Clinical Trials Toolkit

Trial Supplies

Updated March 2018 by Oliver Gupta (MODEPHARMA)

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Risk-Adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

Since 2011 the concept of risk-adapted approaches to clinical trials was implemented by the MHRA for UK trials ('notification scheme').

This scheme presents a risk-proportionate approach in applying the principles of GCP to the various types of clinical trials of investigational medicinal products, within the context of the current regulatory framework in the EU, to simplify the processes for initiating and conducting such trials.

The risk-adapted approach relies on a risk-stratification in relation to how much is known about the medicine(s) being investigated. Categorising the risk associated with the IMP allows for several risk adaptations within the scope of the Clinical Trials Directive. For lower-risk trials, this simplifies the requirements for both obtaining regulatory approvals and conducting the trial. Specifically, the following requirements concerning IMPs are impacted:

- Application for clinical trial authorisation
- IMP Dossier
- Good Manufacturing Practice (GMP) compliance
- Labelling of trial drugs
- IMP management (tracking, accountability and storage)

Sponsors may in the first instance use this guidance to carry out a risk assessment based on the potential risks associated with the IMP.

The full guidance on risk-adapted approaches to the management of clinical trials of investigational medical products can be accessed online:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

FAQs and real life examples of risk assessments can also be viewed and discussed on the GCP Forum (a tool created by the MHRA to help all those involved in the conduct of clinical trials of Investigational Medicinal Products to comply with the clinical trials legislation and GCP requirements):

http://forums.mhra.gov.uk/forumdisplay.php?1-Good-Clinical-Practice-(GCP)

Common IMP Challenges

Use the "Trial Supplies Checklist" in this document as an introduction to arranging trial supplies

The following highlights some common IMP-related challenges seen across the initial stages of a clinical trial lifecycle. These challenges can be avoided with diligent planning and awareness of the underlying issues.

CHALLENGE		COMMON RISKS
PROTOCOL DEVELOPMENT PHASE		
• Insufficient consideration of patient population factors • Sub-optimal choice of active/placebo dosage forms • Lack of awareness on regulatory requirements for IMP manufacturing • Inaccurate budgeting of IMP costs	→	• Non-compliance or high withdrawal rate • Poor trial design / wastage of drug • Regulatory approval delayed/failed • Insufficient funding for the trial to continue
TRIAL SETUP PHASE		
• Little or no experience with contract manufacturers • Hidden costs in quotes making them difficult to interpret and compare • Incomplete and/or poorly understood manufacturing specifications • Missing Quality Technical Agreements • Inadequate project planning	→	• Poor IMP quality and design • Paying more than expected • Sponsor's responsibilities not adequately covered • Manufacturing delays
TRIAL IMPLEMENTATION PHASE		
• Insufficient blinding of IMPs • Inadequate labelling of IMPs • Poor quality IMP and packaging • Inappropriate supply chain or processes • IMP adversely affected during storage and transport • Failure to monitor product quality issues including recalls	→	• Credibility of results • Patient safety risk/regulatory non-compliance • Interruption to treatment • Patient loss of confidence and drop-outs • Early trial stop by Sponsor or Competent Authority

Trial Supplies Checklist

This checklist highlights key questions that must be considered when arranging trial supplies. The objective is to consider as many of these as early as possible to (a) establish the most optimal trial medication solution and (b) avoid funding shortfalls during the conduct of the trial.

(A) REGULATORY CONSIDERATIONS:

Is it a Clinical Trial of a medicinal product?

- Does the study fall under the Clinical Trials Directive?
- Is the Product an Investigational Medicinal Product (IMP) or a Non-Investigational Medicinal Product (NIMP)?
- Can the reduced requirements from the MRC/DH/MHRA Joint Project on risk-adapted approaches to the management of clinical trials of IMPs apply?

Does the trial involve multiple countries?

- What are country-specific IMP requirements?

(B) PRODUCT CONSIDERATIONS:

What medicinal products and dosage form will be used?

- Existing commercial products with marketing authorisations in a European Union Member State?
- Commercial product with marketing authorisation in non-EU country?
- Novel substances and products (new product)?
- Placebos (new product) required?

Source of products?

- Sourced directly from Marketing Authorisation holder?
- Purchased via commercial wholesale/hospital channels?
- New manufacture via one or more contract manufacturers?
- Imported from a non-EU country?

What is the approach to blinding?

- How will comparator products including placebos be made to match in appearance, packaging and labelling?
- Is the blinding approach suitable for the trial's patient population?
- What are the randomisation arrangements?
- What are the emergency unblinding arrangements?

(C) GMP MANUFACTURE CONSIDERATIONS:

Is IMP manufacture[1] required?

- Where will manufacturing of IMP take place?
- Can Regulation 37 in Statutory Instrument 2004/103 for "assembly" work be applied?

What pharmaceutical development work is required?

- Development of blinded products?
- Analytical method development and validation?
- Stability testing to establish shelf-life?

Where will the products be manufactured and/or where will the products be released for clinical trial use?

- Are all IMPs including placebos manufactured by a MIA(IMP) holder?
- How will Sponsor assess that manufacturer is suitable for the planned works?
- Will the manufacturer of the marketed product provide the placebo or is placebo manufacture required?
- Is the placebo identical in appearance and packaging?
- In the case of non-EU imports, is an audit necessary?
- What analytical work is required for QP release?

CTA application manufacturing information available?

- Has the final QP releasing site in the EU been selected?
- IMPD: Full/simplified required or will the SmPC suffice?

[1] Manufacture in relation to an investigational medicinal product, includes any process carried out in the course of making the product (including repackaging and labelling), but does not include dissolving or dispersing the product in, or diluting it or mixing it with, some other substance used as a vehicle for the purposes of administering it.

- Labelling requirements fulfilled?
- Shelf-life: Is sufficient data available for the IMP in its final packaging to justify the proposed shelf-life or is a stability study required?

Standards, specifications and manufacturing scope agreed with the manufacturer?

- Blinded product specifications agreed?
- Agreement on number of manufacturing campaigns required to cover the duration of the trial agreed under consideration of the product shelf lives?
- Manufacturing scope and timeline agreed?
- Technical Agreement (table of responsibilities) agreed?

Documentation requirements?

- Documentation system for full IMP accountability in place?

Storage and distribution arrangements considered?

- Who will undertake storage of trial supplies and patient returns?
- Under what temperature conditions will IMP be stored and distributed?
- Will shipments be temperature monitored?
- What happens in the case of temperature deviations during storage and/or transport?
- Has this cost been considered for the duration of the trial?
- Where will reconciliation and destruction be performed?

(D) COSTING CONSIDERATIONS:

Have all IMP-related costs been considered?

- Regulatory costs?
- IMP sourcing, manufacturing, storage, distribution, returns and destruction costs?
- Is VAT applicable?
- Dispensing costs?
- Prescription charge applicability?

EU and UK Regulations Governing IMPs

Clinical trials are investigations in humans intended to discover or verify the effects of one or more investigational medicinal products ("IMPs"). The following summarises the EU and UK regulations as well as practical guidance relating to IMPs:

EU Directives concerning IMPs:

- **Clinical Trials Directive:** Requirements for the conduct of clinical trials in the EU are provided for in "Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" ("the Clinical Trials Directive"). According to the Clinical Trials directive, the principles of Good Manufacturing Practice (GMP) should be applied to investigational medicinal products:
  - Article 9: conduct of a clinical study subject to ethical evaluation and authorisation
  - Article 13: manufacture and import of IMPs subject to holding of an authorisation

  https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

  Clinical Trials Regulation: The Clinical Trials Regulation (EU) No 536/2014 is set to replace the Clinical Trials Directive 2001/20/EC once it comes into application. The Regulation will ensure a greater level of harmonisation of the rules for conducting clinical trials throughout the EU. It introduces an authorisation procedure based on a single submission via a single EU portal, an assessment procedure leading to a single decision, rules on the protection of subjects and informed consent, and transparency requirements.

  Although the Regulation entered into force on 16 June 2014 the timing of its application depends on the development of a fully functional EU clinical trials portal and database, which will be confirmed by an independent audit. The Regulation becomes applicable six months after the European Commission publishes a notice of this confirmation. The entry into application of the Regulation is currently estimated to occur in 2019. **Until the new Regulation will become applicable, all clinical trials performed in the European Union are required to be conducted in accordance with the Clinical Trials Directive.**

  https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
- **GCP Directive 2005/28/EC:** Additional principles and detailed guidelines with regards to IMPs are specified to verify compliance of clinical trials with the Clinical Trials Directive 2001/20/EC
  - Article 10: requirements for obtaining the manufacturing / import authorisation

  https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf

- **GMP Directive 2003/94/EC:** Replaces original GMP Directive 91/356/EEC

  https://ec.europa.eu/health/documents/eudralex/vol-4_en

Transposed into Member State Laws:

- UK: Statutory Instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments

  http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf

- Rest of EU: despite EU harmonisation differences remain between Member States in clinical trial requirements. It is advised to refer to each Member State's Competent Authority for the most up-to-date legislation.

  The following website lists national competent authorities of the Member States of the European Union (EU) and the European Economic Area (EEA) responsible for human medicines:

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp

Detailed guidance on the manufacture and import of IMPs:

- GCP: ICH Guidelines for GCP
  http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF

- GMP: EudraLex Vol 4 (EU GMP Guide aka “Orange Guide”)
  - Part I (Finished Products) + Annex 13 (IMPs)
  - Part II Section 19 (APIs for Use in Clinical Trials)
  - Other Annexes as applicable (e.g. Annex 1 for Steriles, Annex 2 for Biologicals etc.)

  Whereas GMP is compulsory in the EU due to the Directives and national laws, the Rules set out in the EU/Orange Guide are a guide only and they are more general rather than specific and are intended to set an objective which the manufacturer must achieve.

  Of this guide, Annex 13 of EudraLex Vol 4 is the most important to consider for IMP trials containing detailed guidance on good manufacturing practices in relation to the manufacture of IMPs.

- GMP: EudraLex Vol 10 (Clinical trials – Notice to applicants) is based on the corresponding Directives (2001/20/EC, 2005/28/EC, 2003/94/EC) and summarises existing GCP and GMP guidelines/guidances.
  https://ec.europa.eu/health/documents/eudralex_en
- MHRA guidance on risk-adapted approaches to the management of clinical trials of IMPs:
  https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

Manufacture of Investigational Medicinal Products

Is it a Clinical Trial of a Medicinal Product?

To find out if a study needs MHRA authorization use the MHRA's online algorithm 'Is it a clinical trial of a medicinal product?':

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf

If, after using the algorithm, you are still unsure whether or not the clinical study is covered by the Directive then send an email to the clinical trial helpline (e-mail: *mailto:clintrialhelpline@mhra.gov.uk*) marked 'Scope - protocol review' followed by the short study title in the subject line and request an opinion on the status of the study. A copy of the protocol should be provided with the request. Where possible, the MHRA responds to such queries within seven days.

Additional information is available on the MHRA website:

https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

Is the Product an Investigational Medicinal Product (IMP) or a Non-Investigational Medicinal Product (NIMP)?

Article 2(d) of the Directive 2001/20/EC defines an “investigational medicinal product” as:

- “A pharmaceutical form of an **active substance** or **placebo** being tested or used as a reference in a clinical trial,
- including products already with a marketing authorisation but
  - used or assembled (formulated or packaged) in a way different from the authorised form,
  - or when used for an unauthorised indication,
  - or when used to gain further information about the authorised form.”

Some clinical trial protocols require the use of Non Investigational Medicinal Products (NIMPs) such as support or escape medication for preventive, 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 in the Directive and may be supplied by the sponsor. The sponsor should provide details of these NIMPs and their proposed use in the trial protocol and ensure that they are of the necessary quality for human use after seeking advice and/or involvement of a Qualified Person where appropriate. The decision as to whether a product is an IMP or a NIMP depends on the product being used and the design of the study. Further guidance on NIMPs is available here:

http://ec.europa.eu/health/files/eudralex/vol-10/imp_03-2011.pdf

IMPs Require Manufacturing Under MIA(IMP)

The manufacture of an IMP into its final dosage form as well as the operations of packaging, labelling and assembly for clinical trial use are considered to be 'manufacture' according to Directive 2001/20/EC. Therefore, there is a requirement for the site undertaking such IMP work to be a holder of MIA(IMP) and that the IMP must subsequently be QP released for clinical trial use. The purpose is to ensure that IMPs have been manufactured and prepared according to EU Good Manufacturing Practice and are safe for human use.

However, Regulation 37 of The Medicines for Human Use (Clinical Trial) Regulations 2004 as amended [SI 2004 1031] allows for situations where this requirement to hold a manufacturer's authorisation does not apply. The regulation specifically applies to "assembly" carried out in a hospital or health centre by a doctor, a pharmacist or a person acting under the supervision of a pharmacist.

Read the legislation here: *http://www.legislation.gov.uk/uksi/2004/1031/regulation/37/made*

There are restrictions that apply to this regulation. "Assembly" is tightly defined in the statutory instrument as:

(a) enclosing the product (with or without other medicinal products of the same description) in a container which is labelled before the product is sold or supplied, or used in a clinical trial;

(b) where the product (with or without other medicinal products of the same description) is already in a container, labelling the container before the product is sold or supplied, or used in a clinical trial, in that container.

Furthermore, the IMPs being assembled must be exclusively for use in that hospital or health centre or in any other hospital or health centre which is a trial site for the clinical trial in which the product is to be used.

The exemption also does not apply to Phase 1 units or contract packaging organisations as they do not meet the criteria of being a hospital or health centre.

The Sponsor should also be aware that irrespective of the way in which this work is done (i.e. under an MIA-IMP or under the exemption) there is an expectation by the Competent Authority that GMP will be applied.

Technical Agreements

Technical Agreements are non-commercial contracts that set out the roles and responsibilities between the Contract Giver (e.g. Sponsor) and Contract Acceptor (e.g. manufacturer of IMP).

Technical Agreements are the basic requirement for ensuring compliance with regard to:

- Manufacturing Authorisation
- Marketing Authorisation
- Responsibilities of Contract Givers and Contract Acceptors

They are essential in the setup of IMPs given the complexity of:

- Manufacturing operations particularly when 2 or more sites often involved including overseas sites
- Contract manufacture
- Contract analysis
- Regulatory activities
- Complaints
- Pharmacovigilance
- Good distribution practice

According to the MHRA, commonly found deficiencies concerning Technical Agreements are:

- No agreement is in place between the contract giver and contract acceptor (i.e. technical Agreement not written)
- Essentially commercial in nature
- Agreement not in place before manufacturing commences
- Refer to Appendices that do not exist
- Lack of detail concerning GMP and GDP responsibilities including:
  - Sourcing of materials
  - QP duties
  - Recall responsibilities
  - Approval and supply of relevant documents
  - Taking of samples/testing/retention
  - Temperature monitoring

Stability Testing of IMPs

Stability Testing – the Basics

When arranging the manufacture of an investigational medicinal product (IMP), the requirement to provide data for the new dosage form has to be considered. Clinical research involving placebos or comparator products are likely to require modification of a dosage form of a product to render it indistinguishable from another product (for example – over encapsulation or film coating of a product). Alternatively, the packaging of a product has to be changed for concealment purposes.

Modifying Medicines May Alter Original Quality Characteristics

The marketing authorisation holder of a product is only responsible for the unchanged product in its designated and authorised packaging. In other words, there is a need to ensure that the quality of the product is not negatively affected by any modifications performed to obtain the IMP.

Annex 13 (Paragraph 19) of the EU Guidelines to Good Manufacturing Practice stipulates: If a product is modified, data should be available (e.g. stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product. Where a product has been repackaged in a different container that may not offer equivalent protection or be compatible with the product, a suitable use-by-date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, should be determined by or on behalf of the Sponsor of a clinical trial. Such a date should be justified and must not be later than the expiry date of the original package. Furthermore, there should be compatibility of expiry dating and clinical trial duration.

This additional data for the justification is obtained via carrying out stability studies on the new dosage form. The MHRA guidance on risk-adapted approaches to the management of clinical trials of IMPs (Section 2) offers guidance on reduced stability justification based on the level of modification undertaken.

About Stability Studies

Stability studies evaluate the appearance and physical attributes (e.g. colour, caking, hardness, phase separation, re-suspendibility), potency, and purity of a drug product throughout its stated shelf-life and are essential to determine the quality of a modified or repacked drug product. Stability testing should be conducted on the dosage form packaged in the container closure system proposed to be used in the clinical trial. The testing parameters will vary with different dosage forms; stability studies should include testing of those attributes of the pharmaceutical product that are susceptible to change during storage and are likely to influence quality, safety and efficacy.

Types of Stability Testing

Commonly, two types of stability tests are employed: real-time stability tests and accelerated stability tests. Real-time tests store the product at recommended storage conditions and monitor the product until it fails the specification. Real-time stability should typically be done at 0, 3, 6, 9, 12 months on the first year, every 6 months on the second year and once every year afterwards. In accelerated stability studies, the product is stored at elevated stress conditions (such as temperature and humidity). Accelerated stability testing should at the minimum be done at 0, 3 and 6 months. Degradation at the recommended storage conditions can then be predicted by using known relationships between the acceleration factor and the degradation rate.

Stability Test Requirements for Clinical Trial Medication

Stability studies are a regulatory requirement. They determine the shelf-life and provide evidence that the quality of a drug product, over time and under the influence of various environmental conditions, remains acceptable for the duration of its stipulated shelf-life. Both current GCP and EU GMP guidelines explicitly state that it is the responsibility of a clinical trial's Sponsor to determine how the stability of the product will be affected and what shelf-life should be assigned. According to EU Guidelines the shelf-life of the IMP can be based on extrapolation provided that stability studies are conducted in parallel to the clinical trial and throughout its duration. When planning a clinical trial involving medication it is therefore necessary to factor in the cost of any required stability studies and implications from a reduced shelf-life. Any reduction of shelf-life and restriction of storage conditions will require a notification of a Clinical Trial Authorisation substantial amendment to the regulatory agency. For products coming within the scope of the 'Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials', an acceptable shelf life extension plan can be included in the IMP dossier and no substantial amendment will be required to extend the shelf life of the drug product.

Researchers should consider that a stability study can be costly to undertake and test results may require the trial medication to be prepared in several manufacturing campaigns thereby significantly impacting total cost of manufacture. The Sponsor and the IMP manufacturing company therefore need to have procedures in place on decisions on stability programs for IMPs. With careful planning of the right medication solution (i.e. blinding approach, dosage form and packaging) it is possible to optimise manufacturing and stability requirements and keep costs under control. Sponsors, investigators and trial managers should keep this requirement in mind and seek additional guidance when planning their research.

Investigational Medicinal Product Dossiers

The Investigational Medicinal Product Dossier (IMPD) is one of several pieces of IMP-related data required whenever the performance of a clinical trial is intended in one or more European Union Member States. The IMPD includes summaries of information related to the quality, manufacture and control of any IMP (including reference product and placebo), and data from non-clinical and clinical studies. This may either be provided as a stand-alone IMPD or cross-refer to the Investigator's Brochure (IB) for the preclinical/clinical parts of the IMPD.

An IMP dossier should accompany each CTA application. On a case by case basis, this may be a full dossier, a simplified dossier or be replaced by the Summary of Product Characteristics (SmPC).

Detailed guidance concerning IMPDs, including when a type of IMPD is applicable, can be found in the European Commission communication:

> "Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial":
>
> *http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF*

In the UK, there are reduced IMPD requirements for trials that fall under the notification scheme. These are trials involving medicinal products licensed in any EU Member State if:

- the trial relates to the licensed range of indications, dosage and form of the product
- the trial involves off-label use (such as in paediatrics and oncology) that is established practice and supported by enough published evidence and/or guidelines

Information on the content of the IMPD can be found in the following resources:

> "Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials":
>
> *http://ec.europa.eu/health/files/eudralex/vol-10/18540104en_en.pdf*
>
> "Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials":
>
> *http://ec.europa.eu/health/files/eudralex/vol-10/2012-05_quality_for_biological.pdf*

In addition, the MHRA website contains points to consider when preparing the IMPD:

> *https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317987/Points_to_consider_when_preparing_the_IMP_dossier.pdf*

Imports of IMPs from Non-EU/European Economic Area (EEA) Countries

Investigational medicinal products from outside the EU must conform to Good Manufacturing Practices (GMP) at least equivalent to EU standards (i.e. EU GMP compliance). Where manufacture and/or assembly of a medicinal product for clinical trial use (including placebos) occurs outside of the EU the product has to be imported by the holder of a manufacturer's authorisation covering the activity of importation of IMPs.

In the UK, there are modified GMP compliance requirements for trials that fall under the notification scheme (reduced-risk categories e.g. Type B and Type C trials). These are further described in Appendix 1 of the MRC/DH/MHRA Joint Project document on risk-adapted approaches to clinical trials involving IMPs:

http://www.ctu.mrc.ac.uk/our_research/research_types/methodology/Trial_conduct_methodology/risk_adapted_approaches_to_the_management_of_clinical_trials/

In addition to the certification of batches by a QP named on the MIA(IMP) of IMP upon importation, there is a requirement for a QP declaration that manufacture has been in accordance with EU GMP. This declaration must be submitted with the CTA. The starting point for a QP declaration of EU GMP should be an audit conducted by or on behalf of the importing company. Any departure from this should be justified and documented and will be subject to scrutiny during an MHRA inspection. The audit does not need to be done by the QP himself but the QP needs to be satisfied that it has been done correctly by an appropriately trained individual as the QP will be taking final responsibility. Additional analytical testing of IMPs may also be required on import to Europe.

Annex 13 Table 2 summarises the elements that need to be considered in relation to investigational medicinal products imported from third countries:

https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf

The QP declaration is usually signed by a QP named on the manufacturer's authorisation of the importer but may be signed by a QP at the batch certification site. In such cases, a copy of the manufacturer's authorisation for the batch release site is also required. The QP declaration is trial and product specific.

According to the MHRA, commonly seen import-related IMP deficiencies include:

- Lack of substance behind QP declaration (e.g. How does the QP know the actual site of manufacture? How does the QP assure EU GMP?)
- Transportation conditions not known
- The QP certified an imported IMP as free of Transmissible Spongiform Encephalopathy (TSE) but no evidence was available to support this decision.

Advanced Therapy Investigational Medicinal Products

The requirements for the manufacture and import of Advanced Therapy Medicinal Products (ATMPs) are laid down in Article 13 of Directive 2001/20/EC. The following guidelines have been developed to address specific issues and responsibilities for clinical trials involving advanced therapy medicinal products:

https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/2009_11_03_guideline.pdf

The MHRA has a specific section on its website providing help and advice regarding ATMPs and clinical trials:

https://www.gov.uk/advanced-therapy-medicinal-products-regulation-and-licensing

Labelling of Investigational Medicinal Products

This section covers the following guidelines concerning the labelling of Investigational Medicinal Products:

(A) Labelling requirements
(B) Where labelling operations are undertaken
(C) Labelling Post QP Certification

(A) Labelling Requirements

Labelling of an IMP is intended to:

- Ensure protection of the participant and traceability
- Enable identification of the product and trial
- Facilitate proper use of the investigational medicinal product

There are three cases of labelling requirements that can be considered for medicinal products intended for clinical trial use:

1. Investigational Medicinal Products (covers most cases)
2. Marketed products in circumstances as set out in the second paragraph of Article 14 of the Directive 2001/20/EC
3. Non Investigational Medicinal Products (nIMPs)

1. Investigational Medicinal Products

- All IMPs[2] (including placebos) are required to be labelled for use in clinical trials under consideration of the requirements provided in Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices (Paragraph 26 and the summary contained in Table 1 of Annex 13 set out the information that should be included on IMP labels:

  https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf

- A sample of the labelling is required as part of the clinical trial authorisation (CTA) application (Paragraph 12 of Part 2 of Schedule 3 to the Medicines for Human Use (Clinical Trials) Regulations 2004). This sample should include the text of the labelling to be used. Samples of the actual labels to be used may be provided but are not required.

- Where labelling is not included as part of the CTA application or where the labelling to be used does not contain all the items required by Annex 13, this should be justified. The MHRA document on risk-adapted approaches to clinical trials involving IMPs provides further guidance on reduced labelling requirements in Section 3 of Appendix 1:

  https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

- In placebo controlled and cross-over trials, where it is necessary to present all trial supplies in consistent packaging to maintain blinding, it is essential that labelling at the time of manufacture is consistent across the IMPs. This includes variable

[2] The Medicines for Human Use (Clinical Trial) Regulations (Article 2) define an investigational medicinal product as a pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial
(a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorization,
(b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or
(c) used to gain further information about the form of that product as authorised under the authorisation;

manufacturing information such as batch numbers and expiry dates which should be considered to minimise the unblinding of research staff and trial patients.

2. Marketed products in circumstances as set out in the second paragraph of Article 14 of the Directive 2001/20/EC

- Regulation 46 (2) of The Medicines for Human Use (Clinical Trial) Regulations 2004 allows for a particular situation where trial specific labelling is not required:

  http://www.legislation.gov.uk/uksi/2004/1031/regulation/46/made

- This applies to trials of marketed products being (a) used within the terms of their marketing authorisation, (b) dispensed to a subject in accordance with a prescription given by an authorised health care professional and (c) labelled in accordance with the regulations that apply to dispensed relevant medicinal products (in the UK this is accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI 1994/3194) Regulations 1994).

- The application of Regulation 46 remains the exception and even when applicable, Sponsors may wish their products be labelled following the guidance in Annex 13:

  https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf

3. Non Investigational Medicinal Products (nIMPs)

- There may be other medicinal products with pharmacological effects used in a clinical trial, but which are ‘not IMPs’ (nIMPs) as defined in Article 2(d) of Directive 2001/20/EC. nIMPs include challenge agents, rescue medication, agents used to assess end points and others.

- As nIMPs do not fall within the definition of investigational medicinal products, the labelling provisions of Directive 2001/20/EC Article 13 and 14 do not apply to these products.

- However, the labelling requirements of a nIMP are not considered the same in each Member State of the European Union. Therefore the labelling of nIMPs should be in accordance with good practice for the type of product concerned and any specific national requirements.

(B) Where Labelling Operations Are Undertaken

The labelling of IMPs is considered to be manufacture according to Directive 2001/20/EC. Therefore, there is a requirement for the site undertaking IMP labelling to be a holder of MIA(IMP) and that the IMP must subsequently be QP released for clinical trial use.

However, Regulation 37 of The Medicines for Human Use (Clinical Trial) Regulations 2004 as amended [SI 2004 1031] allows for situations where this requirement to hold a manufacturer's authorisation does not apply. The regulation specifically applies to "assembly" carried out in a hospital or health centre by a doctor, a pharmacist or a person acting under the supervision of a pharmacist.

There are restrictions that apply to this regulation. "Assembly" is tightly defined in the statutory instrument as:

(a) enclosing the product (with or without other medicinal products of the same description) in a container which is labelled before the product is sold or supplied, or used in a clinical trial;

(b) where the product (with or without other medicinal products of the same description) is already in a container, labelling the container before the product is sold or supplied, or used in a clinical trial, in that container.

Furthermore, the IMPs being assembled must be exclusively for use in that hospital or health centre or in any other hospital or health centre which is a trial site for the clinical trial in which the product is to be used.

The exemption also does not apply to Phase 1 units or contract packaging organisations as they do not meet the criteria of being a hospital or health centre.

Researchers should also be aware that irrespective of the way in which this work is done (i.e. under an MIA-IMP or under the exemption) there is an expectation by the Competent Authority that GMP will be applied.

The legislation can be viewed here:
http://www.legislation.gov.uk/uksi/2004/1031/regulation/37/made

(C) Labelling Post QP Certification

The Paragraphs 33 and 42 of Annex 13 of the Orange Guide allow for some packaging and labelling to take place after QP certification. This 'post certification labelling' can be used for the following and is usually performed prior to despatch in the distribution area or immediately prior to administration to a subject or patient:

- application of an identifier to ensure that a reconstituted IMP in its final container is administered to the correct subject
- application of expiry date labelling (or revised expiry date labelling).
  - In the case of revised expiry date labelling, this is subject to stability information being available to support the extended shelf-life and the MHRA being informed of the substantial amendment to the CTA
- application of an investigator name
- application of a protocol number

It should, in the first instance, be done at a site with an MIA(IMP) unless the risk to the quality of the product is unacceptably elevated by any required transportation back to this site. In other words, if IMP stock has already gone out to trial sites, it is not strictly required to bring it back to the site with the MIA(IMP) in order to undertake the relabeling. Although this would be preferable, it is recognised that this shipping backwards and forwards could cause more GMP problems than it solves and it is permissible in these circumstances for the relabeling to be done at the clinical site. The certifying QP should certainly be aware of this and be involved in setting up the required GMP systems. The relabeling should be done by knowledgeable staff, documented, and the records stored in the original trial file. The level of assurance of product quality should not be less than if this labelling were performed prior to QP certification.
A common cause for relabeling is the extension of expiry dates. Note that Paragraph 33 of Annex 13 of the Orange Guide deals specifically with this issue. It states:

> 'If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date and repeat the batch number. It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional in accordance with national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be properly documented in both the trial documentation and in the batch records.'

Checklist for IMP-Related Documents

The following can be used as checklist of IMP-related documents to be included in the Trial Master File. Further guidance on reduced documentation requirements can be found in the MRC/DH/MHRA Joint Project document on risk-adapted approaches to clinical trials involving IMPs (Section 6 of Appendix 1):

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

Agreements

- IMP supply agreement(s) with contract manufacturer(s) and amendments
- Technical agreement(s) with contract manufacturer(s) and distribution companies

Clinical Trial IMP Documentation

- The CTA and any subsequent amendments
- The MHRA acceptance letter
- Final letter from Research Ethics Committee
- Summary of drug arrangements (normally as part of the Protocol)
- Product Information (Full/Simplified IMPD)
- IMP safety information document (IB or SPC)
- IMP label texts in the national language (matching those submitted to the MHRA)
- MA (IMP) licence of final QP releasing site
- MA (IMP) licence of placebo manufacturing site (if different from final QP releasing site)
- Certified QP release statement
- Import QP release certificate (if applicable)
- QP declaration
- IMP certificate of analysis
- Viral safety studies and data (if applicable)
- BSE-/TSE-free certificate(s)
- Master randomisation list
- IMP code breaks
- IMP prescription template
- IMP accountability log template
- IMP destruction log template
- Temperature log template (if not using site documentation)
- Temperature deviation log template
- IMP recall information

Site Specific Documents (Per Site)

- Local dispensing/pharmacy procedure SOPs
- IMP ordering and shipping records
- Acknowledgement of receipt
- Completed IMP prescriptions
- IMP accountability log
- IMP storage records
- IMP temperature records

Checklist of Manufacturing Costs for Trial Supplies

This checklist of common costs involved in arranging trial supplies can be used when considering and/or comparing quotes for IMP manufacturing work. The objective is to consider as many of the possible variables as early as possible to (a) establish the most optimal trial medication solution and (b) avoid funding shortfalls during the conduct of the trial.

Note that this list is not exhaustive and not all cost factors may be applicable.

Manufacturing Cost Item	Applicable?	Considered?
Procurement of active products		
Receipt and analysis of incoming products		
IMP development work		
Analytical method development and verification		
Stability study to justify shelf-life		
Tooling for manufacturing		
Manufacture of bulk medicinal products including placebos		
Packaging materials		
Packaging work (including labelling and pack assembly) for all batches		
Code break envelopes		
Release analytics		
QP audit work including imports		
QP release certification		
Archiving of batch documentation		
Project management fees		
Regulatory assistance fees		
Storage		
Despatch		
Shipment/courier charges (with or without temperature monitoring and insurance)		
Return of unused medication to Sponsor		
Reconciliation and destruction		
VAT applicability		

VAT and Trial Medication

Most contract manufacturers of Investigational Medicinal Products and suppliers of trial medication are required to charge VAT on their supplies even if the medication is intended for non-commercial/academic trials.

HM Revenue and Customs have issued several guidance notes about medical services and exemption from VAT. The key points from these guidance notes are:

1. HMRC Guidance Notice 701/57: This includes information about exemption from VAT in relation to clinical research but only explains when the health professionals should and should not charge VAT for their services. Clinical research undertaken by health professionals is exempt from VAT only if it involves patient care, e.g. to monitor a patient involved in the trial for adverse reactions which may be detrimental to their health. If involvement with the patient is restricted to monitoring side-effects for analytical purposes, or to provide analytical testing services with no patient contact, this service is standard-rated.

   https://www.gov.uk/government/publications/vat-notice-70157-health-professionals-and-pharmaceutical-products

2. As a general guideline, the VAT status of a clinical trial medication is dependent on how the trial is funded. Only if a trial is funded by a charity and fulfils the criteria of Notice 701/6 or Notice 701/1 (Part 6) can the supply of trial medication be zero-rated. In these cases the manufacturer/supplier requires a valid exemption certificate.

   VAT Notice 701/6: charity funding equipment for medical, veterinary etc uses

   https://www.gov.uk/government/publications/vat-notice-7016-charity-funded-equipment-for-medical-veterinary-etc-uses

   VAT Notice 701/1: charities
   https://www.gov.uk/government/publications/vat-notice-7011-charities

Each clinical trial supply must be looked at on an individual basis and the advice of the procurement/finance department should be sought. The manufacturer/supplier must agree to zero-rating a clinical trial supply and until this agreement is obtained, it should be assumed that VAT is applicable on clinical trial supplies.

Distinguishing Between Pharmacy's GCP and GMP Responsibilities

This guidance document addresses the distinction between GCP and GMP responsibilities that must be undertaken by pharmacies involved in a clinical trial.

All pharmacy teams involved in the setting up of clinical trials and dispensing of trial medication must adhere to GCP which ensures

- the protection of participants involved in trials and
- the credibility of the data generated in the trial.

The activities that the pharmacy are expected to maintain (including tracking, accountability and storage of IMP) are to ensure these two GCP purposes are fulfilled.

The pharmacy team may, however, also be involved in GMP-related activities such as sourcing, manufacture, assembly and/or labelling of IMPs. In contrast to GCP, GMP is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification.

In these cases, the GMP responsibilities will differ depending on the involvement of the pharmacy with regards to the manufacture of the IMP:

- **Sourcing of IMPs from an external manufacturer:** The dispensing pharmacy team may be involved in finding and selecting an external MIA(IMP) manufacturing site to manufacture a trial IMP. In this case the pharmacy must ensure the requirements of EU GMP are fulfilled for the manufacture of the IMP. This includes confirming that the manufacturer has the appropriate licence for the required work and IMP dosage form. The pharmacy must also satisfy itself that the particular IMP manufacturer is suitable for the planned works.
- **Manufacture of IMPs at local pharmacy production unit:** Some pharmacies have a production unit in which case the manufacture should be carried out under an MIA(IMP) if the IMP is manufactured there.
- **Assembly and relabeling of IMPs at a pharmacy:** In pharmacies without a production unit, the dispensing pharmacy team may assemble and label/re-label IMPs in certain cases. Regulation 37 of The Medicines for Human Use (Clinical Trial) Regulations 2004 as amended [SI 2004 1031] allows for situations where this requirement to hold a manufacturer's authorisation does not apply. There are restrictions that apply to this regulation and there is an expectation by the Competent Authority that GMP will be applied for any work undertaken on the IMP.
- **Dispensing of IMP for clinical trial use:** If the pharmacy team's involvement does not include any manufacture or assembly there are no GMP requirements to be met. In this case only GCP requirements must be ensured.

Working with Pharmacy Services

Professional Guidance on Pharmacy Services for Clinical Trials

This professional guidance on pharmacy services for clinical trials was initially prepared in 2005 on behalf of the Royal Pharmaceutical Society of Great Britain and the Institute of Clinical Research. This brief guide has been produced to help researchers to work smoothly with pharmacy departments to manage on-site clinical trial medication as effectively as possible. It has been reviewed and subsequently revised in 2013:

https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Hospital%20Pharmacy%20Hub/professional-guidance--n-pharmacy-services-for-clinical-trials-141013.pdf

Frequently Asked Questions

The following resources contain commonly asked questions discussed at symposia, Good Manufacturing Practice (GMP) Consultative Committee meetings and others received by the MHRA GMP Inspectorate and European Medicines Agency. The Q&As should be considered carefully in relation to individual circumstances and any specific concerns should be discussed with the QP and/or relevant Competent Authority.

FAQ by European Commission: Guidance on Applying for Clinical Trials

https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/ctqa_v10.pdf

FAQ by MHRA: Good Manufacturing Practice (GMP): Investigational medicinal products (IMP)

https://www.gov.uk/good-manufacturing-practice-and-good-distribution-practice

http://forums.mhra.gov.uk/showthread.php?32-Frequently-Asked-Questions-for-Investigational-Medicinal-Product-(IMP)

FAQ by European Medicines Agency: Good Manufacturing Practice (GMP): Annex 13

http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca#section8

FAQ by MHRA: Risk-adapted approaches to clinical trials implemented by the MHRA for UK trials since 1 April 2011

http://forums.mhra.gov.uk/showthread.php?39-Frequently-Asked-Questions-for-Risk-Adaptive-Approach