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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

Authors

Vince L. Mathews, M.S., Mathews Quality Consulting LLC *(Team Leader)*

Loyd V. Allen, Jr., Ph.D, International Journal of Pharmaceutical Compounding

Amy Antipas, Ph.D, R.Ph, Pfizer

Lesley R. Dandoy, M.S., AstraZeneca Pharmaceuticals

Gerald E. Finken, R.Ph., CSM, Inc.

Kathleen S. Greene, Novartis Vaccines and Diagnostics

Richard Hoffman, M.S., RAC, Eli Lilly and Company

Mark D. Leney, Ph.D., MassBiologics, University of Massachusetts Medical School

William Marinaro, Ph.D., R.Ph., Merck & Co., Inc.

Cathy Moll, R.Ph., Covance

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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.