WHITE PAPER

Supporting early clinical development with the right material strategy

A KEY QUESTION

Are you addressing critical CMC considerations early enough in your hAME program?

KEYWORDS hAME Studies, CMC Strategy, Investigational Medicinal Product, Radiolabeled Drug Products, GMP Pharmacy

Why CMC matters in hAME CPS studies

Human Absorption, Metabolism and Excretion (hAME) clinical pharmacology studies rely on well-defined, fit-for-purpose clinical trial materials. Early Chemistry, Manufacturing and Controls (CMC) decisions directly influence data quality, timelines and regulatory alignment in these studies.

A proactive CMC strategy helps ensure that investigational products used in hAME CPS studies are appropriate for their intended use, analytically understood and aligned with global regulatory expectations.

CMC considerations for GMP pharmacy

One of the key elements to the success of hAME studies at the Fortrea Madison and Leeds sites, is the presence of an on-site GMP pharmacy that is capable of handling radiolabeled material, which brings flexibility and cost-saving advantages to our sponsors.

- We can handle and prepare a variety of different formulations, and most commonly the drug product is manufactured on-site. Our strict adherence to quality controls enables us to manufacture a wide variety of drug products in our facility without risk of cross-contamination
- We routinely manufacture non-sterile Investigational Medicinal Product (IMPs) including powder-in-capsule and powder-in-bottle formulations, as well as oral solutions and suspensions
- Our validated aseptic clean rooms and processes enable us to manufacture and sterilize parenteral formulations for injection or infusion
- Less commonly, and depending on the stability of the drug product, we may receive the bulk drug product from a CMO that requires limited manipulation and assembly into unit doses

Fortrea

Radiosynthesis planning

One of the most important considerations is knowing when the hot-API (Active Pharmaceutical Ingredient) from the CMO will be supplied and its stability. The radiosynthesis and release of the hot-API is usually booked many months in advance and has limited flexibility. It forms the linchpin of the study timelines, as the date of manufacture and the date of expiry form a limited window within which all activities must occur.

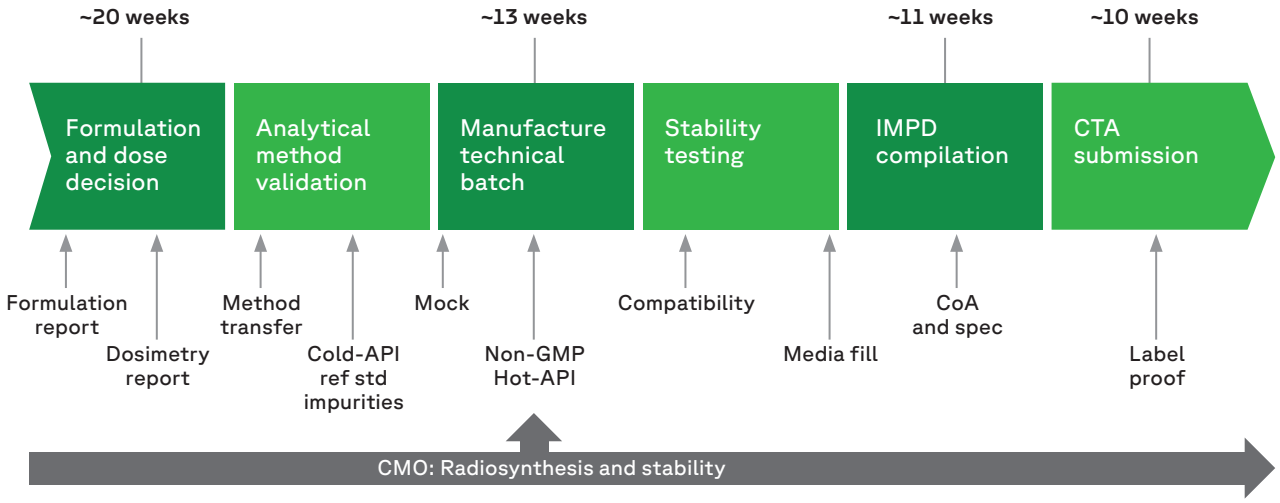
Another consideration is the route of administration, as this will determine the specification and release testing requirements of the drug substance and the IMP. The physicochemical properties of the API may dictate the formulation and route of administration, so understanding the molecule is important.

Absolute Bioavailability (ABA) and hAME studies can be performed using the same batch of radiolabeled drug substance (rDS) if planned correctly.

Leeds

The Investigational Medicinal Product (IMP) dossier must be compiled and submitted as part of the CTA application, and it includes details pertaining to the manufacture, formulation, stability, specification and testing of the hot-API and the radiolabeled IMP. Knowing how and when this data is being generated needs to be factored into the planning of the timelines.

Pharmacy activities and critical path (pre-approval)



The length of the timeline can vary, but generally pharmacy activities would start at least 20 weeks from dosing. We would begin by gathering key information, including the target dose level, which would be based on the dosimetry report. The formulation is often unique and will be dependent on the physicochemical properties of the API, the route of administration, as well as what is feasible in our facility.

Once the dose and formulation are known, the specification and release tests can be devised and the analytical methods can be validated. For this, the test methods are generally provided by the hot-API CMO or sponsor, as well as non-radiolabeled API, reference standards and samples of any known impurities for the validation to be performed. In addition to the standard tests, the radiolabeled IMP will be tested for radioactivity concentration and radiochemical purity, where possible.

At approximately 13 weeks from dosing, and once validation of the analytical methods is complete, we would look to manufacture a technical batch using non-GMP hot-API to demonstrate achievability and stability of the radiolabeled drug product. For more challenging or unconventional formulations, we may first perform a mock batch using cold-API to preserve the limited and expensive hot-API.

Following manufacture of the hot-IMP technical batch, its stability will be tested and we generally aim to establish an in-use shelf-life of 72-96 hours. This period would be sufficient for on-site manufacture of the clinical batch, release testing, QP release and dose administration. The advantages of this strategy include mitigating the risk, time and cost associated with targeting long term storage.

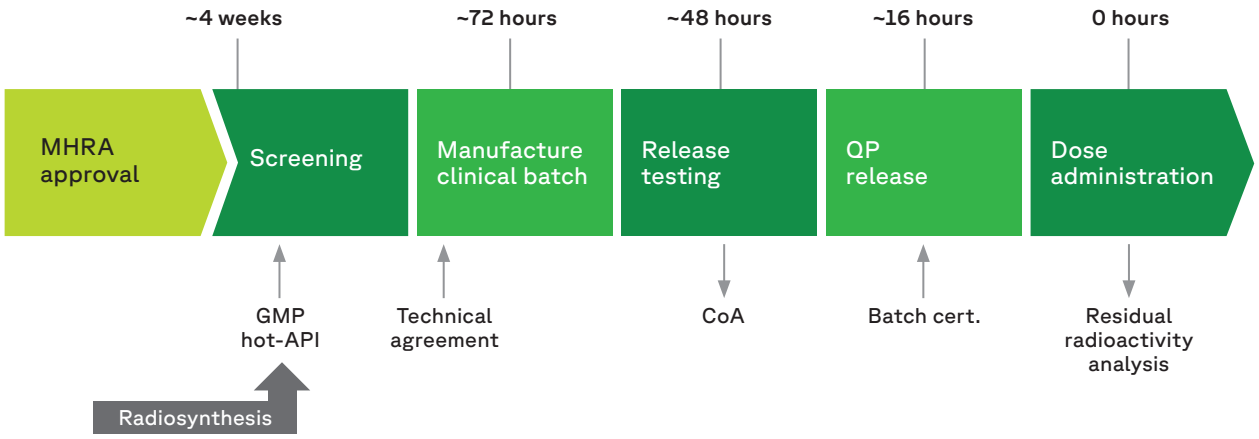
At this stage, the technical batch of IMP can also be used to determine compatibility of the drug solution with dosing materials, such as syringes and infusion sets. For parenteral drug products, we may also perform a media fill with tryptic soy broth to demonstrate the validity of the sterilization process.

The results from the technical batch and stability testing would be provided in the form of a certificate of analysis that would then be included in the IMP dossier being compiled by the regulatory team, along with the IMP formulation and manufacture details.

At approximately 10 weeks from dosing, the IMP dossier is submitted as part of the CTA application, along with the label proof for the IMP. Currently we estimate six weeks for the MHRA to review and issue approval.

As mentioned, this timeline must align with the radiosynthesis and supply schedule of the hot-API from the manufacturer (represented here by the green arrow). It is not uncommon for the dates and slot to have been booked many months in advance with little flexibility to reschedule—so planning and coordination is critical.

Pharmacy activities and critical path (post-approval)



Approximately six weeks later, once MHRA approval has been granted, the clinic would start screening potential volunteers to participate in the trial.

The screening window is usually four weeks leading to dosing and during this period, pharmacy would plan to receive the GMP hot-API from the manufacturer.

Prior to the manufacture of the clinical batch, the technical agreement must be final. This document outlines the GMP responsibilities between the sponsor and Fortrea as they are applicable to the clinical batch.

Within 72 hours of dosing, the clinical batch will be manufactured on site in accordance with an approved batch record, and a sample will be sent to our analytical vendor.

Our vendor is capable of release testing and issuing a certificate of analysis within 48 hours. The ability to turn around the results so quickly cannot be understated, as it enables us to remain within that advantageously short 72-hour shelf-life.

As a side note, not all IMPs require release testing but whenever preparing a bulk solution is involved, then we would opt for testing the solution.

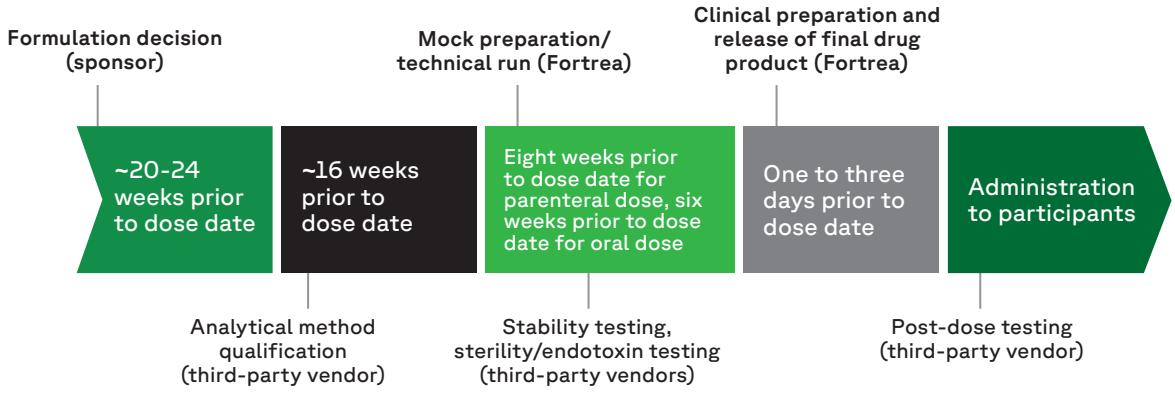
The certificate of analysis and executed batch record are then provided to the QP, along with other quality documents, for them to perform batch certification and release of the IMP on the day before dosing.

The IMP will then be dispensed and transferred to the clinic team for dose administration. Once the doses are administered, the empty used dose containers are sent for residual radioactivity analysis to confirm the dose has been fully administered. Whenever there might be small variability between subject doses due to inherent variability in the prepared IMP unit doses, then the exact dose for each subject will be calculated and provided to the radioanalysis team for accurate recovery measurements.

Madison

The IMP dossier must be compiled and submitted as part of the CTA application, and it includes details pertaining to the manufacture, formulation, stability, specification and testing of the hot-API and the radiolabeled IMP. Knowing how and when this data is being generated needs to be factored into the planning of the timelines.

Pharmacy activities and critical path



The length of the timeline can vary but generally pharmacy activities would start at least 20 weeks from dosing. We would begin by gathering key information including the target dose level which would be confirmed based on the dosimetry report, when available. The formulation is often unique and will be dependent on the physicochemical properties of the API, the route of administration, as well as what is feasible in our facility.

Once the dose and formulation are known, the specification and release tests can be devised, and the analytical methods can be validated. For this, the test methods are generally provided by the hot-API CMO or sponsor, as well as non-radiolabeled API, reference standards and samples of any known impurities for the validation to be performed. In addition to the standard tests, the radiolabeled IMP will be tested for radioactivity concentration and radiochemical purity, where possible.

At approximately four to six weeks from dosing, and once validation of the analytical methods is complete, we would look to manufacture a technical batch to demonstrate achievability and stability of the radiolabeled drug product and perform sterility, endotoxin and bioburden testing in the case of sterile formulations. For more challenging or unconventional formulations we may first perform a mock batch using cold-API to preserve the limited and expensive hot-API.

Following manufacture of the hot-IMP technical batch, its stability will be tested and we generally aim to establish an in-use shelf-life of 48–72 hours. This period would be sufficient for on-site manufacture of the clinical batch, and eventual GMP release of the clinical batch for dose administration. The advantages of this strategy include mitigating the risk, time and cost associated with targeting long term storage.

At this stage, and if needed, compatibility testing of the drug solution with dosing materials, such as syringes and infusion sets can be performed. For parenteral drug products, we may also perform a media fill with tryptic soy broth to demonstrate the validity of the sterilization process.

The results from the technical batch and stability testing would be provided in the form of a certificate of analysis that could then be included in the CMC amendment for the IND being compiled by the Sponsor's regulatory team, along with the IMP formulation and manufacture details, as required.

As mentioned, this timeline must align with the radiosynthesis and supply schedule of the hot-API from the manufacturer. It is not uncommon for the dates and slot to have been booked many months in advance with little flexibility to reschedule—so planning and coordination is critical.

Pharmacy activities and critical path

GMP hot-API should be received by the site at least four weeks prior to dose administration if not provided for the technical batch.

Prior to the manufacture of the clinical batch, the technical agreement must be final. This document outlines the GMP responsibilities between the sponsor and Fortrea as they are applicable to the clinical batch.

Within 72 hours of dosing, the clinical batch will be manufactured on site in accordance with an approved batch record. Release of the drug product is performed by a member of the Fortrea GMP Quality Assurance group.

The IMP will then be transferred to the clinic team for dose administration. If used, the empty used dose bottles are sent for residual radioactivity analysis by the DMPK lab. If a syringe is used for dose administration, the weight of the dose administered is calculated by the Fortrea pharmacist using weights collected of the full and empty syringes and the weight of the dose administered is provided to the DMPK lab. If required, postdose analysis of the drug product can be performed by the analytical laboratory.

Stakeholders

The timeline and considerations involve several multidisciplinary stakeholders, who must be involved in discussions at critical stages in the process. Communication and coordination are key as upstream decisions are difficult to reverse and will often dictate downstream activities; therefore, the Fortrea pharmacy team aims to initiate discussions as early as possible with all parties involved.

Potential pharmacy challenges

The process of taking the API through development and to a clinical batch of IMP is not always straightforward and smooth, and we can sometimes run into various challenges, for example:

- Having a limited quantity of API must be known and considered when planning the size of technical and clinical batches, and any additional testing requirements. API expectations must be communicated between pharmacy and the CMO early on
- Having limited stability may compress timelines and create a hard deadline for dosing with little flexibility
- Additionally, the specific activity of an unstable API may change between issuance of the CoA by the manufacturer and when the API is used for the clinical batch. Therefore, a confirmatory test soon before the clinical batch can be beneficial
- Precision of manufacture will decrease for low concentration microtracers, and therefore, wider acceptance criteria is tolerated (typically ±20%). Additionally, the use of AMS for microtracers reduces the risk of the administered dose not achieving the study objective. However, at low concentrations, compatibility issues arising from drug adhesion becomes a greater risk
- All considerations can have an added layer of complexity when a study combines an AME arm and an absolute bioavailability arm, as planning for both formulations is compounded as they often utilize two separate APIs with different strengths of radioactivity
- Combining hot- and cold-API is a common approach, as labeling an API should not affect physicochemical properties. However, the ability to process hot-API in ways such as milling and particle size reduction may be limited due to contamination considerations, resulting in a disparity between the cold- and hot-API. This can influence the performance of the drug product and may call for additional testing of homogeneity
- BCS Class II and IV drugs which possess poor solubility limit formulation options and may result in an unknown, and potentially poor, bioavailability. It may not be known if the drug will be sufficiently absorbed, adding uncertainty to the achievability of the study objectives

These challenges can force outside-the-box problem solving and flexibility, and so we recommend engaging with us as early as possible so we can help you plan the details.

For questions relating to Fortrea's hAME pharmacy services,

CONNECT at fortrea.com

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