THREE KEY BENEFITS

Phase I cGMP Drug Manufacturing at the CRU

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.

Marcus Stavchansky, PharmD, Director, Pharmacy Services

The regulatory environment continues to move toward requiring drug manufacturing at current good manufacturing practice (cGMP)-compliant pharmacies. This trend and other factors make it increasingly attractive to use cGMP compounding on-site at your CRU for early development.

Let's look at Three Key Benefits for Phase I drug manufacturing:

1. Quality and Safety
2. Timeline Reduction
3. Cost Efficiency

Industry Trends and Regulatory Changes

As background, let's review industry trends to see how regulatory changes are affecting Phase I drug manufacture. In recent years, catastrophic events have driven an uptick in regulatory activity. In 2011, a Massachusetts compounding pharmacy produced tainted steroid injections for pain management. Their faulty compounding practice led to 700 cases of fungal meningitis across 20 states, resulting in 64 deaths. This occurrence caused an uproar in the pharmaceutical compounding industry and increased fear among companies preparing products for physician offices, patients and clinical trials. The event led to strong oversight by the FDA, resulting in criminal charges against individuals involved. Their review showed that maximizing profit had driven the business, and the company had sacrificed quality in the process.

Since then, the Food and Drug Administration (FDA) has issued 130+ Forms 483s (investigator observations that conditions or practices indicate a possible violation of FDA requirements) to pharmacy compounders across the U.S. These warnings focused on training, facilities, processes and quality expected at GMP facilities. Investigations led to legislation, namely the Compounding Quality Act, Title I of the 2013 Drug Quality and Security Act, which changed the pharmaceutical compounding industry. This federal oversight for compounding translates to requirements for pharmacies that compound sterile drug products. In short, we see that the inevitable move to cGMP is a result of increasing FDA oversight to protect the public. The investment required for organizations makes sense from a quality standpoint – to ensure that products produced at CRUs meet cGMP requirements.

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 Chemical Manufacturing and Control 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.

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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 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 0and 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 processes

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[1]

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 Labcorp Approach

Labcorp 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. (2013) *Applied Clinical Trials* 2013 Aug 05.

Marcus Stavchansky, PharmD
Dr. Stavchansky is director of pharmacy services for Labcorp, overseeing four clinical pharmacy teams in North America. He has 15 years of experience as a registered pharmacist in Texas and 8 years of experience in the Phase I CRU space.

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