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PHARMACY SERVICES IN A PHASE I CLINICAL RESEARCH UNIT

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Phase I clinical studies form an important foundation for drug development and eventual approval of life-saving therapies. Potential drug candidates are screened for entry into Phase I trials by extensive in-vitro testing and tolerance in several animal species. Early in-vitro testing establishes potential mechanisms of action, such as binding to a receptor or enzyme. Animal toxicology at large doses is used to determine a small, safe starting dose for first-in-human trials. In light of limited published literature about pharmacy services in a Phase I setting, this article explores the inner workings of a highly active pharmacy in a modern Phase I clinical research unit (CRU).

A typical Phase I program consists of a series of studies to carefully define the safety and pharmacokinetics (PK) of a compound in humans, beginning with a single dose per subject and increasing the dose in subsequent cohorts of volunteer subjects until it reaches either maximum tolerated dose (MTD)¹⁻³, a calculated exposure limit based on animal toxicology, or a pre established biological endpoint has been reached. The latter is often an estimation of the eventual effect in the targeted patient population. Such

a study is then typically followed by a multiple-dose per subject scheme of escalating doses in volunteers to further characterize the safety and pharmacokinetics of the compound at steady-state conditions. Additional Phase I studies, including AME (absorption, metabolism, and excretion), drug-interaction, food effect studies, and even MTD studies in subjects may also be conducted. Given the pressures to develop drugs more quickly, Phase I studies have in recent years also incorporated sophisticated pharmacodynamics assessments and biomarkers to better understand the safety and pharmacology of a compound prior to initiating Phase II studies in patients⁴.

17,000 STUDY VOLUNTEERS ENROLLED IN 3 YEARS

In this early phase of clinical research there is compelling need for high quality systems and facilities to ensure safety.

Worldwides' Early Phase Services is a 300-bed clinical research facility with limited-access Phase I and telemetry units, adaptable procedure spaces, a safety lab certified under the Clinical Laboratory Improvement Amendments (CLIA) and a fully equipped sample processing laboratory. A centralized atomic clock system throughout ensures uniformity of timed study events. A physician serves as the principal investigator for each study and is supported by physician sub-investigators, project managers, clinical coordinators and pharmacists to ensure proper study conduct and collection of quality research data. Additional support staff includes paramedics, nurses, phlebotomists, lab technicians, medical technicians, pharmacy technicians, floor monitors, and operations supervisors. Over 17,000 healthy volunteers have participated in Phase I clinical trials at the research center in San Antonio, TX, over the last 3 years. The recruitment database includes a diverse ethnic and gender balance as well as populations of elderly, obese otherwise healthy volunteers and diabetic patients. The pharmacy occupies approximately 1,200 square feet under HEPA filtration.

The pharmacy includes an ISO Class 7 clean room with ISO Class 5 laminar flow hood for compounding sterile products and an additional spacious compounding suite for preparing oral and topical dosage forms. Secure drug storage is available in the main pharmacy for active studies with additional space for long-term storage of retention samples available in separate areas. The Worldwide pharmacy operates under GCP, U.S. Pharmacopeia 797 Compounding Standards, and U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCP) and current Good Manufacturing Practice (cGMP) guidance for Phase I Investigational Drugs. All drug storage areas have limited access with continuous temperature and humidity monitoring.

PHARMACY STAFF

Clinical research units that are located within a university hospital system typically receive and distribute investigational drugs through the established pharmacy services at that institution, with assigned pharmacy staff who are familiar with research procedures. However, many standalone Phase I clinical research units have no such precedent for pharmacy operations, and often non pharmacy trained staff, such as RNs or clinical coordinators, will handle drug preparation and dispensing within the unit.

The pharmacy operates 7 days/week, and is staffed by 3 full-time licensed pharmacists, 5 FTE certified pharmacy technicians and pharmacist and physician support/oversight from Medical & Scientific Affairs. Staff pharmacists have a combined 20 years of prior research, compounding and specialized drug delivery experience. Pharmacists report directly to the Medical Director of the clinical research unit, which allows input and quick resolution of any issues with minimal obstacles. This management structure fosters the critically time dependent nature of procedures in clinical research which include the time of dosing and PK samples. Delayed resolution of issues or omissions can result in protocol violations that compromise the integrity of the study objectives. A lead pharmacist is assigned to each protocol and a pharmacist attends all study initiation and study progress meetings.

FACILITIES FOR CONTROLLED SUBSTANCES, FROZEN STORAGE

The main pharmacy is used primarily for preparing and storing investigational drugs needed for active research protocols. Drugs are stored in locked cabinets, refrigerators or freezers. Controlled substances are stored separately from other investigational drugs. Three refrigerators, two -20°C freezers and one -70°C freezer provide cold storage and are continuously monitored by two independent electronic systems with automated alerts sent by phone, text and email should out-of-range temperature excursions occur. All drug storage areas are backed up by a dedicated emergency generator which can supply power for 20 uninterrupted hours. All room-temperature drug storage

areas have continuous temperature and humidity monitoring with immediate alerts generated as previously described. The pharmacy has a yellow light system available which can be activated when compounding or dispensing lightsensitive drugs. The main pharmacy is adjoined by a 250 square foot room used for compounding pharmaceuticals not provided in finished form. The compounding suite houses a Mettler Toledo XS105DU analytical balance and a Mettler-Toledo XPE56 micro-analytical balances which have minimum weighing capabilities of 200mg and 2mg respectively, for accurately preparing capsules and powder-in-bottle dosage units. An ante-room and clean room with ISO Class 5 laminar airflow workbench completes the main pharmacy area and is used for preparing sterile products. A separate pharmacy area is dedicated for the preparation of radiolabel compounds. The area includes dedicated analytical balances, preparation equipment and supplies and a scintillation counter. In addition, there are two separate rooms used for long-term storage of retention samples. All pharmacy equipment is certified and/or calibrated by outside vendors according to manufacturer recommendations and/or applicable GCP and cGMP standards. All Pharmacy areas are secured by ID badge or key access with video surveillance. Access is strictly limited to pharmacy staff and the Medical Director.

PHARMACISTS REVIEW PROTOCOL

Pharmacists are involved in reviewing and contributing to research trials from the earliest stages of protocol development. Once a draft protocol is received, the pharmacist is on the distribution list with other team members to provide crucial feedback to the Medical Director and Medical and Scientific Affairs staff. Pharmacists may also be asked to provide guidance on test article procurement, storage, handling and dose preparation prior to the initial draft protocol. Often, the first task is to

decide whether the CRU can execute the study properly and recruit the necessary subjects and/or patients for the study. Recommendations which the team believes are necessary to successfully carry out the study are supplied to the Sponsor. These recommendations often include slight alterations in subject inclusion or exclusion criteria, based on prior experience with similar protocols, or pointing out various inconsistencies within the protocol which could interfere with successful execution. While pharmacists review the entire protocol, they focus their expertise on sections pertaining to safe dose selection (usually based on the No Observed Adverse Effect Level (NOAEL) dose found in animal species), dose preparation, blinding procedures, dose administration, and drug storage. As appropriate, they make recommendations regarding subject training when necessary. Pharmacists also complete Abbreviated New Drug Application (ANDA) and FDA product information tables for the final study report. Given that the investigational drug is the very central core of the protocol, the pharmacists review and comment on this information is crucial. In cases where the Sponsor provides only a general outline for the study, the pharmacist supplies more detailed information to the Worldwide medical writer who is responsible for creating the full protocol. In such instances, information provided by the pharmacist is vital to ensure that all aspects relating to study medication are spelled out in detail by the protocol.

DRUG ACCOUNTABILITY

After a protocol has been finalized and approved by the Institutional Review Board (IRB), the pharmacy will initiate the creation of drug accountability forms. A custom database was created in 2014 to manage all aspects of drug accountability, as well as to manage study-related tasks and to track inventory. The latter is important, as all test articles must be accounted for not only throughout the life of the study conduct, but also may need to be held for much longer after the study is completed. As per 21 Code of Federal Regulations (CFR) 320.38 and 320.63, retention samples for bioavailability/bioequivalence (BA/BE) studies are to be retained by the CRU for at least 5 years following the approval of the application

or supplemental application, or if not approved, at least 5 years following the completion of the study^{5,6}. The database provides protocol-specific summary reports and generates both standard and customized forms for drug accountability, dispensation, retention, inventory and destruction tasks. Database use is restricted to pharmacy personnel only and an audit trail is incorporated into the design. All forms are reviewed and approved by the CRU's Quality Control (QC) department prior to use. Pharmacy staff interact with study monitors who are sent by the pharmaceutical Sponsor of the study to periodically audit study records.

MANUFACTURING AND COMPOUNDING

All manufacturing at Worldwide's company facilities adheres to Phase I cGMP guidelines and site standard operating procedures. The pharmacists create a pharmacy manual in collaboration with the study Sponsor which details the procedures to be used in any study that requires manufacturing or compounding. A Master Batch Record (MBR) is created to specify manufacturing procedures and demonstrate cGMP for Phase I investigational drug compliance. All manufactured products may be quarantined until the MBR is reviewed and product is released by the sponsor's QA department. Any compounding, whether under sterile or non-sterile conditions, adheres to FDA Compounding Guidelines (USP795 and 797) as well as the CRU's own SOPs. Examples of compounding include filling of capsules, preparing oral solutions and suspensions, preparing IV admixtures, and compounding radio-labeled drugs used in specialized AME or micro-dose studies. When the pharmacy needs to source study items or reagents that are not provided by the sponsor, a qualified network of wholesalers, brokers and specialty vendors is utilized. For test articles originating from sources outside the US, pharmacists also provide guidance and submit applications

required to navigate test articles through import regulations as required by the FDA, USDA, and DEA.

INVESTIGATIONAL DRUG BLINDING

Many protocols in Phase I are conducted in a double-blind design (both staff and subject/patient are blind as to whether they receive active medication or placebo). However, the pharmacists are often unblinded because they will prepare the study drugs (active product and matching placebo). A randomization schedule, generated either by the Sponsor or by an independent statistical service, will be provided to the study pharmacist, who reviews it to insure that it matches specifications written in the protocol. The blinded randomization is secured in a locked cabinet which is only accessible to the unblinded pharmacist(s). For dispensing, two unblinded pharmacy staff (at least one being a pharmacist) will prepare the doses per the randomization. Placebo doses are prepared first, and then active doses. A member of Quality Control witnesses all dispensing/ dose prep for blinded studies. Once a staff member is unblinded, they are not able to participate in any subject/patient evaluation aspects of that study. If blinding is required in a study in which the doses are not the same in appearance, quantity, volume, or taste, the following adjustments may be made to mask differences between active and placebo doses:

- **Difference in appearance (oral capsule/tablet):** Utilization of a dosing container that will conceal the appearance of the dose. For example, the dose may be directly administered and consumed from a white opaque narrow-mouth dosing bottle. The subject will be asked to not directly look into the container, but to consume the dose in a blinded manner. Over-encapsulation of the oral dose is a second option in this case.
- **Difference in appearance (IV):** Utilization of an amber bag to cover the IV bag and drip chamber. If the IV line needs to be concealed amber tubing or amber plastic sleeves may be used to conceal all parts of the IV bag/ line. Use of a small curtain may also be utilized to block the subject's view of the IV dose (doser and subject's arm on one side

of the curtain, and then the subject sitting/laying on the other side of the curtain).

- **Difference in taste:** Use of pharmaceutical grade flavoring agents (cherry, bubblegum), juices (apple juice, orange juice), Bitrex, or artificial sweeteners (Orasweet).
- **Differences in Quantity:** If a different number of capsules are being administered between treatments, additional placebo capsules/tablets may be used to ensure the number of pills are equal between treatments.

SUBJECT TRAINING

An increasing number of Phase I studies are conducted with investigational drugs supplied in delivery systems which may be unfamiliar to subjects and/or patients. Such delivery systems include nasal sprays, inhalers, buccal and sublingual tablets and films, sublingual sprays, and orally disintegrating tablets. It is important that subjects be properly trained to administer these test items in order to assure that study drug is properly administered and uniformly absorbed so that the PK of the drug and its metabolites can be measured based on proper and consistent dose administration. The inhalation route is particularly difficult, and subjects must be trained in advance on proper breathing technique and timing so that drug is evenly distributed to the desired areas of the bronchi and lung for maximal effect. In effect, the subject must practice diaphragmatic movement both in the depth and speed of contraction. The Worldwide pharmacy team has procedures in place for specialized dosing that have demonstrated a high degree of precision and consistency and that have resulted in successful regulatory filings.

DISPENSING AND DOSING

There is no room for error when dealing with research medications. Given that such medications are often experimental and their safety is not yet established, they must be given exactly as described in the protocol. To assure that the correct drugs are dispensed, the pharmacy employs a system of double-checks throughout the dispensing process in order to ensure subject safety and compliance with the protocol. The dose labels are barcoded and linked to the barcoded wrist labels on the subject, and additionally, the process is often overseen in complex studies by QC staff. In order to ensure that there is no possibility for error, pharmacists and trained pharmacy technicians dose the subject/patient at Worldwide Clinical Trials. In this regard, the role of dosing is perhaps a unique function for the pharmacy staff compared with other CRUs. Dosing first involves verifying that the subject received the proper dose according to the protocol's randomization sequence. Then, the pharmacy staff give the subject any needed reminders concerning earlier subject practice and training. Following

dosing, the pharmacist checks the subject's hands to ensure medication was taken, and also performs a mouth check using a tongue depressor and small flashlight to explore the oral cavity including under the tongue, cheeks and back of the throat. Post-dose instructions are given and subjects are reminded to notify staff if they feel anything other than normal. Additional instructions may include staying seated upright for four hours after dosing and water restrictions. The pharmacist or pharmacy technician records any observations noted during the dosing session.

CONCLUSION

This paper has reviewed the pharmacy services in a Phase I CRU which are tailored to the complex operations of early clinical research. It will be appreciated that the services span a continuum of pharmacy practice, from compounding and drug preparation to the novel roles of protocol review and drug administration. **Thus, pharmacy provides both support and plays a crucial role in the early drug development process.**

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