

Analytical support for clinical trials: meeting clinical and regulatory needs

An audience of hospital pharmacists, Qualified Persons and sponsors from the pharmaceutical industry heard presentations at a recent meeting on how clinical trials rely on analytical support. **Joseph Chamberlain** reports

Hospital pharmacy departments play a pivotal role in clinical trials, said V'lain Fenton-May, of St Mary's Pharmaceutical Unit, Cardiff. These trials may be purely commercial with an external sponsor, or non-commercial, where the hospital itself sponsors the work, perhaps as part of a research project. Although these trials may be handled in different ways, with overall responsibility at different locations, the information required remains the same. Major hospitals will handle up to 200 concurrent trials, so sponsors should ensure that everything is done to make their particular trial run smoothly.

Mr Fenton-May recommended a comprehensive checklist that a pharmacy should complete before a trial is accepted. The checklist should cover trial sites and patient

numbers, the proposed protocol, the duration of the study, the proposed study start date, randomisation requirements (and who is responsible for this), stability data (supplied by the manufacturer, and probably established by local quality control), specific storage and shipment requirements, dispensing sites, disposal of unused active material at the end of the study, and ethics or peer review approval. As regards drug material used in a trial, any person accepting responsibility for signing off a product must know what is being used and why. Provided the checklist is satisfactorily completed then there should be no difficulty in handling conventional investigational medicinal products, he said.

However future products will offer a different challenge. Gene therapy is coming, and that will use viral vectors for transfer. There

are potential contamination risks and genetically modified organisms can come into contact with humans other than the intended patient via accidental dissemination during handling and use, disposal of unused product or waste products, and disposal of virus-containing patient excreta.

Different viruses will need different levels of care but, at whatever level, the pharmacy must be able to handle the products. Pharmacy departments already handle hazardous materials with no apparent contamination problems. However contamination at some level is inevitable. The important point is to recognise the significance of the possible level of contamination, so the sponsor must provide relevant safety information, and the facility must have appropriate decontamination routines, concluded Mr Fenton-May.

Legal and regulatory aspects: good control of manufacturing process

Elaine Godfrey, of the Medicines and Healthcare products Regulatory Agency, said that the role of the MHRA in clinical trials is to ensure the safety of trial participants and the collection of valid data. The agency does not act as a consultancy for the trial, although if the sponsor has particular problems it does no harm to discuss these with the agency.

The agency makes its decisions solely on the information given by the sponsor in the investigational medicinal products (IMP) dossier, the trial protocol and the investigator's brochure. The agency will review inclusion and exclusion criteria, safety monitoring and reporting, non-clinical data and safety with respect to quality of the product, Dr Godfrey said.

To generate credible trial data, there must be adequate control of the manufacturing process and of the product, and also of the clinical data being produced. There is a guideline on the requirements for the chemical and pharmaceutical quality documentation concerning IMPs in clinical trials available in Volume 10 of "The rules governing medicinal products in the EU". In addition, there are good manufacturing practice requirements covering the manufacture of IMPs. The guideline applies to chemical substances,

synthetic peptides, herbal substances or products, and radioactive or radiolabelled substances. It does not apply to biotechnological or biological substances. This guideline covers both drug substances and drug products, and is divided into information for phase I trials and information for phase II and III trials. There are no specific requirements for phase IV trials since these are performed on marketed products.

The suitability of the analytical methods should be described, and the acceptance limits and parameters for performing validation should be presented in a tabular format, but there is no requirement for a detailed validation of the analytical methods. For pharmacopoeial substances, reference to the relevant pharmacopoeial monograph is sufficient. For biological and biotechnological products, there is no similar guidance, but sponsors may wish to follow similar principles.

Emphasising that the agency's role is in the safe conduct of the trial, Dr Godfrey stated that there is no requirement for detailed analytical methods and their validation for bio-analytical methods in the IMP dossier. This is a separate issue. Sponsors should consider what really needs to be in their dossiers as many of them are far too comprehensive for the purpose, she concluded.

The aim of the biological agents unit of the Health and Safety Executive is to ensure that risks in the workplace from microbiological hazards are properly controlled, said Paul

Logan, of the HSE. All aspects of genetic modification procedures and biotechnology related to human health and environmental safety are covered and the unit provides the secretariat to the Scientific Advisory Committee on Genetic Modification (SACGM). The HSE has an interest in the conduct of clinical trials by virtue of the Health & Safety at Work Act, a European directive, and Control of Substances Hazardous to Health regulations. The contained use regulations apply to any activity in which genetically modified (GM) organisms are cultured, stored, transported, destroyed, disposed of or used in any other way and for which physical, chemical or biological barriers are used to limit contact with humans or the environment to ensure a high degree of safety. Therefore they are considered to cover many, but not all, clinical activities.

Guidance is available on the HSE website (www.hse.gov.uk/biosafety) and in the "Compendium of guidance — part 6 guidance" on the use of genetically modified micro-organisms in a clinical setting issued by the SACGM. The guidance has come about because of the increasing use of genetically modified material in clinical applications. The hospital environment is greatly different from typical laboratory use, with clinicians, nurses, patients, visitors and pharmacy staff all potentially affected by clinical agents. Often there is no GM safety committee or biological safety officer in place, and at present there is no

The Joint Pharmaceutical Analysis Group presented this symposium on 2 May at the Royal Pharmaceutical Society's London headquarters

common position in Europe. Risk assessment considers risk to workers and the wider environment so that it includes staff and visitors in the hospital. It is based on the properties of the genetically modified medicine and how it is to be stored, prepared, used and disposed of. Such properties are usually well understood by the time a drug reaches the clinic.

Containment is an important consideration. Clinical applications often combine

physical containment (sealed containers, refrigerators, freezers, safety cabinets) with biological containment. A GM medicine would be regarded as being biologically contained if it is endowed with inherent or engineered characteristics resulting in sufficient attenuation, disablement or auxotrophy to impair its ability to infect, replicate or survive outside of a specialised environment. Most GM microorganisms in clinical trials are either replication defective, or replication conditional, and

are considered to be biologically contained. The physical containment required to protect workers and the environment will depend on the nature of the gene being delivered. In most cases minimal physical containment is required.

Appropriate training and instruction is crucial to all aspects of handling GM medicines. Dr Logan saw no conflict with Good Laboratory Practice in the conduct of trials complying with health and safety legislation.

Challenge of batch release testing for a live virus can be overcome

Intercytex is a cell therapy company with products that focus on skin and hair and address both aesthetic and medicinal needs, said Gary Wilcock, of Intercytex. Its lead medicinal product, ICX-PRO, is indicated for the treatment of hard-to-heal venous leg ulcers and consists of viable human dermal fibroblasts in a human fibrin matrix. The principal logistical problems associated with the manufacture, testing, release and supply of such biological drugs relate to the requirement for quality parametric release after aseptic manufacture, the need for refrigeration and the extremely short shelf-life of 21 days. Consulting the guidelines and regulations relating to analytical control of such biological products reveals a multitude of apparently relevant documents, but it is useful to go back to basics and consider the main purpose of the analytical support, that is, to ensure quality, safety and efficacy of the material during the trial.

Two assays based upon the measurement of cell outputs were therefore developed for ICX-PRO. The Alamar Blue fluorescent assay for cellular growth and viability measures a function of the total metabolism of the cell, whereas the vascular endothelial growth factor secretion assay measures a discrete molecule secreted from the cells, this molecule being known to form part of the wound healing process. Both tests require stringently controlled sample preparation, so much so that the sample preparation systems employed have required optimisation and validation akin to process validation. Additionally, in-process checks form an integral part of the release system helping to maintain consistency of manufacture. Mr Wilcock commented that proving the safety, efficacy and quality of such products required the

business to move from an R&D culture to a more operational business culture, the emphasis being firmly placed on continuous improvements and key performance indicators to optimise every aspect in the product chain.

Similarly, Colin Love, of BioVex, described the sponsor's expectations of the contractor, with reference to OncoVex, a lead product for the treatment of cancer currently being tested in clinical trials for melanoma, pancreatic and head and neck cancer. The product is based on a proprietary, engineered form of herpes simplex virus, a potent virus that infects and destroys cells through the process of lysis, in which the virus replicates inside a cell and ultimately ruptures the cell membrane, killing it. The deletion of a specific gene means the virus is able to replicate in tumour cells but not in the surrounding healthy tissue.

Analytical support at the clinical site is wide-ranging, addressing the problems of product stability during transport, storage and dispensing, virus containment and virus efficacy. Thus a range of specific analytical methods is required to support clinical trials with a live viral product. Several potency assays may be required because viruses have more than one mode of action, and further tests are required for purity, impurities, content and identity. Many of these safety tests require a rapid turn-around during first dosing of the product to patients in the early stages of the first clinical trials. For this product the challenges of batch-release testing for a live virus have been overcome, and product characterisation can be used to provide support for process change and scale up, concluded Dr Love.

Bioanalysis and trials: regulatory aspects becoming more stringent

As well as providing analytical support ensuring the quality of material used in clinical trials, analytical support is also required in the analysis of biological samples generated in trials carried out in support of safety data. Thus bioanalysis is a critical element in the clinical drug development process, said Andy Brown, of Bioanalytical Systems.

Bioanalysis is traditionally the measurement of small chemical entities in biological samples, such as plasma, urine, serum, saliva, semen, sputum, milk, CSF, tissues, tumours and faeces. A high proportion of such analyses required in clinical trials is outsourced. These may be for first-time-in-man studies, where rapid turn-around of data is required for safety and tolerance, through to lengthy patient studies and bioequivalence studies. Modern drug discovery is directed to highly active molecules and this, in turn, leads to the need for highly sensitive methods to determine the pharmacokinetic parameters needed for those clinical decisions. Although

the advent of LC-MS/MS has enabled highly sensitive and rapid methods to be developed it is not the universal solution, not always being sensitive enough and prone to matrix effects. Other detection methods such as fluorescence and electrochemistry can offer better sensitivity for certain small molecules and immunochemistry methods for biological therapies may also be appropriate. Regardless of the assay method used, it must be validated according to established properties of precision, accuracy and robustness for the duration of the development project. Methods subject to variability will be troublesome and neither cost-effective nor time-efficient. However, none of the methodologies discussed or results obtained is worth anything if the sample has not been collected correctly, said Mr Brown. Over 90 per cent of analytical problems related to clinical bioanalysis, are due to that miscollection, he claimed. This may be due to simple labelling problems or more critical issues of stability, such as inappropriate

use of anticoagulants or other stabilisers, collection devices which adsorb drug onto surfaces, and inadequate control of temperatures during processing as well as during storage. The collection process itself needs to be validated. Methods need to be appropriate for the application. For example, the method should cover expected concentrations encountered in the clinical study and should remain valid in conditions encompassing the targeted disease state in patients, or with co-administered medicines.

The regulatory aspects of bioanalysis are becoming more stringent, as evidenced by the first issuance of a US Food and Drug Administration warning letter to a bioanalytical facility for apparently inadequate analytical methods. The sphere of bioanalysis may be shifting to strategic outsourcing providers that have the infrastructure for permanent regulatory compliance, but the sponsor will want to make sure the analytical base is also competent, said Mr Brown.