Advice for pharmacists who need to comply with clinical trials regulations

Pharmacists are struggling to comply with regulations on clinical trials of medicinal products for humans four years since they were introduced.

Vincent Yeung, Richard Funnell and Rebecca Harrison, of the Medicines and Healthcare products Regulatory Agency, explain the requirements

The regulatory requirements (summarised in Panel 2) are simple and explicit. The common findings are listed in Panel 3. This article will only deal with the four critical areas: the green-light request, protocol amendments, the requirement of manufacturers’ authorisations for investigational medicinal products (MAIMPs) for importation, manufacture/assembly and exemption in the NHS; qualified person release and documentation; and record keeping.

Release process/protocol amendment

In non-commercial clinical trials, the pharmacy performs the role of a clinical trial supply department for the sponsor. Such an interpretation allows the pharmacy to order and hold IM Ps before clinical trial authorisation and ethics approvals have been granted. Pharmacy, in conjunction with trusts (via their research and development departments), should develop a system to enable the pharmacy to be involved in the trial approval process whether or not they are involved in the procurement of IM Ps.

Under such an arrangement, the pharmacy will be able to identify clinical trial prescriptions and will be informed that all necessary approvals are in place before dispensing. Most of the critical findings have arisen because investigators were able to source IMP independently, and subsequently dosed subjects without the necessary approvals. Care must be taken when ward stock (marketed authorised products or specials) is used for a clinical trial and pharmacy is not involved in the custody of the IMP.

For studies that involve more than one trial site, the pharmacy may act as a distributor of IMPs to other pharmacy sites. Alternatively, the sponsor’s clinical trial supplies department relies on the contract manufacture organisation to supply direct to other trial sites where the pharmacy is involved in distribution to other trial sites, its staff should be aware that each trial site should be approved independently by a local, site-specific ethics assessment in addition to the CTA and main ethics approvals for the trial.

Occasionally, a clinical trial authorisation is conditional on the supply of supplementary information from the sponsors or the clinical trial unit in the M HRA makes certain assumptions. Many of the conditions and assumptions are pharmaceutically oriented, for example, label text, MAIMP status of the contract manufacture organisation, stability data etc. A trial cannot take place before the sponsor provides the additional information or if the assumptions are incorrect. Unless the pharmacy is involved in the clinical trial authorisation application and provides appropriate input, the researchers often assume an authorisation has been granted and embark on trial activities. It is the responsibility of the sponsor to provide the information to the M HRA before trial activities start to eliminate the possibility that the application may be turned down after trial activities have begun.

When a substantial amendment is made to the IMP in terms of formulation, a change of supplier, changes in stability data, or dosing schedule, the pharmacy must be involved to ensure that the correct information is provided and the dispensing procedure is updated. In short, the NHS trust should develop a process to inform and involve the pharmacy in the trial approval process.

MHRA expectations

The M HRA requires that the following conditions are met before a pharmacy dispenses an IMP to a subject or supplies it to investigators or other trial sites:

- Clinical trial authorisation has been granted for the trial
- All conditions on the authorisation met
- An ethics approval has been granted
- Each trial site has been approved

MAIMPs

Part 6 of SI 2004 No 1031 (as amended) deals with the need for a MAIMP if IM Ps are to be manufactured, assembled or imported. IMPs include placebos and comparators. Challenge agents, rescue medicines and other contingent medicines are not considered to be IMPs.

The definition of manufacture in the legislation is wide. Essentially, anything done to the IMP, including labelling — but not including reconstituting or diluting for the purposes of administration only — is considered to be manufacture. Therefore, in all such cases an MAIMP is required. One exception to this rule is described in Section 37 of the legislation. In summary, a hospital or health centre does not require an MAIMP if it is engaged in assembly only (packaging and labelling).
IMPs cannot be supplied to “an investigator, health care professional, subject” without a clinical trial authorisation, ethics committee positive opinion and QP certification of IMPs (certification is not required if the IMP is a market-authorised product).

There is a requirement for authorisation to manufacture or import investigational medicinal products (MIAIMP).

An investigational medicinal product shall be labelled in accordance with Article 15 of Commission Directive 2003/94/EC.

All clinical information shall be recorded, handled and stored in such a way that it can be reported, interpreted and verified accurately, while the confidentiality of records of the trial subjects remain protected.

When applying for an MIAIMP it is necessary to name at least one person who is eligible to be a Qualified Person (QP). MIAIMP holders are only authorised to manufacture, assemble or import IMPs, not manufacture specials or licensed medicines. From time to time, it will be necessary to stop a trial and administer the drug for medicinal reasons outside the trial. In these circumstances, the drug ceases to become an IMP and therefore a full MIA licence or a specials licence is required in order to manufacture.

One of the causes of a critical finding is the belief that some manufacturing operations such as the mix of an active ingredient with an ointment base or the extemporaneous preparation of a suspension are examples of “making up for administration” and hence an MIAIMP is not required. In other cases, the pharmacy has been unaware that the supply was to be used for a clinical trial and so could not comply with the regulation.

The widespread use of specials in clinical trials gives rise to issues of data reliability and non-compliance. Specials are unlicensed medicines supplied against an order or prescription by a hospital manufacturing unit or commercial manufacturer holding a specials manufacturing licence. There are provisions in medicines regulations to allow the supply of specials. However, a medicinal product when used in a clinical trial is subsumed under the clinical trial regulation. Therefore, a product manufactured under a specials licence cannot generally be used directly in a clinical trial. In multi-centre studies, the sourcing of IMPs may be delegated to individual pharmacies and each can source the same preparation from different specials manufacturers. The formulation and method of preparation can vary from one manufacturer to another and therefore any variation in bioavailability of different formulations could affect the reliability of the data. Different manufacturers must have MIAIMP licences and not just specials licences.

MHRA expectations The M H R A requires the following to be met:

- All IMPs and comparators used in a clinical trial must have been manufactured to a standard equivalent to EU GMP.
- The manufacturers, assemblers (other than in hospital) and importers must hold an MIAIMP to allow them to supply IMP and comparator to an investigator or a trial site.
- NHS pharmacies are allowed to assemble IMPs for use in a hospital or health centre named in a particular trial without an MIAIMP.
- Assembly consists of packaging and labelling operations. Any operations outside these categories may be deemed to be full manufacture and are likely to lie outside the hospital exemption.
- Bulk supplied to the hospital for assembly will need to have been OP certified by the QP named on the MIAIMP held by the bulk manufacturer.
- Pharmacies are expected to confirm that their suppliers have a MIAIMP licence.
- The IMP suppliers are named in the CTA. Any change of supplier requires submission of a substantial amendment.
- A product manufactured under a specials licence cannot generally be used directly in a clinical trial.
QP release and documentation

All IMPs must be certified by a QP as suitable for release to the trial. This has been known previously as the technical green light. The QP has a legal responsibility to ensure that the IMP has been manufactured in accordance with EU GMP and meets the conditions of the clinical trial authorisation and the product specification file (PSF). The legal duties of a QP are laid out in Article 13 of 2001/20/EC.

Between May 2004 and May 2006, to ease the transition to the new legislation, there was provision to allow some personnel to be transitional IMP QPs. The transition arrangements are no longer available, although existing transitional IMP QPs will retain their status even if they transfer to another MIAIMP licence. Anybody wishing to become a new QP will need to proceed through the professional bodies to attain full QP status (the Royal Pharmaceutical Society, the Royal Society of Chemists or the Institute of Biology).

One of the duties of a QP relates to IMPs imported from outside the European Economic Area (EEA). The duties of ensuring that IMPs have been manufactured in accordance with EU GMP still apply. The QP has to submit a declaration stating this in the clinical trial authorisation. The QP, or his or her representative, is expected to audit the manufacturing site to ensure that products originate to be manufactured in accordance with EU GMP.

Declarations are subject to scrutiny and follow-up by the MHRA.

One of the perennial questions raised by NHS pharmacies is the requirement for a QP release document. As a sponsor (when the NHS trust is the sponsor and has delegated IMP management responsibility to the pharmacy), the pharmacy department must have an oversight of technical release, even though the QP certification may be performed elsewhere.

It is normally expected that the pharmacy has the documentation of QP certification for each batch of IMP released. The responsibility for technical release may be contracted out to a contract manufacturing organisation as defined in the technical agreement. In such cases, the trust pharmacy only needs a confirmation by the chief medical officer that QP certification has taken place and the product is ready for use.

When an NHS trust is a host to a study, the pharmacy needs to ensure the supplier is an MIAIMP licence holder. The degree of non-compliance among non-commercial organisations in relation to IMPs means that the hosting organisation is running a risk of non-compliance.

Any subsequent evidence detected by an MHRA inspection that an IMP had not been QP-certified or that an MIAIMP was not held as required is likely to lead to a critical finding against the pharmacy. This risk can be avoided if documented QP certification is obtained and filed.

Products used in clinical trials that are already marketed in the EU do not need QP certification since they have must be manufactured to EU GMP.

MHRA expectations The MHRA expects the following to be met:

- A sponsor of a clinical trial must demonstrate that IMPs are certified by a QP before the batch is released for use in a clinical trial, unless the product is already marketed in the EU and has not been changed from its original packaging. The QP must be named on the MIAIMP licence.
- A QP must certify a batch against the PSF. Investigational Medicinal Product dossier or the clinical trial authorisation. The wording should appear on a QP certification document.
- When IMP management has been delegated to a third party, such obligation must be defined in a contract and a technical agreement.
- A hosted organisation must have assurance from the sponsor that QP certification has been performed. Such assurance may be a copy of QP certification document or a letter or e-mail confirmation from the sponsor.

Record-keeping

Pharmacists are accustomed to keeping records. There are minimum retention requirements for prescriptions, and records for prescription-only medicines and Controlled Drugs. Yet deficiencies in drug accountability were identified in 10 out of 14 cases. In most cases, investigators were responsible for maintaining their own accountability records. The lack of documentation in trial-related activities is one of the most frequent findings in non-commercial inspections.

SI 2004 1031 defines the principles of GCP (Schedule 1 part 2.9) without defining what records to maintain. One of the objectives of GCP is to ensure that trial data be accurately reconstructed and reported. Data generated from a study may be used for a marketing authorisation application, as a basis for future studies or in defining standard clinical practices. Therefore, to ensure future patient safety, trial results must be credible and reproducible.

Trial data are reconstructed from the source data. Common data sources include case notes, laboratory results, dispensing records, handwritten prescriptions, drug storage temperature logs, randomisation records and calibration records of temperature monitors.

The list is not exhaustive, but the concept is clear: any factors that could affect integrity of the data should be recorded, monitored and maintained.

The principle applies irrespective of the storage medium. Therefore, when a computer program is used for randomisation, dispensing or storage of trial data, the data should be credible and reproducible. How can one perform analysis or preclude bias if the original randomisation list is lost?

A final note is required on keeping dispensing records for trials using marketed authorised products in multicentre studies. Some studies may not define which IMP should be used. For example, some HIV studies only define the class of drugs, rather than a specific drug, for a trial arm. In such a case, how can the sponsor reconstruct what medicine a subject has received during the course of the study?

If a subject experiences adverse events and the batch numbers of the IMP are not recorded, how can the sponsor be assured that the adverse event is not related to a particular batch or to that particular drug?

MHRA expectations The MHRA expects that pharmacy records must be maintained to demonstrate adherence to trial protocol and credibility and integrity of the data. Such records may include but are not limited to the following:

- Original prescription
- Randomisation code and code break
- Drug accountability or dispensing records (include any marketed authorised products used as IMPs comparator or adjuvant therapy) and drug destruction records (electronic or paper)
- Production worksheets or batch sheet
- Storage temperature record
- Transit temperature record
- R labelling records
- Validation document for electronic prescribing system
- Validation document for prescribing module or protocol set up within the electronic prescribing system

In summary

NHS pharmacies have done a great deal to address the new requirements over the past three years, but more is needed. According to the Royal Pharmaceutical Society’s Hospital Pharmacists Group, “these [regulations] need not be a barrier but do mean that more preparatory work is needed”.

The regulation has given the pharmacy professional an opportunity to be the central part, rather than an afterthought, of the clinical trial process. Many NHS trusts have delegated the task of IMP management to their pharmacies and the pharmacy should now form part of the R&D approval decision-making process.

Many findings have resulted from a lack of control and understanding by the NHS trust and its staff. Pharmacy is well placed to fill the gap and make an important contribution in this area.

References