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Quality Requirements for the Extemporaneous Preparation of Clinical Trial Materials

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PDA Quality Requirements for the Extemporaneous Preparation of Clinical Trial Materials

Technical Report Team

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1.0 Introduction

The pharmaceutical industry is under continuous pressure to discover new medicines with fewer resources in faster time frames while maintaining the highest quality. With the exceedingly high costs of the development and launch of each new molecular entity (NME) and the low chance of success due to high attrition, the performance of clinical studies lies on the critical path (1).

Typically, the supply of clinical trial materials (CTMs) is provided through GMP manufacture of fixed-strength formulations. Regulatory guidelines for GMP manufacture and documentation of these materials are available and enforced by regulatory agencies across the world.

However, a recent benchmarking exercise conducted by the PDA technical report team (including large and small pharmaceutical companies, contract organizations and academic institutions) indicates that extemporaneous preparation (EP) techniques are widely used to prepare formulations for a variety of dosage forms for small-scale clinical studies where dosing is in-clinic (see **Section 3.2** for types of formulations and dosage form noted).

The EP approach may occur at pharmacies associated with a hospital, a clinical research unit (CRU), or academic institution (i.e., preparation site) and that specialize in dose preparation activities. These are not traditional GMP manufacturing areas for clinical trial material.

While traditional CGMP systems may not be in place in such areas, there still must be appropriate controls in place to ensure patient safety. Since the quality requirements for dose preparation activities that occur at EP sites is not always clear, this gap becomes very important as investigators are increasingly using EP approaches to support small-scale clinical studies.

1.1 Purpose

This Technical Report describes a quality system that will support the preparation of CTMs in a nonmanufacturing environment (preparation site) in a manner that will ensure product quality and patient safety.

This document will be a useful resource for drug companies, clinical sites, investigators and regulators.

1.2 Scope

This Technical Report gives suggested quality requirements for the preparation of small-scale CTMs utilizing an EP approach for in-clinic dosing. It is not appropriate to support the preparation of commercial materials for sale.

Although alternative approaches may be equally valid, pharmacists, healthcare professionals, and others engaged in the preparation of clinical supplies for small-scale studies are advised to ensure that any approach they choose to adopt is consistent with applicable regional or national laws, regulations, and guidelines.

1.3 Business Considerations

Early phase clinical studies provide critical understanding of a compound's safety and pharmacokinetics, and occasionally insight into early indications of efficacy. Practices which reduce the time to supplying quality, fit-for-purpose formulations for early phase studies are critical in leading to data that reduces later stage attrition and lowers the cost of developing new drugs. In the flexible environment of assessing early drug safety or pharmacokinetics, where the clinical investigator may want to explore a less defined dosing range, the practice of preparing the dose extemporaneously may offer distinct advantages. The benefits of EP include a significant cost savings from reducing clinical manu-

facture, testing and release, as well as accelerating the time the candidate drug reaches the clinic and becomes available to patients.

1.4 Scientific and Clinical Rationale

Extemporaneous preparations are often useful in later phase clinical studies as supplements to traditionally manufactured primary formulations. Typically, these are used in smaller supportive studies in such areas as safety assessment, pharmacokinetics, and formulation enhancement. In safety assessment studies, an extemporaneously prepared solution may be used to achieve exposure levels greater than would be possible with traditional solid oral dosage forms. In pharmacokinetic studies, an alternate formulation or route of administration may be used to obtain pharmacokinetic parameters or gain insight into an Adsorption, Distribution, Metabolism and Excretion (ADME) mechanism. Lastly, EP may be used to efficiently screen innovative formulation concepts in order to provide added value to patients and extend the lifecycle of currently marketed medications.

Preparing the doses at the clinical site allows investigators to adjust the dose, as needed, based on real-time cohort data. This is advantageous when the therapeutic index is still being developed, or the dose can be adjusted based on the patient/subject weight if required. From an Active Pharmaceutical Ingredient (API) perspective, less API is required for the study since doses are prepared based on the actual number of subjects who participate in the study, the overage is limited, and only a small number of dosing units are prepared. From a formulation perspective, there is no need for a long-term stability program for the drug product and there is no need to commit to a large-scale manufacturing campaign. However, data should be available to support the CTM stability for the intended length of storage during the clinical trial.

An added benefit of utilizing EP is that several formulations can be clinically evaluated before committing to a commercial formulation. For methodology studies where biomarkers or other agents are used to ensure that the testing method and design is appropriate to answer a hypothesis for the novel API, EP enables the use of these biomarkers or comparative agents where there is no commercially available product.

Given the compelling case for using EP practices, guidance is needed to ensure that patient safety and the integrity of the scientific process is not compromised. Since EP falls between the traditional practices of GMP manufacture and the practice of pharmacy, this Technical Report describes a quality system and documentation to ensure that patient safety and product quality are maintained.

2.0 Glossary of Terms

Active Pharmaceutical Ingredient (API)

Any substance or mixture of substances intended to be used in the compounding of a drug preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body (2).

Clinical Protocol

A document, together with any amendments to it, that describes the objectives, design, methodology, statistical considerations, and organization of a clinical trial.

Clinical Trial Material (CTM)

A drug or combination of drugs and/or excipients that are produced with the intent that it be used in a clinical trial, or that is released or otherwise authorized for use in such. This could, subject to appropriate regulatory approval, be an experimental medicine, a product with marketing authorization used in a clinical trial within or beyond the approved indication and/or any placebo articles produced for use in a clinical trial.

Compounding

The preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice. Compounding includes the following:

- Preparation of drug dosage forms for both human and animal patients
- Preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns
- Reconstitution or manipulation of commercial products that may require the addition of one or more ingredients
- Preparation of drugs or devices for the purposes of, or as an incident to, research (clinical or academic), teaching, or chemical analysis
- Preparation of drugs and devices for prescriber's office use where permitted by federal and state law (3).

Extemporaneous Preparation (EP)

A type of compounding whereby a drug or combination of drugs and/or excipients is prepared under the supervision of a pharmacist to create a customized medication dosage form in accordance with a clinical protocol.

Investigator

A clinician scientist taking part in a clinical trial having direct and immediate clinical responsibility for the subject or patient and their treatment with the clinical trial material.

Key Attributes

A subset of the characteristics of the drug which are determined to be most important to quality.

Manufacturing

The production, packing, testing, storage, release and distribution of drugs or medical devices for use in humans or animals where the manufacturing is indented to produce doses, typically in significant numbers, for an undefined population of future patients or clinical trial subjects (4).

Pharmacist in Charge

A licensed pharmacist who is assigned the responsibility and authority for establishing and implementing policies and procedures for all operations of the pharmacy and to ensure the pharmacy operations and practices comply with all requirements of national and local pharmacy and drug laws, rules, and regulations.

Pharmacy Manual

A manual typically created and provided by the study sponsor that contains specific information and documentation to allow the clinical sites to properly receive, store, prepare, label, dispense and return clinical trial material and document the related activities at the clinical site.

Note: For this report, the pharmacy manual will also contain specific instructions for the extemporaneous preparation, labeling and dispensing of clinical trial materials.

Practice of Pharmacy

The interpretation, evaluation and implementation of medical orders which may include the administering, preparing, compounding, preserving, and/or the dispensing of drugs, medicines and therapeutic devices on the basis of prescriptions, clinical protocol or other legal authority.

Note: Many localities have broader definitions describing very specific activities and responsibilities that further defines the practice of pharmacy.

Preparation Record

An approved document that gives the detailed instructions for preparation of the Clinical Trial Materials (CTM).

preparation site

The location where extemporaneous preparations of Clinical Trial Materials (CTM) are made.

Reference Standard

A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing. For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and/or controlled, and purity should be measured by a quantitative procedure (5).

Shelf Life (also referred to as expiration dating period)

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label (6).

3.0 Extemporaneous Preparation Studies

While this Technical Report frames a recommended approach to managing the quality of doses produced by extemporaneous preparation, individuals should confirm, and comply with local, national and/or regional regulations wherever applicable.

Prior to administering any investigational drug to human subjects, the investigational plans (protocol) must be approved by an Institutional Review Board (IRB) as well as the governing regulatory body in the country in which the study will occur (i.e., approved Clinical Trial Application (CTA) or open Investigational New Drug (IND)), Radioactive Drug Research Committee (RDRC) approval for radioactive drug studies). Patients must also sign the Informed Consent Form (ICF).

3.1 Study Types Appropriate for EP

The EP approach is appropriate for conducting small-scale in-clinic studies which include First in Human Single/Multiple Ascending Dose, Pharmacokinetic, Pharmacodynamic Assessment, Proof of Concept, Radiolabeled (PET or ADME), and new formulation studies.

Note: This document is not appropriate for use to support the preparation of commercial materials for sale.

3.2 Dose Preparation Activities

Extemporaneous preparation activities may include the following:

- weighing of API for preparation of capsules, tablets, solutions and suspensions
- reconstitution, mixing, and/or diluting solid sterile or nonsterile API
- sterile dose preparation
- over encapsulation
- preparation of radiolabeled materials

These activities produce CTMs that include, but are not limited to, the following:

- powder or drug in capsule
- formulated capsules or tablets
- oral solution including suspensions
- sterile preparations formulated from sterile or nonsterile API
- topical formulations
- inhalation doses
- nasal sprays
- ophthalmics
- radiolabeled dosage forms from radiolabeled API
- comparators or placebos

3.3 Dose Preparation Considerations

EP is intended for the preparation of a limited number of doses. For example, a single ascending dose study involving a small number of subjects is conducive to extemporaneous preparation of CTM, whereas larger studies involving multiple doses for a large number of subjects are not included in the scope of this report.