Medicines & Healthcare products
Regulatory Agency

Regulatory considerations for therapeutic use of bacteriophages in the UK

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1 Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for regulation of medicines, medical devices, and blood components for transfusion in the UK. We also play a vital role in assuring the quality of biological medicines through development and provision of standards and reference materials, control testing, applied research, and the provision of scientific advice.

We operate in a statutory framework set by HM Government, working within government and the wider health system to direct overall policy in our regulatory field.

We act on behalf of the Secretary of State for Health and Social Care, under UK legislation, to regulate medicines, medical devices and blood products for transfusion. In this role, we balance public health expertise, operational delivery, scientific integrity, independence in regulatory decision-making and appropriate ministerial oversight and accountability to command public confidence.

Regulation of medicines in the UK is undertaken in accordance with the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), thereby, ensuring compliance with statutory obligations relating to the manufacture, distribution, sale, labelling, advertising and promotion of medicines.

The purpose of this document is to address regulatory considerations applicable to use, in the UK, of bacteriophages for therapeutic purposes in humans, whether as licensed or unlicensed medicinal products. Weblinks to relevant guidance are provided.

1.1.1 Bacteriophages

Bacteriophages (also known as phages) are viruses that can infect and destroy bacteria. Current understanding is that although bacteriophages cannot infect and replicate in human cells, they play a part of the human microbiome. Bacteriophages can have lytic (phage replicates, then breaks through the cell wall and destroys (lyses) the host cell) or lysogenic (phage DNA is incorporated into the host genome) lifecycles.

There is a history of use for bacteriophages in the eradication of bacterial infections, including those resistant to antibiotics. Bacteriophages may also be of use in the treatment of infections in individuals unable to tolerate traditional antibiotics.

1.1.2 Phage therapy

Phage therapy involves the use of bacteriophages to treat bacterial infections, which can be in conjunction with other antibiotics. Routes of administration include, but are not limited to,

oral, rectal, vaginal, intravesical, topical, intravenous, or inhalation. Phage therapy may involve the use of a defined cocktail that shows effective killing of the patient clinical isolate, or, in some instances, a more personalised approach might be necessary.

Phages currently used in a therapeutic context are exclusively lytic. Should lysogeny be critical to the mechanism of action of a phage therapy, sufficient evidence would need to be provided that this does not pose an unacceptable risk.

Personalised phage therapy uses one or more bacteriophage(s), tailored to treat a specific infection in a particular individual. Such a “customised” approach may be required where a bacterial infection is resistant to treatment, or the individual is intolerant to standard antibiotics. In such instances, bacteriophages with lytic activity for the disease-causing bacteria will be identified (for example, library screening, or *de novo* from the environment) and used accordingly. In some cases, adaptation or engineering may be required.

2 Scope

All bacteriophages intended for medicinal use in humans (refer to Glossary to definition of what is a medicinal product), including mono-phage products and multi-phage products (“cocktails”). Both natural and engineered (but not synthetic) phages are within the scope of this document.

Applications in disciplines such as, the food industry, and veterinary products are out of scope of this document.

Exemption under Section 10 of the Medicines Act 1968 and Regulation 4 of the HMRs falls outside the scope of this document, because the conditions under which extemporaneous preparations are prepared are not determined by the MHRA.

3 Regulatory status and legal basis for supply

Bacteriophages made with the intention of treating a medical condition in humans fall within the definition of a medicinal product:

- any substance or combination of substances presented as having properties of preventing or treating disease in human beings; or
- any substance or combination of substances that may be used by or administered to human beings with a view to

- restoring, correcting or modifying a physiological function by exerting a pharmacological, immunological or metabolic action, or
- making a medical diagnosis.

Consequently, they are subject to the Human Medicines Regulations 2012, as amended (HMRs). Bacteriophages are biological medicines, a class of medicines that includes active substances grown and purified from cultures of bacteria, yeast, plant or animal cells. The legal definition of a biological medicine is detailed in the Glossary. Anyone producing phages in a cell-free system should contact the MHRA for advice.

Some bacteriophage medicinal products could also fall within the definition of gene therapy medicinal products (GTMPs), where genetic modification relates to therapeutic, prophylactic or diagnostic effect.

3.1.1 Licensed medicines

At the date of publication, no marketing authorisations (MA; product licences) for bacteriophage medicinal products have been granted in the UK. The requirement of when to obtain a marketing authorisation is covered by Regulation 46 of the HMRs; Regulations 49 and 50 address applications for grant of UK marketing authorisation and accompanying material respectively. Having evaluated the application and accompanying material, the licensing authority (MHRA) may grant the application only if it considers:

- the applicant has established the therapeutic efficacy of the product to which the application relates;
- the positive therapeutic effects of the product outweigh the risks to the health of patients or of the public associated with the product;
- the application (and accompanying material) complies with regulations 49 to 55; and
- the qualitative and quantitative composition of the product is as described in the application and the accompanying material.

Schedule 8 (material to accompany an application for a UK marketing authorisation) of the HMRs details the information required for grant of a UK marketing authorisation for a relevant medicinal product.

Legal classification

The legal classification of a licensed medicinal product determines the level of control over its supply. The fundamental principle guiding the classification of medicines is to optimise timely access to effective treatments while reducing the risk of harm from improper use. In part, this depends on the necessary level of input from health professional(s) to diagnose and treat the condition(s) for which a medicine might be used.

In the UK, there are three categories for sale or supply of medicines:

- Prescription-only medicine [POM] – from a pharmacy or other specifically licensed premises, on the prescription of an independent prescriber (such as a doctor, dentist or other authorised health professional);
- Pharmacy medicine [P] – from a pharmacy, without prescription, under the supervision of a pharmacist;
- General sale list medicine [GSL] – from general retail outlets, for example, newsagent, supermarket, or a vending machine in a shop, without the supervision of a pharmacist.

3.1.2 Investigational medicinal products

An investigational medicinal product (IMP) is a medicine that is being tested or used as a reference, including as a placebo, in a clinical trial.

Supply of investigational medicinal products for the purpose of clinical trials is covered in Regulation 13 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031).

3.1.3 Unlicensed medicines – "specials" and imports

Regulation 167 of the HMRs provides an exemption from Regulation 46 and allows for medicines without a MA – sometimes also referred to as a product licence (PL) – to be supplied under certain circumstances.

An unlicensed medicinal product (or "special"), formulated in accordance with the specific requirements of the prescriber, and either manufactured in the UK or imported into the UK, may be supplied in response to a *bona fide* unsolicited order. Deciding whether an individual patient has special needs that cannot be met by a licensed available medicine is a matter for the prescriber responsible for the care of individual patients.

Responsibility for use of unlicensed medicines rests with the prescriber. Those involved in the prescribing, supply or administration of unlicensed medicines should be aware of the status of the product in question, relevant risks associated with its proposed use, and their position regarding liability.

MHRA Guidance Note 14: The supply of unlicensed medicinal products ("specials") provides advice on the manufacture, importation, distribution and supply of unlicensed medicinal products for human use that have been specially manufactured or imported to the order of a prescriber for the treatment of individual patients.

3.1.4 Section 10 exemption

Section 10 of the Medicines Act 1968 and Regulation 4 of the HMRs provide an exemption from the restrictions imposed by regulations 17(1) (manufacturing of medicinal products) and 46 (requirement for authorisation) [of the HMRs] for *"anything which is done in a registered pharmacy, a hospital, a care home service or a health centre and is done there by or under the supervision of a pharmacist and consists of preparing or dispensing a medicinal product in accordance with a prescription given by an appropriate practitioner, or assembling a medicinal product".*

Pharmacists and pharmacies in Great Britain are regulated by the General Pharmaceutical Council (GPhC), and in Northern Ireland by the Pharmaceutical Society of Northern Ireland (PSNI). Hospital pharmacies that are not GPhC or PSNI registered are regulated by the relevant Care Quality Commission for the respective territory in the UK.

Since the circumstances under which extemporaneous preparations are prepared are not determined by the MHRA, this aspect falls outside the scope of this document and is not addressed further.

4 Supply chain

Manufacture, assembly or importation, and distribution of medicinal products are covered by Regulation 17 (manufacturing of medicinal products) and Regulation 18 (wholesale dealing in medicinal products) of the HMRs, respectively. Actors responsible for, or operating within, supply chains for phage therapy products will need to hold necessary licences for such undertakings. Manufacturer's licence holders, wholesale dealer's licence holders, and non-UK sites employed by UK marketing authorisation holders are expected to comply with appropriate standards of good manufacturing practice (GMP) and/or good distribution practice (GDP).

Manufacturer's licences

A manufacturer's licence is required for making, assembling or importing human medicines in the UK; for which compliance with EU good manufacturing practice, as demonstrated by satisfactory outcomes from regular GMP inspection(s) of relevant site(s), is necessary.

Different types of manufacturer's licences are required for the manufacture of licensed, unlicensed or investigational medicinal products:

MIA: Manufacture/importation of licensed medicinal products for human use	• Manufacture and/or assembly of licensed medicines, including export to a country outside the EEA • Importation of licensed medicines from countries outside the EEA
MS: Manufacture/importation of unlicensed medicinal products for human use	• Manufacture of unlicensed medicines ("specials") • Importation of unlicensed medicinal products from countries other than an approved country for import or, if the importer is based in Northern Ireland, from outside the EEA
MIA(IMP): Manufacture/importation of investigational medicinal products for human use	• Manufacture of investigational medicinal products for use in clinical trials

Wholesale distribution licence

A wholesale dealer's distribution licence – also known as wholesale distribution authorisation – WDA(H) is required to offer, sell or supply medicinal products for human use to anyone other than the patient using the medicine; for which compliance with good distribution practice, as demonstrated by satisfactory outcomes from regular GDP inspection(s) of relevant site(s), is necessary.

Importation of unlicensed medicinal products from an approved country for import requires an WDA(H) – Condition F (Regulation 167 of the HMRs).

Apply for manufacturer or wholesaler of medicines licences

MHRA Process Licensing Portal

4.1.1 Manufacture of unlicensed medicines ("specials")

In the UK, manufacture or assembly of unlicensed medicines must be undertaken by the holder of a Manufacturer's Specials (MS) Licence, within the exemption provided by Regulation 167 of the 2012 Regulations.

Manufacture of unlicensed medicines must be in accordance with GMP expectations and the conditions of the MS licence. Manufacture and assembly of unlicensed medicines must only be undertaken by competent staff within suitable facilities and using equipment appropriate for the scale of manufacture and specific dosage form.

Unlicensed medicinal products must also comply with the requirements of the British Pharmacopeia (BP): General Monograph for Pharmaceutical Preparations; General Monograph for Unlicensed Medicines; and the relevant General Monograph for the specific dosage form.

Guidance – supply unlicensed medicinal products (specials)

4.1.2 Importation of unlicensed medicines

Provisions for importation of unlicensed medicines are in section 22 of Part 2 of Schedule 4 of the HMRs.

The importer of an unlicensed medicinal product into the UK must be suitably licensed to import unlicensed medicines. Prior to importation taking place, the importer must notify the MHRA of their intent to import the unlicensed medicine and provide a set of supportive documentation that will be assessed by the Agency.

Medicines imported into the UK as unlicensed medicines would be expected to comply with GMP expectations like unlicensed medicines manufactured in the UK.

The MHRA may object to the importation and supply of unlicensed medicines where there are significant risks that may adversely impact patients.

Guidance – supply unlicensed medicinal products (specials)

Guidance – how to import an unlicensed medicine

Guidance – notification of intent to import an unlicensed medicinal product

4.1.3 Manufacture of investigational medicinal products

Manufacture and importation of Investigational Medicinal Products is covered in Part 6 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031).

In the UK, manufacture (or importation) of IMPs – involving total or partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding) – must be undertaken by the holder of an authorisation for manufacture/importation of investigational medicinal products for human use MIA(IMP).

Investigational medicinal products must be produced in accordance with the principles and detailed guidelines on GMP for medicinal products. Where applicable, other relevant guidelines must be considered, as appropriate to the stage of development of the product.

Application of GMP to the manufacture or importation of investigational medicinal products is intended to ensure that clinical trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in all relevant clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified.

Due to a lack of fixed routines, variety of clinical trial designs and consequent packaging designs, production of investigational medicinal products involves additional complexity. Randomisation and blinding add to that complexity an increased risk of product cross-contamination and mix-up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product, or a lack of full process validation. These challenges require personnel with a thorough understanding of, and training in, the application of GMP to investigational medicinal products. Co-operation is required with trial sponsors, who assume ultimate responsibility for all aspects of the clinical trial, including the quality of investigational medicinal products.

Manufacture of Investigational Medicinal Products – Frequently Asked Questions – MHRA Inspectorate

4.1.4 Manufacture of licensed medicinal products

In the UK, manufacture (or importation) of licensed medicinal products for human use must be undertaken by the holder of the relevant licence (for manufacture/importation of licensed medicinal products for human use – MIA.

Licensed medicinal products must be produced in accordance with the principles and detailed guidelines on of GMP and the Marketing Authorisation. Compliance with applicable guidance and relevant details contained in marketing authorisations ensures that medicines supplied to the UK market consistently meet high standards of quality, safety and efficacy.

Apply for a licence to market a medicine in the UK

Apply for manufacturer or wholesaler of medicines licences

5 Standards and guidance

5.1.1 Pharmacopeial monographs and standards

Pharmacopoeias are collections of drug quality standards published by national authorities. There are four major pharmacopeias (United States, British, European, and Japanese) but other pharmacopeias are available. In the UK, the British Pharmacopoeia (BP) provides the only comprehensive collection of authoritative official standards for UK pharmaceutical substances and medicinal products, including all the monographs and texts of the European Pharmacopoeia (Ph. Eur.) that apply.

The BP has been providing official standards for medicines since 1864, and provides the only comprehensive collection of authoritative official standards for UK pharmaceutical substances and medicinal products, including all the monographs and texts of the European Pharmacopoeia (Ph. Eur.).

Pharmacopoeias that have legal status within the UK are the British Pharmacopoeia (BP), including the BP (Veterinary), and the Ph. Eur. The BP is published every year in August, and becomes legally effective on January 1st of the following year.

British Pharmacopeia

Volume III – Formulated Preparations: General Monographs – Unlicensed Medicines

Supplementary Chapter V Unlicensed Medicines

- SC V D Storage and Stability of Unlicensed Medicines
- SC V E Extemporaneous Preparations
- SC V F Aseptic Preparation of Unlicensed Medicines

European Pharmacopeia

European Pharmacopoeia 11.6 - 5.31 Phage Therapy Medicinal Products [01/2025:53100]

5.1.2 Good practices (GxPs)

Good Laboratory Practice (GLP)

Any test facility that conducts, or intends to conduct, regulatory studies must comply with GLP regulations when carrying out safety tests on pharmaceuticals. The principles are set out in Schedule 1 of The Good Laboratory Practice Regulations 1999.

A regulatory study is any non-clinical experiment or set of experiments whereby an item is examined under laboratory conditions or in the environment in order to obtain data on its properties or its safety (or both) with respect to human health, animal health or the

environment; the results of which are intended for submission to the appropriate regulatory authorities; and in respect of which compliance with the principles of good laboratory practice is required in respect of such experiment(s) by the appropriate regulatory authorities.

Good laboratory practice (GLP) for safety tests on chemicals

Good Clinical Practice (GCP)

GCP is a set of internationally recognised ethical and scientific quality requirements that must be followed when designing, conducting, recording and reporting clinical trials that involve people.

ICH E6(R2) Good Clinical Practice guideline

Good clinical practice for clinical trials

GCP and the Conduct of Clinical Trials is covered in Part 4 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031).

The MHRA Good Clinical Practice Guide covers the legislation, guidance and good practice relating to the conduct of clinical trials of medicinal products for human use in the UK.

Good Manufacturing Practice (GMP)

GMP is the minimum standard that must be met by the production processes used by manufacturers of medicines to ensure that medicinal products are of consistently high quality, appropriate to their intended use, and meet the requirements of the marketing authorisation (MA) or product specification.

Medicines: good manufacturing practice and good distribution practice

The MHRA's Orange Guide (Rules and Guidance for Pharmaceutical Manufacturers and Distributors) offers a single authoritative source of European and UK guidance, and UK legislation on the manufacture and distribution of human medicines, active substances, and brokering medicines..

Good Distribution Practice (GDP)

GDP requires that medicines are obtained from the licensed supply chain and are consistently stored, transported and handled under suitable conditions, as required by the MA or product specification.

Medicines: good manufacturing practice and good distribution practice

The MHRA Green Guide (Rules and Guidance for Pharmaceutical Distributors) offers a single authoritative source of European good distribution practices and UK guidance, information, and legislation.

Good Pharmacovigilance Practice (GPvP)

GPvP is the minimum standard for monitoring the safety of medicines on sale to the public in the UK.

Good pharmacovigilance practice (GPvP)

Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK MAHs and the MHRA.

5.2 Updates to this page

5.2.1 Regulatory guidance

Below are lists of documents, with corresponding links, containing information relating to the development, manufacture, and use of bacteriophage as a medicinal product. There are also more general guidance notes. Not all will be relevant, and it is up to the developer to use the guidance most suitable for the product being developed.

MHRA guidance

GN 5: Notes for applicants and holders of a Manufacturer's Licence

GN 6: Guidance Notes for applicants and holders of a Wholesale Dealer's Licence (WDA(H)) or Broker Registration

GN 8: A guide to what is a medicinal product

GN 14: The supply of unlicensed medicinal products ("specials")

Guidance for "specials" manufacturers - provides guidance for Manufacturing Specials (MS) licence holders in the interpretation of the GMP requirements to be applied when manufacturing unlicensed medicines

Guidance: Supply unlicensed medicinal products (specials)

Guidance: Import a human medicine

Guidance: Notification of intent to import an unlicensed medicinal product

Guidance: Authorisations and procedures required for importing Investigational Medicinal Products to Great Britain from approved countries

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines

The MHRA is a full Member of the ICH; the following ICH Guidelines (some of which may be relevant to bacteriophages as medicinal products) have been implemented by the MHRA:

ICH guidelines on Quality

- Q1A(R2) – Stability Testing of New Drug Substances and Products
- Q4B Annex 14 – Bacterial Endotoxins Test General Chapter
- Q5B – Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
- Q5C – Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
- Q5D – Derivation and Characterisation of Cell Substrates Used for Productions of Biotechnological/Biological Products
- Q5E – Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

ICH guidelines on Safety

Many of the ICH safety guidelines do not apply to phage therapy medicinal products; developers should identify those guidelines that are relevant and apply as required. Examples could include:

- S6(R1) – Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- S8 – Immunotoxicity Studies for Human Pharmaceuticals
- S11 – Nonclinical Safety Testing in Support of Development of Paediatric Medicines

ICH guidelines on Efficacy

- E1 - The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions
- E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- E2B(R3) – Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs); E2B(R3) – Questions and Answers
- E2C(R2) – Periodic Benefit-Risk Evaluation Report; E2C(R2) – Questions and Answers
- E2D – Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

- E2E – Pharmacovigilance Planning
- E2F – Development Safety Update Report
- E3 – Structure and Content of Clinical Study Reports; E3 – Questions and Answers (R1)
- E4 – Dose-Response Information to Support Drug Registration
- E5(R1) – Ethnic Factors in the Acceptability of Foreign Clinical Data; E5 – Questions and Answers
- E6(R2) – Good Clinical Practice (GCP)
- E7 – Studies in Support of Special Populations: Geriatrics; E7 – Questions and Answers
- E9 – Statistical Principles for Clinical Trials
- E9(R1) – Addendum: Statistical Principles for Clinical Trials
- E10 – Choice of Control Group and Related Issues in Clinical Trials
- E11(R1) – Clinical Investigation of Medicinal Products in the Paediatric Populations: Guideline and Addendum
- E14 – The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; E14 – Questions and Answers (R3)
- E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
- E16 – Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions
- E17 – General Principles for planning and design of Multi-Regional Clinical Trials
- E18 – Genomic Samples and Management of Genomic Data

Multidisciplinary ICH guidelines

- M1 – MedDRA – Medical Dictionary for Regulatory Activities
- M3(R2) – Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals; M3(R2) – Questions and Answers (R2)
- M4(R4) – Organisation Including the Granularity document that provides guidance on document location and paginations; M4 – Questions and Answers (R3)
- M4Q(R1) – CTD on Quality; M4Q – Questions and Answers (R1)
- M4S(R2) – CTD on Safety; M4S – Questions and Answers (R2)
- M4E(R2) – CTD on Efficacy; M4E – Questions and Answers (R4)

- M7(R2) – Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- M7(R2) – Addendum Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- M8 – Electronic Common Technical Document (eCTD) v3.2.2
- M8 – Electronic Common Technical Document (eCTD) v4.0
- M9 – Biopharmaceutics Classification System-based Biowaivers
- M9 – Questions and Answers
- M10 – Bioanalytical Method Validation and Study Sample Analysis

N.B. Whilst the above list was current at the time of publication (March 2025); the relevant webpage should be checked for updates as new guidelines are implemented by the MHRA.

EU scientific guidelines

Guidelines in use at the time of the UK's exit from the EU were carried over as EU guidance documents referred to in the Human Medicines Regulations 2012.

5.3 Practice guidance

Below are links to guidance published by organisations outside of the MHRA that may contain helpful information, but please note that the MHRA acts independently of these guidance documents.

Royal Pharmaceutical Society (RPS)

Professional Guidance for the Procurement and Supply of Specials (December 2015)

Prescribing Specials – Guidance for the prescribers of Specials (April 2016)

General Pharmaceutical Council (GPhC)

Guidance for registered pharmacies preparing unlicensed medicines (August 2018)

General Medical Council (GMC)

Prescribing unlicensed medicines

6 Clinical trials

6.1 How to compile and submit an application

Clinical trials for medicines: how apply for authorisation in the UK

Clinical Trials Authorisation (CTA)

When a clinical trial authorisation (CTA) is needed

Relevant guidance (such as CT-1) remains the best source of information for understanding the requirements for a CTA application submission.

Useful resources

Investigational Medicinal Product Dossier (IMPD)

Each CTA application should be accompanied by an IMPD; together with other supporting documentation such as labelling, manufacturer's authorisations, and a Qualified Person's (QP) declaration on GMP equivalence to EU GMP. The quality section of the IMPD should include information and data describing the manufacture, characterisation, testing, control and stability of the drug substance (active ingredient) and drug product.

Points to consider when preparing an IMPD

Investigator's Brochure (IB)

The sponsor of a clinical trial – the person who takes responsibility for the initiation, management and financing (or arranging the financing) – needs to ensure that the investigator's brochure for that trial (and any updates) presents information in a concise, simple, objective, balanced and non-promotional form, thereby, enabling a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial.

How to apply

All applications for new Clinical Trials of Investigational Medicinal Products (CTIMPs) are prepared, submitted and reviewed by means of a combined review process that offers applicants and sponsors a single application route and co-ordinated review by the MHRA and the research ethics committee (REC), leading to a single UK decision.

Applications for combined review are prepared and submitted via the Integrated Research Application System (IRAS); further information on the process is available via the Health Research Authority (HRA): Clinical Trials of Investigational Medicinal Products (CTIMPs) and Combined Review.

The IRAS portal includes a list of documentation to submit for combined review of a CTA application.

Guidance - common issues with validation and assessment of clinical trial applications and how to avoid them

7 Marketing authorisation

7.1.1 Required information

Regulations 49 and 50 of the HMRs address applications for granting of UK marketing authorisation and accompanying material, respectively. There are further specific provisions applicable to paediatric products (50A to F), orphan medicinal products (50G), advanced therapy medicinal products – of relevance for GTMPs (50H), and GMOs (50J).

Information relating to the product, required to accompany an application for a UK marketing authorisation, is specified in Schedule 8 of the HMRs. Schedule 8B (modifications of Annex I to the 2001 Directive) assists with cross-referencing aspects of Directive 2001/83/EC with continued relevance. Part II of Annex I (Specific Marketing Authorisation Dossiers and Requirements) addresses adaptions to requirements for presentation of the marketing authorisation application dossier appropriate to particular circumstances. It is considered that a full application based on original data under regulation 50 is likely to be appropriate. Other legal basis available in specific circumstances are:

Mixed Marketing Authorisation Application [Regulation 50]

As an alternative to a dossier based entirely on original data, a dossier where Module(s) 4 and/or 5 consists of a combination of (i) reports of limited non-clinical and/or clinical studies carried out by the applicant and (ii) relevant bibliographical references.

7.1.2 How to submit an application

Marketing authorisation applications should be submitted via the MHRA submissions portal.

How to register on the MHRA portal and use it to apply for and update marketing authorisations and make other applications

The electronic Application Form (eAF) and cover letter tool should be used to determine specific additional information requirements for the type of submission. All questions in the tool should be answered fully to ensure that all the required information is correctly included in the application. Failure to submit the appropriate information in the cover letter and/or dossier may result in the application being invalidated.

Apply for a licence to market a medicine in the UK

8 Presentation of regulatory data and evidence

8.1.1 Common Technical Document (CTD)

The Common Technical Document is how the modules, sections and documents of the dossier for a marketing authorisation application for a medicinal product for human use are organised. Module 1 is region specific; Modules 2, 3, 4 and 5, comprising quality, nonclinical and clinical information, are intended to be common to all regions:

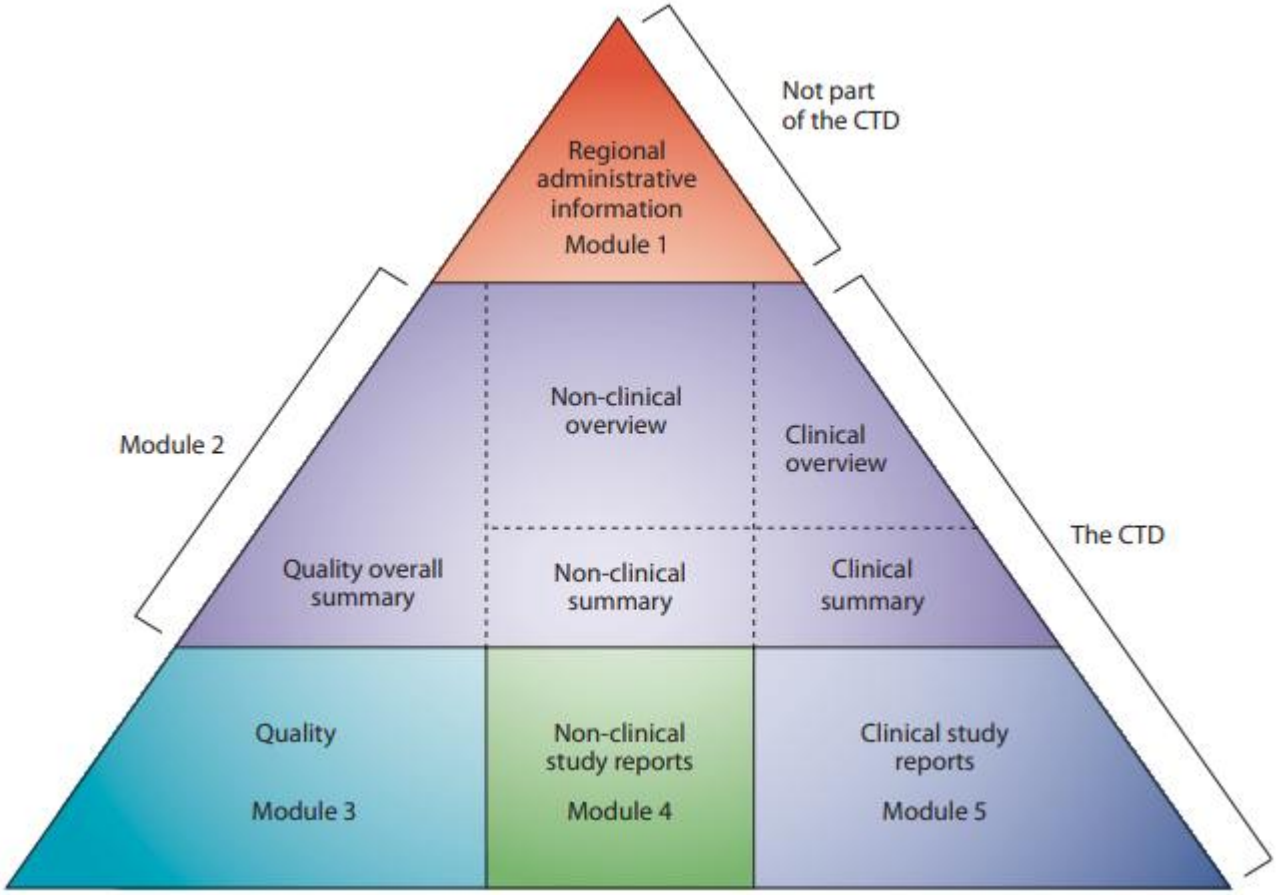

Figure 1: The CTD Triangle, reproduced from the ICH Common Technical Document guidance.

Regional administrative information: Module 1 – eCTD Specification

The content and numbering of Module 1 is specified in the latest version of the EU Notice to Applicants Volume 2B: presentation and content of the dossier. The following items should be included with an initial application:

- cover letter

- comprehensive table of contents (XML backbone acts as a table of contents in an eCTD)
- application form
- product information documents
- information on the experts
- specific requirements for different types of applications (if required)
- environmental risk assessment
- information relating to orphan market exclusivity (if required),
- information relating to pharmacovigilance [Pharmacovigilance System, Risk-management System]
- information relating to clinical trials (if required)
- information relating to paediatrics

Quality M4Q(R1): Module 2 Quality Overall Summary and Module 3 Quality

Safety M4S(R2): Module 2 Nonclinical Overview and Nonclinical Summaries and Module 4 Nonclinical Study Reports

Efficacy M4E(R2): Module 2 Clinical Overview and Clinical Summaries and Module 5 Clinical Study Reports

8.1.2 Electronic Common Technical Document (eCTD)

The eCTD is a harmonised technical solution for electronic submission of a CTD; facilitating submission of PDF documents, stored in the eCTD directory structure, accessed through the XML backbone, with the integrity of the files guaranteed by the MD5 Checksum.

The MHRA checks eCTD submissions for technical validity using the Lorenz Docubridge validation tool that strictly aligns validation against ICH international standards and eCTD 3.2 regional requirements. Validity of an eCTD can be checked before submission of an application using the LORENZ eValidator Basic validation software for eCTD.

9 Safety and surveillance

Reporting, via the MHRA's Yellow Card scheme, of suspected adverse drug reactions (ADRs) to **all** medicines is highly encouraged.

Guidance on pharmacovigilance procedures

9.1 Obligations

Clinical trials

Pharmacovigilance requirements are covered in Part 5 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031).

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

See also MHRA Guidance Note 14.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The sponsor of the trial (or any other person to whom the sponsor has delegated this responsibility) must report all SUSARs that happen during the course of the trial to the MHRA.

Fatal or life-threatening SUSARs must be reported as soon as possible, but no later than 7 days after first becoming aware of the reaction. Any additional relevant information must be provided within 8 days of the initial report.

Non-fatal or non-life-threatening SUSARs must be reported as soon as possible but no later than 15 days after first becoming aware of the reaction.

The sponsor of a “trial performed in the UK” (UK trial) must report the following UK-relevant SUSARs to the MHRA:

- All SUSARs occurring in that trial in UK sites;
- All SUSARs occurring in that trial in sites outside the UK;
- All SUSARs originating in a non-UK trial of the same medicinal product if the trial is run by the same sponsor of the trial running in the UK;
- All SUSARs originating in a non-UK trial of the same medicinal product if the sponsor of the trial outside the UK is either part of the same mother company or develops the medicinal product jointly, on the basis of a formal agreement, with the sponsor of the UK trial.

Detailed records of all adverse reactions relating to a clinical trial must be kept; copies may be required by the MHRA should there be an investigation.

Licensed medicines

Holders of UK MA(s), known as a Marketing Authorisation Holder (MAH), are required to operate a pharmacovigilance system (Regulation 182 of the HMRs).

MAHs must record all suspected adverse reactions to the product occurring in the UK or another country that are brought to its attention irrespective of whether the reaction is reported spontaneously by patients or health care professionals; or occurred in the context of a post-authorisation study (Regulation 187 of the HMRs).

For all serious suspected adverse reactions that occur in the UK, and countries other than the UK, a report should be submitted electronically to the MHRA before the end of a period of 15 days beginning on the day following the day on which the MAH gained knowledge of the reaction. Similarly, for all non-serious suspected adverse reactions that occur in the UK a report should be submitted electronically to the MHRA before the end of the period of 90 days beginning on the day following the day on which the MAH gained knowledge of the reaction (Regulation 188 of the HMRs).

9.1 Yellow Card Scheme

The MHRA collects information on suspected safety concerns involving healthcare products (like side effects caused by a medicine or adverse incidents involving medical devices) through the Yellow Card scheme, which is vital in helping to monitor the safety of all healthcare products in the UK to ensure they are acceptably safe for patients and users. The scheme relies on voluntary reporting of any problems with a healthcare product by the public (including patients, parents, and carers), as well as healthcare professionals. Anyone can report an issue with a medicine, vaccine, medical device, blood product or e-cigarette.

The Yellow Card scheme: guidance for healthcare professionals, patients and the public

10 Further sources of information and assistance

10.1 MHRA Innovation Accelerator

The MHRA Innovation Accelerator brings together the Innovation Office, the Regulatory Advice Service for Regenerative Medicines (RASRM), regulatory science, and horizon scanning. This service can assist developers of innovative products (medicines, medical devices (including software) or blood components for transfusion) with accessing MHRA scientific expertise and regulatory guidance.

Innovation Accelerator – How to get in touch

10.2 Scientific Advice

Scientific advice can be sought from the MHRA at any stage of the regulatory development of a medicine prior to submitting an application for marketing authorisation, and during subsequent lifecycle stages.

Questions should be prospective and relate to the future development of a medicinal product, addressing specific scientific aspects, for example:

- Quality (for example, chemical, pharmaceutical and biological testing necessary to demonstrate the quality of a medicinal product);
- Non-clinical (for example, toxicological and pharmacological testing necessary to demonstrate the safety of a medicinal product);
- Clinical (for example, endpoints, trial duration, target population, choice of comparator and so on).

Scientific advice is provided in response to the specific questions and documentation submitted and cannot, therefore, account for future changes and developments in scientific knowledge or regulatory requirements. It is not legally binding for any future application of the product discussed, either on the part of the MHRA or the enquirer; nor, can it be taken as indicative of any future agreed position.

Broader scope scientific advice typically involves general approaches to product development, rather than being specific to a particular product.

Medicines: get scientific advice from MHRA

10.3 Clinical Trials Helpline

Advice on specific scientific or regulatory aspects of a clinical trial can be obtained via the Clinical Trials Helpline at clintrialhelpline@mhra.gov.uk.

10.4 Innovative Licensing and Access Pathway (ILAP)

The ILAP is a single integrated platform for sustained collaborative working between product developers, the Regulator (MHRA), the UK Health Technology Assessment (HTA) bodies and the National Health Service (NHS), as well as patients with the aim of accelerating the time to patient care for transformative new medicines and drug-device combinations,

The ILAP is open to both commercial and non-commercial developers (UK based or global) of potentially transformative medicines or drug-device combination products that have a

therapeutic aim and there is evidence of safe use in humans, but confirmatory trials have not yet started.

Innovative Licensing and Access Pathway (ILAP).

Abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTD	Common Technical Document
DP	Drug Product
DS	Drug Substance
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GMO/GMM	Genetically Modified Organism/Microorganism
GTMP	Gene Therapy Medicinal Product
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPvP	Good Pharmacovigilance Practice
HMRs	The Human Medicines Regulations 2012 (as amended)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILAP	Innovative Licensing and Access Pathway
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
Ph Eur	European Pharmacopeia
PL	Product Licence
SUSAR	Suspected Unexpected Serious Adverse Reaction

Glossary

Please note that the definitions below are not intended to be legal definitions; references to legislation, where cited, are to assist fuller appreciation by a lay reader.

Active substance: Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis [The Human Medicines Regulations 2012 Regulation 8].

Biological medicine: Legal definition of biological medicine: “biological medicinal product” and “biological substance” have the meaning given in the third indent of paragraph 3.2.1.1.(b) of Annex I to the 2001 Directive; A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93.

Genetically modified microorganism (GMM): A genetically modified microorganism, i.e. not naturally occurring.

Gene therapy medicinal product (GTMP): A biological medicinal product with an active substance that contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and the therapeutic, prophylactic or diagnostic effect of which relates directly to the recombinant nucleic acid sequence therein, or to the product of genetic expression of this sequence [The Human Medicines Regulations 2012 Regulation 2A–2].

Medicinal product: “Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; [the first/presentational limb]” or “Any substance or combination of substances which may be used in, or administered to, human beings, either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [the second/functional limb]” [MHRA Guidance Note 8: A guide to what is a medicinal product].

Phage cocktail: a mixture of bacteriophages.