Worldwide Clinical Trials

Beyond Dispensing: cGMP and the Role of Pharmacy in Early Phase Clinical Trials

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Clinical Pharmacology Units (CPUs) are actively involved throughout early phase clinical trials, keeping strict adherence to highly regulated manufacturing and study processes. The clinical study research pharmacist often goes unseen, hidden behind the walls of the pharmacy. However, their role in clinical trials does not go unnoticed. While complying with Current Good Manufacturing Practice (cGMP) set by the FDA, the CPU ensures that the clinical trial runs safely and smoothly through processes such as investigational drug product (IDP) compounding, dose management, blinding, dose delivery, and administration. These processes ensure that patients and trial personnel remain safe, that the IDP provided remains uncompromised, and that the data captured is based on IDP manufactured according to tested and respected compounding and manufacturing techniques.

During Phase 1 clinical trials, pharmacy plays a critical role. The pharmacists working in a Clinical Pharmacology Unit (CPU) do not simply pass out pills in little white cups; these are professionals — including clinical study research pharmacists, certified clinical study research pharmacy technicians, and quality control pharmacy technicians — who are actively involved with the compounding, maintenance, and distribution of investigational drug products (IDPs) in multiple forms and doses. If the trial requires a placebo for a blinded study, the pharmacists may need to prepare one that appears in distinguishable from — i.e., that it looks, smells, and tastes like — the IDP itself and may need to do this rapidly to ensure that the trial stays on schedule). Additionally, the pharmacy team is in charge of maintaining the security of the blinding during the trial by monitoring the compounding, storage, and IDP administration and ensuring that neither the study participants nor trial personnel know who is receiving the IDP and who is receiving placebo. And as though all these tasks presented insufficient challenges on their own, a CPU supporting a Phase 1 trial in the US must comply with the FDA's Current Good Manufacturing Practice (cGMP) guidelines. Pharmacists and CPUs involved in a Phase 1 study must have access to well-controlled equipment, a cGMP-compliant manufacturing environment, accurate recorded data, and well-defined procedures. Moreover, to ensure compliance, a comprehensive and systematic evaluation of the manufacturing setting must be conducted to identify potential hazards — and appropriate actions should be taken prior to and during manufacturing to mitigate potential hazards and safeguard the quality of the Phase 1 investigational drug.[1]

What is cGMP?

Current Good Manufacturing Practice, also known as cGMP, is based on the Federal Food, Drug and Cosmetic Act, part of the US Code of Federal Regulation (CFR) Title 21. It consists of a set of regulations intended to ensure the quality of pharmaceutical products, medical devices, biotechnology products, and food and dietary supplements. cGMP compliance is monitored by the Food and Drug Administration (FDA), and the regulations apply to facilities, equipment, production, process controls, lab controls, packaging, and labeling of investigational drug products. While cGMP compliance is critical at every stage of drug development and commercialization, it can be particularly important during Phase 1 clinical trials where on-site pharmaceutical operations may be intimately involved in in the compounding and manufacturing processes of investigational drug products.

Investigational Drug Product Compounding and Dose Management

Manufacturing a single dose level for a clinical trial requires multiple intensive steps:

1. Project planning
2. Supplier management
3. Drug product analytical development
4. Batch manufacturing

These steps not only require time to develop, but also have large associated costs ranging from ~$300,000 to well over $1,000,000, depending on the type of product being manufactured.

Compounding doses of an investigational drug product requires close attention to detail. Depending on the investigational drug product being studied, there are a variety of dosage forms that may be used. The compounding process can involve preparing sterile intravenous (IV) parenteral preparations, encapsulation, over-capsulation, preparing oral solutions or suspensions, or the compounding radioactive medications. A CPU must build in multiple checks to ensure that each dose prepared is accurate for administration. cGMP guidelines regulate a range of storage conditions, compounding equipment, calibration testing, capsule-fill units, and analytical weighing balances that can be used to support the efforts of an on-site CPU.

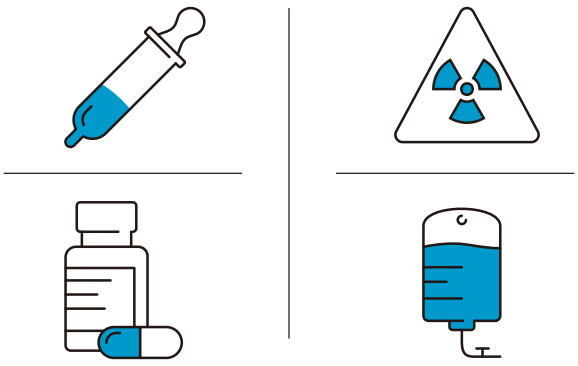

Figure 1: *Investigational drug product compounding can include preparing sterile IV preparations, encapsulation, compounding radioactive medications, and more.*

In addition to batch manufacturing an investigational drug, a clinical study research pharmacist may be called upon to create an extemporaneous preparation (EP) of an investigational drug. An EP may involve the preparation of a very small number of doses compounded for a very specific study scenario. At Worldwide Clinical Trials, compounding pharmacists rely on a fit-for-purpose formulation design and preparation methodology built on safe, flexible, costeffective, and adaptable compounding procedures. Such preparations are common in pediatric study scenarios because they can provide age-appropriate doses of an IDP in easily swallowable liquid form.[2]

Blinding

Blinding in a clinical trial is a concept of keeping one or more parties of the trial unaware of the treatment assignments. Many Phase 1 clinical trials have a double-blind design, which helps eliminate bias in the study because neither the patient nor the study team know whether a patient is receiving the investigational product or placebo.

To facilitate blinding, the compounding pharmacist on site may manipulate the pH and compatibility of oral solutions. Liquid oral solutions may also facilitate the blinding of multiple doses in a single solution (which is not as easily accomplished when compounding solid dosage forms of an IDP). This can be done by dilutions to achieve target drug concentration. This is especially important when safety and therapeutic index are not yet established on an investigational drug product.

Blinding can also extend to taste and color specifications of the treatment doses. To ensure the placebo cannot be distinguished from the IDP, it is important that the IDP and placebo look and taste the same. There are several compounding techniques that a pharmacist can use to alter the appearance of the placebo to match the appearance of the IDP (or vice versa). Adjusting pH and adding flavoring agents can mask the taste so that the placebo and investigational drug are indistinguishable.

Once the IDP and placebo have been compounded so as to appear to be the same, a randomized assignment sequence — identifying which patient gets which dose — is sent directly to the CPU. Following site-specific SOP and work-instructions, the randomization sequence is retained in a secure area, where it is known only to the pharmacist. Following IDP and placebo dose preparation, the unblinded pharmacist, with the help of pharmacy staff, dispenses the treatment doses to study participants.[3]

Dose-Delivery and Administration

In clinical trials, it is critical that the dose delivery in terms of drug concentration is accurate. For parenteral dose administration, syringe pump systems have proven to be effective. Syringe pumps may administer doses as low as 0.1 mL/h. However, if these devices are not monitored correctly, they carry the risk of overdose or underdose due to errors in VTBI (volume to be infused) specifications, IV infiltration, and extravasation. Clinical study research pharmacists with an understanding of both clinical and operational issues can act as subject matter experts, here, identifying suitable infusion delivery systems, creating a drug base library to alert the user about dosage errors, and monitoring of dose delivery parameters.[4] It is crucial to monitor delivery devices by appropriate in-process testing and regularly scheduled device calibrations.[5]

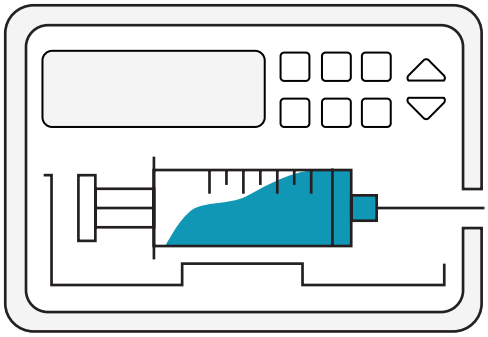

Figure 2: *Syringe pump systems have proven to be effective for parenteral dose administration*

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Conclusion

Clinical Pharmacy is involved in a wide range of roles throughout Phase 1 clinical trials. Consisting of a team of specialized clinicians, scientists, and researchers, a CPU's job is to improve healthcare by establishing evidence objectively and credibly from the earliest stages of human exposure to the IDP. From dose preparation to dose administration management — and every step in between — clinical pharmacists work to ensure that every aspect of the services and support they provide comply with cGMP standards — and by doing so work to ensure that patients and trial personnel remain safe, that the IDP provided remains uncompromised, and that the data captured is based on IDP manufactured according to tested and respected compounding and manufacturing techniques.

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