

# Onsite manufacture can accelerate your Phase I small molecule program

## A KEY QUESTION



How can biotech companies minimize manufacturing costs for small molecule investigation product by leveraging onsite GMP manufacturing capabilities at Phase I clinics?



## KEYWORDS

cGMP Pharmacy, Phase I Drug Manufacturing, Time and Cost Efficiency, Safety, Biotech

**Using a cGMP pharmacy at your Clinical Research Unit (CRU) for Phase I drug manufacturing yields benefits in quality and safety, timeline reduction and cost efficiency.**

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## 1. Quality and Safety

The premier benefit to cGMP combines quality and safety. Quality is inherent in any part of clinical drug development and manufacture, and Phase I trials are all about safety. Phase I is where we look for initial safety responses to medicines, as it is the entry point from the preclinical process to the clinical world.

Why use a cGMP pharmacy located on-site at your CRU? The real distinction between a cGMP pharmacy and a traditional compounding pharmacy is that a cGMP pharmacy offers a quality management system (QMS), not just pharmacist oversight. A Phase I CRU having a cGMP pharmacy on-site can meet quality specifications and also leverage complete process information related to chemistry, manufacturing and controls (CMC)—including sterilization and containment systems—for use in later trial stages and investigational new drug (IND) amendments.

## Phase I regulatory oversight

While regulatory oversight is a key concern, the amount of information needed for FDA review to ensure quality varies at each phase of clinical drug development. In Phase I development, we already know several facts:

- Drug substance and product purity profiles are available
- The drug is used for a short duration
- There are a limited number of patients involved
- There is complete control over making and administering the drug

Therefore, the FDA realizes that drug manufacture for Phase I should not require the same level of information necessary for oversight in later stages. Current regulation and guidance require a level of quality to comply with a standard manufacturing practice, specifying:

- Innovation should not be impeded in early clinical development stages due to risk and costs to sponsors in early drug development
- Sufficient Chemistry, Manufacturing and Controls (CMC) information should be provided in an IND which increases as development of the drug progresses

While this gives some flexibility to organizations manufacturing drugs for Phase I trials, the guidance document does say that the FDA will exercise oversight of the study drug under general cGMP authority. In July of 2008, the FDA released a guidance document for investigational drugs detailing the exemption of drugs manufactured to meet cGMP for Phase I trials. This document is helpful if you are looking for a CRU that can meet Phase I manufacturing requirements.

## 2. Timeline Reduction

The second benefit of Phase I drug production at a CRU cGMP pharmacy is timeline reduction. A full run of GMP product at a contract manufacturing organization (CMO) takes significant time and investment plus a full supply of active pharmaceutical ingredient (API). Phase I manufacture, however, requires only a small batch of the compound, using far less API. A CRU cGMP pharmacy can supply a small run quickly, on-site, with a QMS and data to meet regulatory requirements.

You gain significant control over your schedule for Phase I studies with cGMP manufacture at the CRU versus at a CMO. After the API arrives at the CRU pharmacy and is released for use by GMP Quality Assurance (QA), the staff can manufacture doses quickly. Also, sponsors appreciate the reduction in stability testing and data needed when the CRU makes drugs on-site and administers them immediately. Not having to run full-fledged stability studies saves significant time.

Another timesaving involves the data you gain during the cGMP manufacturing process. Master Batch Records (MBR) detail the drug manufacturing process, and accountability logs document drug administration. The information is available immediately on-site. Evaluations of the final drug product are provided as part of the GMP dose analysis, detailing characteristics such as ID test, purity and strength, provided on a Certificate of Analysis. The benefit? You have the criteria you need to ensure quality.

**Finally, sponsors enjoy the flexibility and speed of making “on-the-fly” adjustments in dosage with on-site drug manufacture. Whether the pharmacy is producing capsules or oral solutions in small batches, on-site manufacturing allows you to adjust protocol designs and make last-minute dosage adjustments based on safety markers that meet your adaptive trial design needs.**

### 3. Cost Efficiency

The third benefit of Phase I manufacture at the CRU entails increased cost efficiency and reduced financial risk. Cost is a major factor in executing a clinical trial. You can reduce your financial risk by not beginning a full CMC campaign only to have to cancel it or change formulation based on late toxicology results or safety data. Manufacturing doses at a CRU allows you to accommodate variability in your formulation without incurring expensive delays.

With large-run drug manufacture at a CMO, you waste a large amount of API if you need to change your formulation. Remember that a contract development and manufacturing organization (CDMO) requires large batches with minimum sizes for drug products to be created; however, Phase I trials do not require a large amount of drug, so small runs with small amounts of API can easily meet your need.

**We estimate that cGMP at a CMO results in 200-300 percent excess API, while cGMP at a CRU results in only 1-25 percent excess API (see Table 1).**

By manufacturing at a Phase I unit, you can make wise decisions and use your materials efficiently. You also benefit by increasing local control, because you have the ability to maintain your drug within a single space instead of working across multiple locations. You gain control of your formulation and timeline, maintain quality and enhance API management for a higher-quality process.

Manufacturing your Phase I drug at the CRU versus a CMO is the more progressive process and part of the advantage to an integrative relationship between sponsor and CRU. A cGMP pharmacy at the CRU clearly provides a lower-cost alternative for Phase I drug manufacture.

### Summary of benefits

This table is a summary comparing the three different spaces available for Phase I drug manufacture—according to quality, time, quantity, cost and risk involved. You can see that cGMP at the CRU provides high quality, shorter timelines, less API waste, reduced costs and a neutral risk for your program when compared to the alternatives.

Table 1: Comparative benefits for Phase I drug manufacturing sources

| Benefits overview | cGMP at CMO           | cGMP at CRU        | Non-cGMP                 |
|-------------------|-----------------------|--------------------|--------------------------|
| Quality           | Oversight by QMS      | Oversight by QMS   | Oversight by Pharmacists |
| Time              | Longest               | Shorter            | Shortest                 |
| Quantity          | 200 - 300% excess API | 1 - 25% excess API | 1 - 25% excess API       |
| Cost              | \$\$\$\$              | \$                 | \$                       |
| Risk              | ↓                     | ↔                  | ↑↑                       |

## Exploring benefits by study type

Next, let's explore benefits of Phase I cGMP drug manufacture at the CRU according to study type:

- **Exploratory IND trials** – provides small amount of doses for subjects in Phase I studies
- **First-in-human studies** – provides flexibility to manufacture doses at the trial site to help manage cost and timelines
- **Absorption, metabolism and excretion (AME) studies** – meets quality demands with speed and allows exploration of micro-dosing for Phase 0
- **Single ascending dose (SAD)/multiple ascending dose (MAD) trials** – accommodates on-site changes in dosing for maximum flexibility and time savings
- **Trials requiring quick dosage change** – maintains quality using cGMP process

## Streamlining the process

The manufacture of Phase I drugs at the CRU streamlines your process from beginning to end, providing quality and flexibility to meet your needs. For example, these types of studies present special challenges and present opportunities for benefit by cGMP at the CRU:

- **AME** – handling hot/cold radiolabeled material quickly on-site for proper evaluation
- **SAD/MAD** – changing dosages to deliver pharmaceutically elegant formulations leading to Phase II and commercial approach

You can see that a cGMP CRU pharmacy is uniquely positioned to accommodate adaptive trial design in early clinical development.

## Meshing manufacture and trial

Integrating cGMP manufacturing and clinical conduct at the same facility allows more control over the process, and therefore over timelines and costs. Meshing the processes requires the construction of clean rooms (ISO 7 and ISO 8) for sterile and non-sterile manufacturing in controlled environments. Additional working enclosures

must meet ISO 5 air quality standards for sterile manufacturing or assembly (such as a BSC and CACI), and containment equipment includes powder cabinets for non-sterile manufacturing.

**The GMP space must be validated to perform various types of drug formulations, including:**

- Capsules (liquid and powder)
- Oral solutions and suspensions
- Injectable (sterile) solutions

Updated standard operating procedures maximize efficiency and consistency. These include procedures for drug receipt, cleaning and gowning plus QA release to the clinic. Manufacturing at the CRU also requires a robust environmental monitoring program plus final drug product sterility and endotoxin testing to meet USP <71> and <85> under cGMP conditions. The Phase I cGMP pharmacy must accommodate technical batches or engineering runs to deliver confidence to sponsors regarding their final drug product.



## A key benefit:

You eliminate the transfer of the product from CRU manufacture suite to the clinic because doses are delivered straight to the CRU nurse within minutes with no shipping or packaging required.

Sponsors of early clinical drug development are always looking for tools to help reduce timelines and manage costs. **WHY?**

Manufacturing costs are estimated at 20 - 40 percent for the entire development of a drug product through all phases<sup>1</sup>

Much of this investment is spent during early clinical development. If we can help reduce costs and timelines by providing Phase I trial drugs on-site at the CRU according to cGMP guidelines, this is a major benefit to sponsors. How much time and money could you save?

## THE FORTREA APPROACH

Fortrea can help you make informed decisions about your formulation to be compliant with FDA cGMP guidance for the design, monitoring and control of your drug manufacturing. Working together, we can achieve the three key benefits of cGMP drug manufacturing at the CRU for your Phase I trial: **quality and safety, timeline reduction and cost efficiency.**

### References

1. Zhao Y, Fleischhacker A. [Contract development and manufacturing costs during clinical development of a new drug](#). *Applied Clinical Trials* 2013 Aug 05.

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