

One year on: what has been the impact of the clinical trials directive?

The impact of the legislation on clinical trials was reviewed before a large audience of representatives from the pharmaceutical industry and the National Health Service at a recent meeting. **Joseph Chamberlain** reports

Impact on medicines regulators

After a background paper on the development and the requirements of the clinical trials directive (CTD) by Brian Davis of the Medicines and Healthcare products Regulatory Agency, the feedback from the regulators was presented. Bronwyn Phillips, an MHRA inspector, explained that from 1 May 2004 the voluntary programme of inspection had ceased. Around 175 applications have since been received, the majority (120) from existing licensed sites.

An important aspect of inspections has been the assessment of the Qualified Person (QP). Transitional arrangements are used by about 40 per cent of applicants but such arrangements will apply only until May 2006. QPs must not only have the appropriate qualifications, as laid out in the directive, but must have demonstrated competence to carry out the duties. Prioritising inspections has been based on risk, with first-time applicants and applicants making sterile products being high on the list. Inspections are announced and are concerned mainly with facilities. Key issues uncovered included poorly developed quality systems, inadequate facilities, inadequate validation, poorly defined QP responsibilities, insecure chain maintenance in transit and on site, poor practices in the design and printing of labels, careless handling of randomisation codes, and a failure to address issues surrounding transmissible spongiform encephalopathies. Ms Phillips gave numerous specific examples of major problems encountered during inspections, including a case where the management blamed lack of training for a deficiency when it was apparent that it was the system that was at fault. Nevertheless Ms Phillips concluded that the UK industry was generally in good shape. There was still lots to learn and it is important to maintain an effective dialogue with the regulatory authorities.

Elaine Godfrey, of the MHRA clinical trials unit, provided the experiences of an assessor. The implementation of the CTD represented the biggest change in clinical trials legislation since the introduction of the clinical trials exemption (CTX) more than 20 years ago. The changes occurring in the UK represented the difference between the previous legislation and the current legislation and were, therefore, not the same as those occurring in other member states which previously

had different systems of regulating clinical trials. Important changes have been that healthy volunteer trials are now regulated with authorisation of the trial rather than the supply of a product. Good manufacturing practice, good clinical practice, labelling and the system of ethics committees are now better integrated. Regulation of human volunteer trials by the MHRA is new but initial concerns about delays resulting from this change have not been realised. The MHRA consulted widely and the new process is in fact speedier than that under the ethics committees.

Additionally, under the previous legislation approximately 10 per cent of CTX applications were refused, whereas under the new legislation grounds for non-approval (GNA) at the appropriate decision point are only 1 to 2 per cent. Applicants receiving GNA letters receive these for safety reasons and most GNA applications are approved after further information has been provided. Safety issues may arise from the product or the protocol, and are due to a lack of discussion of potential issues. Major problems included data not summarised or incomplete, applications not page-numbered or not indexed, over-use of appendices, and inappropriate font size. Sometimes the supporting scientific data were incomplete, the study rationale was unclear, the data package did not comply with guidelines, or there was no integrated safety summary. The new requirements were often overlooked, labelling was not presented in the format to be used or even not presented at all; there may have been no QP statement on GMP, or there was no copy of the marketing authorisation (MA) for the investigational medicinal product (IMP) or equivalent. The assessor would like to see clearly presented applications with summarised data, which follow commission guidance and are structured according to the common technical document. All necessary components from the commission guidance must be included with no unasked-for documents added. Only substantial amendments should be submitted. After a gestation of 10 years, the implementation of the directive is now complete. It is no longer permissible to use the previous forms of documentation, no matter how beautifully presented. The future has arrived, concluded Dr Godfrey.

Impact on industry

Robert Smith, of Genzyme, presented the experiences of an international biotech company manufacturing clinical trial supplies. An important aspect of the new directive is the requirement for a Qualified Person to be legally responsible for certifying and releasing clinical trial materials. The QP is involved in many aspects of the clinical trial process, from visiting third country manufacturing sites to giving advice to a number of different professionals on a whole range of topics.

The recently approved good clinical practice directive also impacts on the manufacturers of clinical trial materials. As well as this directive, Annex 19 on "Retain and reference samples" also may affect the samples that clinical trial material manufacturers may have to keep in the future. Finally, there are International Conference on Harmonization guidelines that are being worked on that in the future will affect the manufacture of clinical supplies.

Philip Butson, of GlaxoSmithKline, had distilled the views of many colleagues to give an industrial perspective of the effect of the clinical trials directive. Experiences with inspections suggest they are primarily general inspections of quality systems and good manufacturing practice, with the specifics of the investigational new product forming a part.

The use of published information to identify the main areas where the MHRA has historically identified issues is to be encouraged. Mr Butson commented that it made sense to carry out self-inspections of these quality indicators, such as deviations, out-of-specification laboratory results, batch rejections, customer complaints and recalls. Inspections of IMP activities may start with a high level question such as determining how clinical requirements are determined and met, then move on to look at the components of the answer in more detail.

Systems in place to prevent mix-ups are particularly scrutinised because blinding of placebos and comparators means products not distinguishable by appearance must be well controlled.

This one-day update symposium was organised by the **Joint Pharmaceutical Analysis Group** in association with the **Academy of Pharmaceutical Scientists** and the **Royal Pharmaceutical Society Hospital Pharmacists Group** on 19 May

Impact on the health service

The directive has had a huge impact on the NHS because 96 per cent of all hospitals are involved in clinical trials in some form, said Paul Forsey, of Guy's and St Thomas' NHS Trust. Most effect is on non-commercial trials which, before May 2004, were run under the DDX (doctors and dentists exemption) and CTX (clinical trials exemption) schemes. About 20 NHS sites have applied for an MA. The directive definition of manufacture is helpful when assessing whether a trial fits under the directive or whether the activity is exempt from the need for a marketing authorisation (MA). Studies that have purely physiological outcomes and are not assessing safety or efficacy are considered to be outside the scope of the directive. Exemptions in terms of reconstitution or assembly do not require the need for an MA but there are a number of areas requiring clarification. The role of the Qualified Person needs to be seen as releasing material within the context of the trial, which includes all aspects, including the final link to the patient. The QP is involved from the initial discussions with the investigator or sponsor, said Mr Forsey. There is a need to develop a generic NHS QP specification in terms of essential experience and qualifications required. There will be a requirement to link this to the Knowledge and Skills Framework. When designing packaging and labelling for IMPs the process of supply to the patient needs to be taken into consideration as this can significantly affect the outcome. There is a need to provide some good practice guidance to support professional judgements. One year on, we do have clarification on a number of issues especially with regards defining what is covered by the directive and in what circumstances an MA (IMP) is not required. However, further work is required but it is imperative that local interpretations are shared where possible to promulgate best practice. Where sufficient support and expertise exists there is no reason why the requirements under the directive should be a barrier to undertaking non-commercial trials.

V'lain Fenton-May, of St Mary's Pharmaceutical Unit, Cardiff, reviewed experience in the NHS and Europe, particularly with reference to non-commercial clinical trials. Activities associated with hospital clinical trials (both commercial and non-commercial) include dispensing, preparation, labelling,



Geoff Tompkinson/STL

Clinical trials form part of the work of 96 per cent of NHS hospitals

blinding, organising and manufacturing. The directive applies equally to commercial and non-commercial trials but we need sponsors for doctor-led trials. There is now an added cost, not just that of registration fees, but the expense and difficulty in obtaining insurance on anything with a clinical trials label attached. There is also a perceived increase in bureaucracy as well as a lack of understanding among colleagues. Real difficulties are foreseen with the successful establishment of QPs.

Non-commercial trials are still in the transition between DDX and clinical trials authorisation, and more training is needed in all spheres. Mr Fenton-May also pointed out the particular difficulties with commercial trials, including the real possibility of confusion in labelling of dispensed items. There will need to be a move to realistic costing and support. The relationship on both sides needs to mature.

Before 2003 the perception in European hospitals was that there were few non-commercial trials, said Mr Fenton-May. Most EU countries believed that the laws already covered the needs of the directive, and that the pharmacist was a QP by right and needed no additional training or experience. Although by 2005 it was recognised that there are indeed non-commercial trials in Europe, and that there was a need for a MA (IMP) and therefore inspections by a competent authority, Europeans still do not seem to recognise the special duties and attributes of the QP.

Implementation of the directive in the Netherlands

Helena van den Dungen, of the inspectorate of health care, Ministry of Health, the Netherlands, undertook to describe experiences with implementation of the directive in Europe but had to confess that, at the time of the meeting, the EU clinical trials directive has not yet been implemented in the Netherlands legal system, making a description of its local impact premature. However, good clinical practice has long been formally implemented in the Dutch legislation and full clinical trials legislation covering all clinical trials was implemented in 1999 as the law on medical research (Wet Medisch Onderzoek).

The WMO ensures protection of subjects by identification of responsibilities, considering informed consent particularly in trials with minors and incapacitated subjects, regulation of ethics committees and ethical review (including a single ethics opinion for multicentre trials), and regulation of insurance. It already contains many of the requirements of the EU CTD.

Important new aspect

The most important new aspect is the installation of a competent authority to which clinical trials are notified. In addition, development of an electronic database, where notification to the competent authority and request for approval by the ethics committee can be made simultaneously, is well advanced. Implementing activities have been pre-empted by the regulatory authorities, for example, through the installation of a ministerial working group where all involved parties are represented.

These would include competent authorities, ethics committees, inspectorate, industry, academic hospitals, contract research organisations and biotech companies. This working group has been active in organising an information platform, channelling questions and identifying potential problems. In addition a manual has been developed to explain the new additions to the legislation and further define the standards.

The Dutch inspectorate has conducted statutory inspections of clinical trials since 1993. Inspections have been carried out in the Netherlands as well as in other EU member states and in third countries.

The inspections have been conducted as the result of national requests (local applications and "for cause" as well as those under the mutual recognition procedure), requests by other EU member states, or instigation by the inspectorate itself.

The Dutch inspectors have been actively involved in the European Medicines Agency Inspection Services GCP inspectors working group since the establishment of the group in 1997.

Panel discussion

In a final session the speakers for the day faced a lively set of questions from the audience. Feelings towards the new directive were positive. Brian Davis said that people are becoming involved in it and are recognising that the existing systems are not adequate to protect the patient and ensure quality new information. The directive has focused a lot of attention and in general, the environment within Europe is going to be much improved as a result of this directive. V'lain Fenton-May thought that if we had had proper clinical trials 20 years ago then perhaps we would not have seen some of the product withdrawals we are seeing today. The new legislation was much welcomed.

A full report on the discussion session can be found on the website of the Joint Pharmaceutical Analysis Group at www.jpag.org.