

GOOD PRACTICE IN RELATION TO SUPPLIES FOR PUBLICLY FUNDED CLINICAL TRIALS OF MEDICINES

1. Introduction

This note is a statement of some elements of good practice for clinical trials of medicines which fall under the Clinical Trials Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 which implements the Directive from 1 May 2004, as related to investigational medicinal products (IMPs). It:

- Draws attention to relevant EU Commission guidance and UK Regulations
- Advises about matters which are best resolved in advance of seeking trial authorisation
- Sets out issues relating to the manufacture, assembly and supply of IMPs.

A [companion note](#) deals with labelling of IMPs in more detail.

2. The Clinical Trials Directive 2001/20/EC

This Directive requires that investigational medicinal products (IMPs) used in such trials are manufactured to Good Manufacturing Practice (GMP) Standards and that Good Clinical Practice (GCP) is adhered to.

The principles and guidelines of Good Manufacturing Practice for marketed products and investigational medicinal products are given in [European Commission Directive 2003/94/EC](#). Detailed guidance on good manufacturing practices in relation to the manufacture of investigational medicinal products is published in a supporting document [Annex 13](#)¹. This latter document sets out requirements also for labelling IMP supplies, along with guidance on ordering, shipping, and returning such supplies.

3. Standard Operating Procedures

Standard Operating Procedures are an integral part of quality systems in this area, and an aid to managing risk.

¹ Not all products used in clinical trials are necessarily investigational medicinal products. The guidance in this note refers to IMPs, although pharmacy or other departmental quality systems may apply in hospitals in respect of such products. Annex 13 includes a note about such other products as follows:

“Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial. Such products may be used as support or escape medication for preventative, diagnostic or therapeutic reasons and/or needed to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These products do not fall within the definition of investigational medicinal products and may be supplied by the sponsor, or the investigator. The sponsor should ensure that they are in accordance with the notification/request for authorisation to conduct the trial and that they are of appropriate quality for the purposes of the trial taking into account the source of the materials, whether or not they are the subject of a marketing authorisation and whether they have been repackaged. The advice and involvement of a Qualified Person is recommended in this task.”

4. UK Regulations

The Medicines (Clinical Trials) Regulations 2004 (SI 2004/1031) transpose the requirements of the Clinical Trials Directive and relevant provisions of the European Commission Directive 2003/94/EC into UK law. The Regulations came into force on 1 May 2004. Particular provisions related to clinical trial supplies include the following:

- Regulation 2: Interpretation, providing legal definitions, including investigational medicinal product, manufacture, qualified person.
- Regulation 13: Supply of investigational medicinal products for the purpose of clinical trials.
- Part 6, Regulations 36 to 45, Manufacture and importation of investigational medicinal products
- Part 7, Regulation 46, Labelling of investigational medicinal products
- Part 8 Enforcement and related provisions
 - Regulation 59 Offences,
 - Regulation 51 Defence of due diligence
- Schedule 1 Conditions and Principles of Good Clinical Practice and for the protection of clinical trial subjects (Part 2, paragraph 12)
- Schedule 3 Particulars and documents that must accompany an application for an ethics committee opinion, a request for authorisation, a notice of amendment and a notification of the conclusion of a trial, Part 2 request for authorisation
- Schedule 6 Particulars that must accompany an application for a manufacturing authorisation
- Schedule 7 Standard provisions for manufacturing authorisations
- Schedule 8 procedural provisions relating to proposals to grant, refuse to grant, vary, suspend or revoke manufacturing authorisations

Under Regulation 28 it is one of the roles of the sponsor to make arrangements to provide the IMPs. This role is part of the requirements for Good Clinical Practice. The IMPs are to be provided free (except that they remain subject to any prescription charges in the NHS). Permitted arrangements for sponsorship are set out in Regulation 3. If the responsibilities of sponsorship are allocated in accordance with Regulation 3 (2)(b), then that person or body who takes on the responsibility for good clinical practice and trial conduct would also have the sponsorship responsibility for trial supplies. (Specific points about not making supplies available before MHRA clinical trial authorisation are included in Regulation 13 within Part 3 of the Regulations “authorisation of clinical trial and ethics committee opinion”.)

5. Practical arrangements

In practice, in publicly-funded clinical trials in the NHS, there are arrangements whereby normal treatment costs – which include normal supplies of medicines – are provided by the NHS hosts for the research. In England these arrangements are set out in HSG(96)32 “Responsibilities for meeting patient care costs associated with Research and Development in the NHS”. The NHS does not cover the costs of medicines when specific

packaging is required for the clinical trial, eg for blinding products, which is not part of normal treatment. Such costs are considered to be research costs, which should be covered by the research funder, not the NHS host.

Labelling requirements are set out in Regulation 46 (see companion document [“Labelling of investigational medicinal products”](#) for more details). Labelling will be necessary whether the trial supplies are dispensed products or part of manufacture/assembly. Hence these requirements would not affect whether supplies for any particular trial are considered as treatment costs or research costs.

Good practice suggests that the arrangements for trial supplies would be best considered along with the development of the protocol for the trial.

6. Trial supplies considerations and the protocol

There are different arrangements for trial supplies depending on the trial protocol, and the Manufacturing Authorisation status of the product involved.

Investigators and sponsors planning trials which commence after 1 May 2004, will need to set out in the request for trial authorisation to the Medicines and Healthcare products Regulatory Agency (MHRA) a description and some other information about the IMPs to be used in the trial, and provide a description or sample labelling for such products. If the IMP is to be sourced from outside the EU, further information would be required, including disclosure of the source and importer. The full requirements are set out in Schedule 3, Part 2, of the UK Regulations.

Where a trial is to take place in an NHS hospital, early discussion with the hospital pharmacist is advised so that plans can be put in place early. The hospital pharmacist's overall responsibilities are set out in the Duthie Guidelines for the Safe and Secure Handling of Medicines (1988, presently being revised) (see also the mandatory minimum standards in the NHS controls assurance standard for [Medicines Management \(Safe and Secure Handling\)](#)). By allowing time during the initiation phase for the pharmacist to be satisfied with the local arrangements, delay to trial commencement can be avoided.

The trial protocol should be available at the pharmacy involved in providing the trial supplies to the patient, and to hospital staff who would be administering the investigational product to the trial participant, (the protocol would include any particular procedures or precautions to be adopted where the IMP is to be administered to the patient by a health professional.)

Where a hospital hosts a number of clinical trials, or where hosted trials have complex protocols, NHS management may wish to control storage and supply through dedicated facilities and staff for reasons of efficiency and minimising the risk of error.

In many cases IMPs are solid dose forms of medicines which are self-administered by the patients participating in a trial. This is the starting point in

the general description that follows. Where other forms of IMPs are required this would affect the details of matters such as the facilities and authorisation for manufacture of that form, storage requirements, instructions for administration, etc. Also there may be other legal restrictions on some medicines (eg controls under the Misuse of Drugs Act). Such matters will depend upon the particulars of the trial itself, and will need to be addressed in planning the arrangements about IMP supply.

7. IMP considerations in different types of trial

In the next section of these notes, different considerations apply to the handling of three different types of clinical trial:

- 7.1 trials of existing marketed medicines used according to their licensed indications
- 7.2 trials involving medicines used outside their marketing authorisations or which otherwise require assembly
- 7.3 other trials of new products or presentations of existing products which require manufacture.

The first group does not normally involve a new manufacturing process. However the repackaging of these products is considered to be an assembly activity.

All manufacturing² and assembly activities will need to be conducted in a unit which has an IMP manufacturing authorisation with a named Qualified Person (QP) from 1 May 2004. However Regulation 37 provides an exception from the requirement to hold an IMP manufacturing authorisation for the assembly of an IMP in a hospital or health centre by a doctor or a pharmacist or a person acting under the supervision of a pharmacist – this is considered below under “repackaging”.

7.1. Trials of EU marketed medicines used in accordance with their marketing authorisations

These trials are common amongst publicly funded trial (eg comparative studies, trials of different treatment combinations of medicines).

Medicines marketed in the EU and certain other countries under the EEA arrangements with a marketing authorisation from a regulatory body are required to be made to GMP standards, so the quality standards are met. Supplies to study participants can take place under normal prescription and dispensing arrangements. (See companion document for information about [labelling](#) of IMPs). For trials in **NHS hospitals**, suitable arrangements should be made with the hospital pharmacist concerned. It may be possible for dispensary labelling machines to be pre-programmed.

² It should be noted that dissolving or dispersing a product in, or diluting it or mixing it with, some other substance used as a vehicle for the purposes of administering it, is not manufacturing – this is made clear in the interpretation of “manufacture” in Regulation 2 of the UK Regulations.

Supply could be made from medicines held as normal pharmacy stock. However:

- In cases where there are documented differences in bioavailability, the trial protocol should state which products are to be used.
- If a trial involves products that are not normally used in the host hospital, special supplies obtained for the purpose will need to be separately controlled.

Some manufacturers may agree to supply specific medicines free or at a reduced rate for trial use. This may involve centralised ordering through one pharmacy, and the hospitals would need to comply with appropriate conditions agreed with the manufacturer. The Department of Health has published separate guidance on commercial sponsorship which covers such arrangements. (Agreement by a commercial manufacturer to contribute medicines free to a collaborative trial does not necessarily imply that the manufacturer is the sponsor for that trial. It is for separate agreement whether the manufacturer would be willing to take on any sponsorship responsibilities. For example, a company might consider joining a collaboration, which is allocating sponsor responsibilities in accordance with Regulation 3(2)(b), and take on sponsorship responsibilities for pharmacovigilance where the trial involves a product that it owns. In that case, it would not take on the other responsibilities it would normally have when it is the single sponsor for a commercial trial leading to a marketing authorisation.)

Repackaging can be undertaken in a hospital or health centre by a pharmacist or a person acting under his/her control or a doctor, for use within that institution. Supply can be made to other hospitals or health centres which are trial sites involved in the trial of that product (under provisions of Regulation 37 of the UK Regulations). This would reduce the extent of variation (and hence potential for misunderstanding) in such products within a single trial. Although batch sign off by a QP is not required for products repackaged under these “exemption” provisions, it would be good practice for a quality control pharmacist to be invited to comment on proposed arrangements. It may be able to arrange this as part of a normal NHS independent quality control audit on facilities taking place at regular intervals. Assembling pre-labelled supplies can help with the arrangements to supply to individual patients in the trial.

It would be normal practice for a pharmacy department to maintain records of goods received. There would also normally be some record of supply such as through endorsement on the prescribing physician’s prescription card, which would be retained with the patient’s notes. There is advantage in agreement between the local investigator and pharmacy department for a trial specific direction or prescription form, which, where retained in the pharmacy after dispensing, can help with record keeping.

Although good practice suggests that records be made of the batch number of the medication supplied in case of a product recall for a faulty batch (this

information could indicate that the fault may affect the results of the trial) it is unlikely to be presently practical to undertake such recording.

Where the trial takes place in **primary care** the arrangements would most likely be different from trials in hospitals, unless a trial was undertaken in a single locality with local coordination and cooperation with the health professionals who may interact with the patient as trial participant.

In the normal NHS prescribing and dispensing arrangements, patients cannot be directed to a specific pharmacy to receive their medication. Thus it is likely that the dispenser may not be aware of the patient's involvement in a trial, and so the dispensed medicine would be labelled in conformity with the normal requirements, rather than those for a clinical trial. The UK Regulations (Regulation 46, labelling) address this situation by permitting the use of the normal dispensing label for use in trials which have the characteristics specified in the second paragraph of Article 14³ of the Clinical Trials Directive. Thus trials which fall outside these characteristics need to be supplied with the fuller clinical trials labelling as per paragraph 26 of Annex 13 (see companion document "[Labelling of investigational medicinal products](#)" for more details).

It may be possible to arrange to supply the clinical trial medicines from the surgery that the patient attends, where there are a limited number of practices involved. Dispensing would then take place under the supervision of the doctor, by a responsible person who has received appropriate training. Pre-labelled supplies prepared by an assembly unit can help to facilitate this.

³ Article 14 (second paragraph) of the Directive points to adapted provisions for labelling IMPs intended for clinical trials with the following characteristics:

- the planning of the trial does not require particular manufacturing or packaging processes;
- the trial is conducted with medicinal products with, in the Member States concerned by the study, a marketing authorisation, manufactured or imported in accordance with the provisions of Directive 2001/83/EC
- the patients participating in the trial have the same characteristics as those covered by the indication specified in the above mentioned authorisation.

7.2 Trials involving medicines used outside their marketing authorisations or which otherwise require assembly

7.2.1 IMP assembly and manufacturing in a unit with IMP manufacturing authorisation

Assembly will be necessary in circumstances such as the following:

- where the trial involves an EU marketed medicine to be used with participant patients who do not have the same characteristics as those covered by the licensed indication for the marketed medicine; or
- where there is to be blinding of the investigator to an active medicine eg in comparative trials.

The marketing company may be willing to provide supplies in the first example.

In this case the label on the assembled product would need to comply with paragraph 26 of Annex 13 [web link]. A sample label would need to be provided to the MHRA as part of the application for clinical trial authorisation. The choice of packaging material and description of the finished product may need discussion with the pharmacist in charge of the assembly unit.

7.3 Other trials of new products or presentations of existing products which require manufacture.

New products or presentations of existing products will require **manufacturing**. (This would include placebos and disguising active products by reprocessing them for blinding purposes.)

All medicinal products for use by humans are required to be manufactured to Good Manufacturing Practice standards and released by a Qualified Person. GMP principles have been established for marketed products for many years, and they are now set out for both marketed products and IMPs in the in [European Commission Directive 2003/94/EC](#). This also points to guidance in [Annex 13](#).

From 1 May 2004, IMP manufacture is required to be undertaken by **manufacturers** with an IMP manufacturing authorisation covering the appropriate activities. The IMP manufacturing authorisation will specify the physical types of medicines that can be manufactured (eg capsules, liquids, sterile injections) and name the QP concerned (separate manufacturing authorisations are not needed for every trial).

An **importer** of an IMP from a third country outside the EU is required to hold a manufacturing authorisation that authorises the importation of IMPs. The importer is expected to name a QP who conducts similar activities to a QP for full manufacture.

The application requirements and standard provisions for IMP manufacturing authorisations are set out in Schedules to the Medicines for Human Use (Clinical Trials) Regulations 2004. The MHRA have published some guidance on the qualifications for QPs (including those who would be included on IMP manufacturing authorisations under the Grandfather provisions of the Directive).

Possible manufacturers

Where commercially manufactured products require a matching placebo form, the most appropriate source would be the original manufacturer, if that organisation is willing to provide such a supply; however while the company would have a manufacturer's licence for the original product, they would still need an IMP manufacturing authorisation to prepare such placebos.

It is known that many NHS hospital manufacturing units are planning to apply for IMP manufacturing authorisations, but the overall range of products is not yet clear. There may be capacity constraints. There is extant advice (under provisions relating to income generation) on the basis for NHS bodies to charge for manufacturing or assembly.

Commercial contract manufacturers may also plan to operate in this market, and the contract research organisations (CROs) who offer a manufacturing service to their clients are likely to continue to do so. It is not known how many university based units there are (eg undertaking manufacturing for phase I/early phase II trials), although those presently without pharmaceutical support may be able to call on hospital based manufacturing pharmacists and QPs to assist them in applying for IMP manufacturing authorisations.

Agreements for the supply of manufactured products are likely to take the form of contracts which specify to some degree of detail what is to be supplied. It may be that more than one organisation will be involved, eg one to prepare a specialised product and supply in quantity to another body which then undertakes filling, packaging, labelling and other finishing operations. In some cases there may need to be preliminary formulation and stability studies to satisfy the MHRA for clinical trial authorisation. This all points to the need particularly to consider the IMP specification early on where it is likely that new products or presentations are concerned.

Manufacturing processes can involve a sequence of different contractors, eg one for manufacturing the bulk forms, another for capsule filling, a third for packaging and labelling. Each contractor would require its own appropriate manufacturing authorisation and QP for that part of the work. The final QP will need to carefully consider the composite process for GMP and compliance with the IMP description in the request for clinical trial authorisation.

QPs are required to certify in a register (or equivalent document) that each production batch satisfies the requirements set out in Article 13 of the Clinical Trials Directive.

Once products are released by the IMP manufacturer's QP, the supplies would normally be transported to a designated store for the trial. Control and distribution of such supplies for a large trial may present logistical difficulties which will need to be considered as part of overall trial management.

Products manufactured/assembled before 1 May 2004

IMPs manufactured/assembled before 1 May can be used and supplied after that date through the exemption in Regulation 13(3). However the specific provision on labelling IMPs does not allow for a transition period, so it would be good practice for those involved in the supply of IMPs after 1 May 2004 to review their labelling for compliance.

Circumstances requiring particular considerations

Normal considerations of **health and safety** (including during transport), temperature, security or other forms of storage, and record keeping will apply to trial supplies as to other medicines. However new products or presentations may introduce new hazards, for which a risk assessment should be undertaken. This should include processes for disposal of unused products at the end of a trial.

Ingredients for manufacturing, for which there are no existing pharmacopoeial or other appropriate standards, will require QP consideration as to their quality. There are also requirements which relate to transmissible spongiform encephalopathies and medicinal products, published by the MHRA.

The QP will also need to decide **whether products manufactured and marketed outside of the EU** have been prepared according to GMP standards as part of the process for importing such products under IMP manufacturing authorisations covering importation.

May 2004. The above is based on the work of a Medical Research Council/Department of Health Joint Project to codify good practice in publicly-funded clinical trials. Anyone reading these notes is invited to comment on what clarifications would help with the practical implementation of the new legal requirements.