must then follow it: compliance with the requirements of the protocol is an essential aspect of good clinical research. If there are minor deviations from the protocol, they must be explained. If there are major deviations, it may be that the protocol is unworkable and in that case suitable amendments must be drafted and agreed, in consultation with the Ethical Committee, when indicated (Table 2) and (Table 3).

TABLE 2. Modern Drug Development

Ethical Review Committee – Constitution

- At least 5 members (varying backgrounds)
- Not all one sex or one profession
- At least one member non-scientific
- No conflicting interest
- Adhoc experts (non-voting)

TABLE 3. Modern Drug Development

Ethical Review Committee – Operation

- Follow written procedures
- Discuss projects with a defined quorum of members present
- Act appropriately in serious cases

It is the investigator's responsibility to liaise with the Ethical Committee. This includes the transmission of the protocol to the Committee and the receipt of information from the Committee.

The success of this liaison depends not only on the investigator but also on the existence of a properly constituted, competently functioning, Ethical Committee. Such bodies are not yet available in sufficient strength, taking Europe as a whole, though the situation is rapidly improving.

The clinical investigator must obtain from each patient, proper informed consent. The Declaration of Helsinki does not insist on written consent. While most people would now agree that written consent is preferable, there may be cases where oral consent, properly witnessed, can be equally acceptable.

The records of receipt and disposition of the

test drug\* are an important part of working to Good Clinical Practice and much of the responsibility for this lies with the investigator. Accounting for unused material is something to which attention should also be paid. When the drug is a controlled substance (for example a narcotic analgesic), then proper, secure, storage procedures must be applied.

Table 4 which refers to the provision of high quality documentation of all aspects of study conduct is central to Good Clinical Practice and should be a major objective of company monitoring activities. The clinical investigator will keep records of the subject entered into the study for the purpose of the hospital or his own office practice. In addition he will report the results of the study on Case Report Forms (CRFs) provided by the company. The issues of CRF design and practicability have already been mentioned. The specified period of time for which records should be retained varies from country to country; it may be five years, 10 years, or longer.

TABLE 4. Full Documentation of Study Conduct

This requires the following:

- Copies of all correspondence between the investigator and the sponsor.
- Transcripts of significant telephone conversations.
- Detailed records of monitors' visits covering what was discussed and what records were checked.
- Accurate and full completion of case report forms.

The inspection of facilities and records is important. The company monitor has a responsibility to ensure that the trial can be conducted according to the protocol, in the light of the facilities that the investigator possesses. If there are proficiency programmes for checking clinical laboratory equipment and its performance, these should be implemented (Table 5).

TABLE 5. Importance of Monitoring

Regular on-site monitoring at intervals appropriate to the nature of the study (usually 4 to 6 weeks) are an essential component of conducting studies to GCP standards. These provide a quality control process that cannot be reproduced in any other way.

The inspection of patient records ('source data') is a more sensitive area. If a pivotal study is performed in Europe, and if the FDA are sufficiently interested

\* The phrase 'test article' as used by the FDA is intended to signify that not all clinical trials are done with drug substances, medical devices, biologicals, vaccines, or other therapeutic modalities may also be tested clinically.

in that study, they will want to inspect the records; they will certainly want to check some of the data in the case report forms against some of the original hospital record data. Suffice to say that there are ways of doing this without breaching patient confidentiality.

Inspection may also be arranged, in consultation with the investigator, by the study monitor or members of the company's Quality Assurance group. Again, the needs of patient confidentiality must be scrupulously observed. This process is much assisted where the company monitors and other staff are perceived by the clinical investigator as being professional, well trained and responsible people.

Reference has already been made to the FDA inspection of foreign studies. The FDA has been inspecting foreign studies for about eight years now. This is normally arranged in consultation with the appropriate authorities; it may occur where, for example, two pivotal studies have not been done domestically in the United States, or where the foreign studies provide a basis for drug approval. As of November 1989, nineteen FDA inspections had been conducted in Europe; about two-thirds were found satisfactory.

Beyond this lies the question of inspection at government level in Europe. The French GCP guidelines already make provision for this and it remains to be seen whether other EC member states, and the Nordic countries will follow suit. It could be argued that establishment of GCP standards for clinical research logically requires that measures for assessing compliance should be available and may then be used to a greater or lesser degree, depending on circumstances.

As far as the grass-roots implementation of GCP in Europe is concerned, there is still some way to go. In overall drug development terms the situation at present is that both GLP and GMP are well established. Furthermore, the principles and practice of GCP are being followed in the majority of European pharmaceutical companies, no matter in which country. However, where the medical community, and in particular, the clinical investigator is concerned, GCP is still at an early stage of development.

This should come as no surprise since the elements of GCP procedure and the background to its implementation are not part of the medical curriculum. Much of the responsibility for involving clinicians in this process and securing their understanding will inevitably fall on the individual companies and will require thoughtful and careful handling.

What are the implications of Good Clinical Practice? Is it going to be worth all the time and effort and trouble?

There is no doubt that clinical trial data represent a valuable international currency in terms of their contribution to a rapid and efficient registration process. Since the 'cost' of a pivotal clinical trial is in all senses enormous it follows that all those involved – the investigator, the company, and last but not least, the patient – must be satisfied that the time, trouble and expense invested in the study is justified in terms of the ultimate acceptability of that work. This objective can best be met by ensuring that all involved, work fully to Good Clinical Practice standards.

This ensures, as far as possible, that not only ethical and scientific but also commercial objectives are sensibly and responsibly met.

This whole process must also be seen against the background of the voluntary framework within which it operates at present. In the United States, companies, investigators and ethics committees are required by law to follow the FDA regulations. In Europe, we currently have to work to something approaching the same standards on a basis of voluntary co-operation. This creates a totally different relationship between the company staff and the investigator – which many feel is healthy and beneficial.

Currently we are seeking the evolution of EEC guidelines for GCP\*. It is most likely that they will certainly, in the first instance, be just that: guidelines and not rules. Whatever the final form taken by 'European' GCP it will certainly require even closer collaboration between the company research staff and the clinical investigators. Such collaboration based on mutual understanding and respect will be the best way to ensure achievement of the necessary standards of clinical drug development for the future.

\* The final EEC guidelines for GCP were issued in May 1990. Whilst refining and giving some additional detail in certain areas, they do not invalidate or require major alteration to the statements made in this paper. GCP, like GLP and GMP, will become well established in Europe in time, thus further enhancing the standards of clinical drug development.