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Good clinical practice: rules, regulations and their impact on the investigator

This article will look at the national and international status of Good Clinical Practice (GCP). It will not cover the same ground as the editorial in this journal (Morice, 1991) which explained what GCP is and how it affects the clinical pharmacologist, except to repeat that the basic aims of GCP are to protect patients' rights, and to ensure the accuracy of records and prevent fraud.

The latter is achieved by establishing a paper trail that allows verification of everything that occurs during the study; by providing effective monitoring of the investigator by the sponsoring company; and eventually by arranging inspection by regulatory authorities to ensure systems are adequate and the record is accurate. The way these principles are realised varies somewhat between countries but, as the editorial explained, differences are not fundamental. Legal status does, however, differ markedly between countries; in some GCP has full legislative backing, in others it remains voluntary. It is the purpose of this article to describe the present legal position of GCP in the United States of America and track moves in Europe which will make the procedures legally binding upon all investigators conducting clinical trials intended to be submitted to regulatory authorities. These, the Medicines Control Agency in the UK and equivalent bodies in other countries, must be consulted by companies which intend to place a new product on the market or alter the indication for an established one.

While there are currently no legal moves in Europe to force clinical trials not intended for regulatory purposes to conform with GCP, the writers of the guidelines hope they will be used more generally. The British Postgraduate Medical Federation is known to be establishing training courses and it is expected that other professional bodies will see the value of GCP. In Sweden the subject is taught in medical schools and to post-graduate physicians as an essential discipline.

Legal status of GCP in the USA

America has a constitutional system in which statute is backed by established regulations. The procedure is for a proposed regulation to be published, comments to be accepted and reviewed, then for a final rule to be established and published. In the case of Food & Drug Regulations, these are then incorporated in Title 21 of the Code of Federal Regulations (21 CFR), which is updated annually to incorporate changes. In contrast, in the UK statute is established and it is then left to case law to determine how the provisions should be interpreted.

The legal status of American GCP is clear. A number of regulations have been codified into 21 CFR which define:

Part 50: how human subjects are to be protected and informed consent obtained;

Part 56: membership, function and operation of the Institutional Review Board (Ethics Committee);

Part 312.50–70: responsibilities of sponsors and investigators;

Part 312.120: requirements to be met for foreign studies not conducted under Investigational New Drug (IND) approval; and

Part 314.106: acceptability of foreign data in a New Drug Application (NDA).

These regulations are enforceable in law and adequate penalties are available. Sponsors, institutional review boards and investigators are all subject to inspection by a large team of Food & Drug Administration (FDA) investigators using published procedures (FDA Compliance Manuals). In short, the American system is fully legislated, regulated and controlled. While in the UK the situation is that the rights of human subjects are protected in accordance with criteria established by medical professional bodies, in America these criteria are established within the law and verified by FDA inspection. To describe how this happened would be outside the remit of this article, but protection of the human subject was taken into statute because of a perceived failure of medical professional bodies to provide adequate protection.

The American system has much to offer the UK and the European Community as they shape future legislation. What it can achieve in the way of detection of fraud is illustrated by material released by the FDA under the Freedom of Information Act on trials conducted by Dr Samuel Feurst. The record shows that an inspection was conducted when a reviewer at the FDA noted inconsistency between the placebo response in one study as compared with others with the same drug. The inspector found some discrepancies on audit. He reported these to the FDA and obtained patient names and addresses so that a more detailed check could be made. The FDA Office of Compliance warned the sponsoring company, who reported within 2 weeks that they had performed audit, found inconsistencies and closed the studies. The FDA then carried out a detailed inspection over a nine day period, documented many inconsistencies, and took statements from staff members and patients which were confirmed by affidavits. The Office of Compliance then reached agreement with Dr Feurst which left him ineligible to conduct further investigations.

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This illustrates well some characteristics of the American system. Action was initiated by the FDA and was legalistic, much as it would be in a police investigation. The doctor concerned was treated with courtesy throughout, but no professional mystique was allowed. Although trials were stopped rapidly and he was disqualified from working with trial drugs, there were no criminal or professional misconduct proceedings. Such proceedings might have followed had he not died, but the regulatory process itself did not involve striking off or loss of income from clinical care which he might have been giving competently. Any judgement on this would have been made quite independently by the relevant professional body.

Legal status of GCP in the UK

As discussed in the previous editorial (Morice, 1991), the guidelines of the Association of the British Pharmaceutical Industry (ABPI, 1988) are an industry initiative and are voluntary. However, the Medicines Control Agency has declared its intention to accept the Note for Guidance of the European Community (Commission of the European Communities, 1990) in principle. The position is changing rapidly and legal underpinning of GCP in the UK, and in the rest of the European Community, is probably not far off. Although politicians continue to argue about British sovereignty within the European Community, many directives relating to healthcare and medicines have already been accepted and implemented in the UK. An EC directive requires that all member states incorporate the provisions detailed within national law by a specified date. The UK will probably conform with progress towards legislation for GCP as it has in other areas. This may offer considerable benefits. Currently the ABPI is working with great diligence to deal with fraud within the present system. It is necessary to go through full criminal and/or professional misconduct proceedings to deal with fraud at present and success may leave the investigator ruined, with loss of reputation and income. Two cases were highlighted by the Sunday Express recently (3rd November 1991): a consultant was struck off the Medical Register, and a general practitioner was found guilty of serious professional misconduct. Cases are likely to come to the attention of the GMC only if reported by a company. Fear of creating bad feeling may tempt companies to turn a blind eye to fraud, and this may contribute to erosion of professional standards. If the directive results in changes in British procedures which allow separation of regulatory from professional offences, there could be considerable gain.

Legal status of GCP in the European Community

Within the Community, Eire, France, Germany and Spain have legislated on GCP, but the other member states have not yet done so. The EC Note for Guidance (Commission of the European Communities, 1990) currently has the status of a recommendation; that is, it is advisory and without legal force. However the Community's intention is clear from Directive 91/507/EEC (Official Journal of the European Community, 1991), which has just been agreed with an implementation date of 1st January 1992 for most of its provisions, including those which relate to GCP. This directive alters an earlier one (Directive 75/318/EEC) concerned with the scientific testing of medicines intended for registration by any member state.

With regard to GCP, the directive states that 'All phases of clinical investigation, including bioavailability and bioequivalence studies, shall be designed, implemented and reported in accordance with good clinical practice'. It then goes on to specify some of the provisions in the EC guidelines. Therefore, from the date of implementation of this directive into member states' legislation, some elements of GCP will acquire firm legal status. These include the following provisions of direct relevance to the investigator: accordance with the ethical principles of the Declaration of Helsinki; obtaining and documenting the informed consent of the patient; Ethics Committee approval in writing; and archiving of patient identity codes for at least 15 years, and of source data for the maximum period permitted by the unit.

The remaining provisions of the guidelines will retain the status of recommendations until a discussion paper on a proposed Directive on Clinical Trials (Commission of the European Communities, 1991) has gone through its consultation period. This discussion paper is of great interest since one of its main aims is to prepare for reciprocal arrangements with countries outside the Community, specifically the United States of America. This suggests that audit of investigator's records by the regulatory authorities, currently only legislated for in France and Germany, will eventually be required in all member states. The earliest date proposed for implementation is October 1992, but major companies have decided not to wait for legislation and are already ensuring that all their projects conform with the EC guidelines.

Implications for the Clinical Pharmacologist

The earlier editorial (Morice, 1991) covered the general implications for investigators of the provisions of GCP. Rapid progress towards legislation and moves by companies to pre-empt legislation make it necessary for clinical pharmacologists involved in new drug development to adapt clinic and personal working practices to standards at least consistent with the EC guidelines.

From the many implications discussed in the previous editorial we would emphasise again some areas where difficulty can be anticipated. Patient records will be checked repeatedly by company and eventually government personnel, and it is essential that patient consent for this be obtained within the informed consent process. Clinic personnel will need to understand the reasons for monitoring and audit visits. The informed consent form and details of payments to patient and investigator must be approved by the Ethics Committee. Companies will not work with investigators who will not do this. Companies will ask investigators to confirm in writing agreement to adhere to EC guidelines. It should be

noted that some additional rights are given to the investigator; for example the company must submit the final report for signature by the investigator. Allowance must be made for prolonged storage of patient records. The current directive states that records should be kept for as long as the clinic allows, but the guidelines add 'but not less than 15 years'. The record which must be kept is the clinic's property, but the responsibility to keep it is placed on the investigator. This is a problem that remains to be resolved in the United Kingdom, as in other EC member states. The EC guidelines aim to share responsibilities between investigator, sponsor and authority in harmony, rather than within a rigid legalistic framework. Correctly implemented they increase the input of investigators, and establish clearly their role as key figures in the investigational programme.

A more complete picture of the complexity of GCP provisions can be obtained from a Handbook (Allen, 1991) which contains the entire text of the Note for Guidance and detailed commentary on the implications for the investigator.

Like the mynah birds on Aldous Huxley's 'Island', some of us in the industry have been crying 'here and now' for some years. It is now clear that, legislation or no legislation, this is a time of change for any clinical pharmacologist who wishes to continue to work in new drug development. The bureaucratic re-organisation of research clinics will indeed be time consuming and will seem to offer little immediate benefit. However, once procedures are in place and suitable staff employed, clinical pharmacologists should be freed from day-to-day duties to concentrate upon their own speciality. The cost will be substantial and will need to be met by companies within their trial budgets. The eventual benefits will be better protection of human subjects and absolutely reliable clinical trial data if they are generated in areas subscribing to the discipline of GCP.

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