EXECUTIVE SUMMARY

Early drug development requires adherence to Good Manufacturing Practices (GMP) guidelines when manufacturing investigational medicinal products (IMPs) for clinical studies conducted within Europe.

IMP manufacturing can be considered an extension of activities of the clinical team if the IMP is manufactured on site and released based on the analysis performed by an in-house quality control (QC) laboratory. Timelines can be shortened by the technical and clinical
teams working in parallel during the start-up phase in early drug development. This allows for quicker Clinical Study Report (CSR) finalization and speeds up progress toward the next stage in clinical drug development.

On-site manufacturing offers several advantages, such as:

- Requiring only short-term stability data of the intended dose range.
- Providing flexibility to adjust the dose strengths prior to or during the clinical trial.
- Developing a complicated formulation with extensive stability data is not required.
- Expediting data turnaround time through on-site QC and qualified person (QP) release.
- Allowing for on-site manufacturing of radiolabeled IMPs at equipped, licensed facilities.

Due to the expense of each of these time-consuming tasks, clinical studies directly supported by GMP-compliant on-site manufacturing facilities add substantial value by significantly cutting costs and timelines through proven, efficiency-focused processes.
BACKGROUND

The European Union clinical directive (Directive 2001/20/EC) and Annex 13 of the EudraLex—Volume 4 GMP guidelines specify the requirements for the conduct of clinical trials within the EU. This directive clearly states that every IMP must be manufactured according to the EU’s GMP guidelines by a manufacturing authorization holder. The application of GMP standards in clinical drug development provides assurance that all stakeholders involved in the process are confident in the safety, quality, and efficacy of the manufacturing of the IMP.

The GMP guidelines also guarantee thorough quality evaluations of the facility, equipment; and personnel; ensure consistency between batches; and provide the required information to manufacture the same product again. Unlike marketed products, the production of IMPs is more complex due to the lack of fixed routines. In addition, pharmaceutical aspects are developed throughout different clinical phases and products are (re)packaged.

FORMULATION DEVELOPMENT

Formulation development can either be performed by the sponsor or outsourced to a contract manufacturing organization (CMO) or a contract research organization (CRO) with an on-site GMP-compliant manufacturing facility. Extensive formulation development performed by CMOs generates data that may be used in the later phases of clinical drug development. Collaboration between the sponsor and a CMO requires extensive and detailed planning for both parties. This implies that if an IMP ends its lifecycle during early clinical drug development, significantly more time and money will have been spent.

For the early clinical drug development program, the IMP formulation can be developed and manufactured on a small or medium scale according to the EU GMP guidelines.

Formulation development may be required if:

- Adaptation of IMP formulations used in preclinical trials continues through the clinical program to ensure the volunteers’ safety.

- Availability of only a GMP-grade active pharmaceutical ingredient (API) without an IMP suitable for use within early clinical drug development studies.
• Study objectives require a study-specific formulation (ie, a bioavailability study).

• Formulation parameters are being adapted, such as route of administration, solubility, and osmolality.

• Tolerance improvement of the IMP is needed.

At a minimum, the final IMP formulation must be compatible with and stable within the primary packaging and additional administration sets (if applicable) during conduct of the trial. A shorter time period between manufacturing and administration of the IMP requires less stability data, making it possible to run an ongoing stability program in parallel with the clinical program.

QC TESTS NEEDED ARE DEVELOPED AND IMPLEMENTED

ALL TESTS ARE VALIDATED

Development report will be issued

Validation report will be issued

DEVELOPMENT ON LAB SCALE

Final formulation

MOCK RUN

Stability Compatibility

Figure 1: Formulation Development

The formulation development on lab scale can directly be up-scaled to a clinical batch size in a GMP-compliant on-site facility. A beneficial approach would be to bring together formulation development, on-site manufacturing, and QC analysis into a continuous workflow performed by a single vendor. As described above, the timeframe between IMP manufacturing and administration can be shortened with this model.

Since the IMP formulation in some studies is only for research purposes ie, a pilot study, a different administration route, or absorption, distribution, metabolism, excretion [ADME] studies), developing a study-specific formulation proves more cost and time efficient.

Physically or chemically unstable APIs can benefit from on-site manufacturing since there is no need for stabilization over a longer period by additional excipients.
that may affect the pharmacokinetic/pharmacodynamic parameters. The time between manufacturing and administration can be within a few hours or days, and no preservative is needed to prevent microbial growth. Risk assessments should be in place to describe the low level of risk and the risk mitigation, which may require a rationale when using the shortened timelines.

**QUALITY CONTROL & RELEASE**

**Quality Control Laboratory**

On-site manufacturing QC and IMP batch release adhere to the same standards as CMOs. The QC analysis of the IMP has to be conducted in a GMP-compliant facility, and the laboratory procedures are in accordance with the EU GMP guidelines. In addition to developing the formulation, a suitable analytical method has to be developed, implemented, and validated in accordance with International Conference on Harmonization (ICH) harmonized tripartite guideline Q2 (R1).

The QC laboratory and the on-site manufacturer work in tandem to expedite the turnaround time (4-8 hours) of the QC tests, as required for the release of the clinical batches.

Combining clinical, manufacturing, and laboratory resources into a single internal project team with harmonized procedures streamlines communication pathways and collaboration in the early drug development clinical phase, improving each stakeholder’s overall satisfaction. Furthermore, changes in dose and/or dosage form during the clinical phase can be easily manufactured and analyzed.

Studies conducted with a radiolabeled IMP require an isotope lab with capabilities to perform additional QC release tests needed for batch release, such as total radioactivity (by liquid scintillation counting) and determination of radiochemical purity.

**Release**

Every holder of a manufacturing authorization within Europe is required to have a QP for batch release, as described in Article 13(2) of Directive 2001/20/EC of the GMP guidance. Annex 16 of the EU GMP guidelines provides a detailed description of a QP’s responsibilities.

In addition to batch release, (re)packaging and (re)labeling require QP release when used for manufacturing purposes; however, when used for blinding purposes, they are considered a dispensing step by local interpretation of the EU directive and do not require a release.
MANUFACTURING

Flexibility

Early clinical drug development studies require significant variability in dose levels, necessitating the development of several IMP formulations. These dynamic needs can be met by having access to a flexible, high-quality manufacturing unit that understands the importance of rapidly responding to new data in the early learning phase of clinical drug development.

A GMP on-site manufacturer requires only in-use data for the planned product dose range. This creates flexibility not only in planning, but also in the formulation and strength of the IMP. Changes can be made in dose selection just prior to and during the conduct of the trial as long as the adapted dose remains within the envisioned dose range, as defined in the clinical study protocol and for which short-term stability data are given in the Investigational Medicinal Product Dossier (IMPD). Therefore, this increased flexibility shortens the timelines from IMP formulation development to IMP administration in subjects.

Blinding

A bioequivalence study with a comparison to marketed products may require (re)packaging, which can be performed on site in accordance with the EU GMP guidelines. This is similar to a double-blinded study design, in which the primary (re)packaging of the IMP and placebo can be supported by the same manufacturer. Prior to (re)packaging into the new primary packaging material, a compatibility and stability study should be performed over a few days to ensure retained product quality.

Labeling

Besides the manufacturing of bulk IMP, the dispensing of bulk IMP into subject-specific dosing units must meet GMP requirements as well. If a GMP facility is available on site, the amount dispensed can be adjusted based on the need of IMP during the clinical conduct, eliminating the waste of valuable IMP.

The manufactured products or study-specific labeled units can be directly labeled with a subject-specific label in compliance with Annex 13 in the local language.
RADIOLabeled IMPS

If a study is conducted with a radiolabeled IMP, then the radiolabeled IMP needs to be manufactured according to the EU GMP guidelines. For the majority of these studies, the radiolabeled API is a blend of non-radiolabeled API and radiolabeled API. It is evident that the non-radiolabeled API needs to be GMP compliant. Manufacturing of the radiolabeled API according to the GMP guidelines is preferred, but non-GMP material may be used when proper justification is proposed to and accepted by the local ethics committee. Most of the radiosynthesis will be done on a laboratory scale under appropriate conditions, but GMP is typically not claimed for this activity by the isotope laboratory.

An example of an accepted rationale is to use non-GMP material for an ADME study if the non-GMP material is less than 0.15% of the total dose. Such a low percentage could be considered as an impurity. It is preferred that radiolabeled material will be purified under GMP conditions, if no manufacturing under GMP is possible.

In addition to the IMP requirements, a facility that can manufacture the final radiolabeled IMP under GMP conditions is needed. The GMP-compliant facility must adhere to local laws on nuclear energy and must be separated from areas used for manufacturing on-radiolabeled IMPs. While a GMP facility ensures maximum protection of the product, the facility manufacturing radiolabeled IMP has to guarantee a healthy and safe environment for the staff and operators as well.

The manufacturer needs to have 1 or more licensed radiation safety officers on duty. Radiolabeled materials may only be handled by operators who are qualified and trained on working with these high-risk compounds. It is an advantage to perform such radiolabeled IMP manufacturing on site, where the route between manufacturing, QC lab, and administration is very short. Radiolabeled compounds with poor stability, which lack long-term stability data, can especially benefit from on-site manufacturing to speed up the clinical program.

FACILITIES

All IMP manufacturing must be performed within a facility holding a manufacturing authorization.

IMP manufacturing in early clinical drug development requires mainly small batch production along with GMP certification for all different manufacturing activities performed. Small clinical batches can easily be manufactured on site if the CRO has a certified GMP facility with a “cleanroom” to ensure cleanliness of the manufacturing environment. Mix-up and cross-contamination between different batches of products
and placebo/verum must be prevented by segregating equipment, materials, and personnel routes.

The production environment requirements depend on the dosage formulation to be manufactured. The manufacturing of sterile products requires an appropriate environmental cleanliness level to minimize the risk of contaminating materials or products. Depending on the critical steps in the manufacturing procedure, an appropriate classified and validated area has to be used. The gradation of areas for sterile production, for example, is described in Annex 1 of the EU GMP and ranges from Grade A (most clean) to Grade D (wider limits of cleanliness).

An example of a suitable facility is a Grade A area within a Grade B area for manufacturing of parenteral formulations. Along with these areas, the availability of segregated manufacturing areas for handling high-risk compounds can expand the manufacturing possibilities on site, such as a Grade D area for manufacturing oral radioactive IMPs and a Grade A area for manufacturing parenteral radioactive IMPs.

![Figure 2: Example of an On-Site Manufacturing Facility's Manufacturing Areas](image)

If the manufacturing facility is not located in the EU, yet the clinical conduct of the early drug development will be done within the EU, the production of the IMP has to be done under equivalent conditions as described in the EU GMP guidelines. If a facility claims to be GMP compliant, then it must also be qualified and verified.
The manufacturing area requires restricted access that is only accessible by authorized personnel of the on-site manufacturing facility.

**BUDGET & TIMELINES**

An on-site GMP pharmacy can cut 6 months from development time while saving the research and development (R&D) budget up to $1M.

The indicative timelines for manufacturing and formulation development are:

- QC method development: 4-8 weeks
- Formulation development: 4-8 weeks
- Mock run and stability/compatibility study: 1-4 weeks

The parallel development of clinical and technical aspects not only shortens the total start-up time, but it also restricts numerous contracts with different parties and limits additional start-up costs.

In The Netherlands, PRA has a GMP-compliant manufacturing pharmacy on-site with an in-house QC laboratory. This setting at PRA supports manufacturing of (radiolabeled) IMPs for early drug development in volunteer and patient studies conducted within Europe. PRA has more than 10 years of experience in supporting formulation development and on-site manufacturing of clinical batches under the GMP requirements. This approach has proven successful in increasing flexibility in dose escalation, shortening timelines, and providing cost reduction in IMP development and stability programs.
CONTACT INFORMATION

For further information or to discuss any aspect of PRA’s services offered in the field of on-site manufacturing, please contact your Business Development Manager or the employees listed below:

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ABOUT PRA HEALTH SCIENCES

PRA Health Sciences delivers innovative drug development solutions that improve patients’ lives. Our people are passionate about clinical research, working tirelessly to provide quality results for clients. We offer exceptional experience across all phases, therapeutic areas, and a broad spectrum of solutions, ranging from full-service clinical development to our pioneering Embedded model.

With 12,000+ employees covering 80+ countries, we bolster an impressive global presence with keen local insights. Our project teams harness their understanding of local regulations, standards of care, and cultural customs to effectively align our approaches with each study’s unique goals.

At PRA, we love what we do because we are making a difference in the lives of patients and their family members worldwide. Over the years, we have contributed to the development of numerous drugs now available to countless patients. From our scientific and medical experts to therapeutically aligned project managers and monitors, we provide the commitment and expertise needed for today’s complex studies.

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