Quality Systems Appropriate for Extemporaneously Prepared Early Phase Clinical Trial Materials

Richard Hoffman, MS
Eli Lilly & Co.
Principal Consultant - Regulatory
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Agenda Topics for Discussion

- PDA Task Force Team Technical Report
- Extemporaneously Prepared Clinical Trial Materials (EP CTMs)
- Advantages / Disadvantages of EP
- Scope of EP CTMs
- Governing Quality Systems
  - Quality systems management, facilities & equipment, materials management, preparation instructions, packaging, labeling, release
- Regulatory Submission Requirements
PDA Task Force Team

- Initiated in late 2009
- PDA sanctioned team to write technical report
- Survey conducted which assessed prevalence
- Reviewed multiple regulations & guidance documents to assess quality requirements
- “Quality Requirements for the Ex. Prep. of CTMs”
- Position paper status:
  - Initial draft out for review /comment – Target Sept. 2011
  - Review process through ~Q4 2011
  - Finalize following PDA board approval – target Q1 2012

PDA Task Force Team

- **Vince L. Mathews, M.S., Co-Leader**, Eli Lilly and Company
- **Kathleen S. Greene, Co-Leader**, Novartis Vaccines & Diagnostics
- **Loyd V. Allen, Jr., Ph.D.,** International J. of Pharm. Compounding
- **Amy Antipas, Ph.D., R.Ph.,** Pfizer
- **Robert L. Dana, R.Ph.,** Parenteral Drug Association
- **Lesley R. Dandoy, M.S.,** AstraZeneca Pharmaceutical
- **Gerald E. Finken, R.Ph.,** CSM, Inc.
- **Richard Hoffman, M.S.,** Eli Lilly and Company
- **Mark D. Leney, Ph.D.,** MassBiologics, U. of Mass. Medical School
- **William Marinaro, Ph.D., R.Ph.,** Merck & Co., Inc.
- **Cathy Moll, R.Ph.,** Covance
- **Monica Caphart, M.S., M.P.H.,** FDA (Consulting Role)
**EP Definition**

Extemporaneous (ek-stem-pə-rā-nē-əs) Preparation (EP)

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

* Draft definition from technical report

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**Advantages / Disadvantages of EP**

**Advantages**

- Reduce API needs, no CT manufacture & packaging
- No long term stability & reduced analytical method support
- Overall reduced expenses, shorter timeline, less resources needed
- Flexible dosing to enable response to emerging clinical data
- Ideal for small scale (e.g., Ph I) studies

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[Diagram: Time-Line showing EP, Dev, CT, Simple, Complex]
Advantages / Disadvantages - EP

Disadvantages
- Only qualified Phase I sites will have the capabilities to perform EP
- May not be suitable for hazardous drugs or complex formulations
- Less learning for the formulation development organization
- Potential internal challenges to new approach within organizations
- Uncertainties regarding regulatory requirements & guidance

Formation of PDA Task Force Team & Technical Report

Draft PDA Paper: Scope

- Small scale CTM dose preparation
  - Phase 1 studies (SAD/MAD, Pharmacokinetic, Pharmacodynamic, Radiolabeled (ADME), etc.)
  - Small Phase 2a or Phase IV in-clinic studies, where feasible
- Hospital, CRU, University, etc., specializing in CTM activities
- Comply with state & federal laws, regulations and guidelines
- Requires IND or CTA, & IRB approval
Draft PDA Paper: Scope

EP activities may include the following:

- weighing of API for capsules, tablets, solutions & suspensions
- mixing and/or diluting solid sterile or non-sterile API
- preparation of radiolabeled drug product

Produced CTMs include:

- powder or drug in capsule or bottle
- oral solution including suspensions
- sterile preparations formulated from sterile or nonsterile API
- topical formulations
- nasal sprays
- ophthalmics
- radiolabeled dosage forms from radiolabeled API

Draft PDA Paper: Regulatory Overview

Where does GMP manuf. stop & the Practice of Pharmacy start?

GMP Manufacturing  ?  Practice of Pharmacy

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21CFR210/211

State laws / Local Rqts.

By Richard Hoffman, MS
Extemporaneous Preparation (EP) is a subset of Compounding

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/pharmacist/patient/compounder relationship in the course of professional practice. Compounding includes the following:

- Preparation of drugs or devices for the purposes of, or as an incident to, research (clinical or academic), teaching, or chemical analysis

* USP<795> Pharmaceutical Compounding – Nonsterile Preparations
Draft PDA Paper: General Approach

- Presents a Life-cycle approach
  - Qualification of site through preparation and monitoring
- Leverages Pharmacy setting (e.g., facility, personnel)
- Requires supporting information/data from Sponsor
- Ensures appropriate regulatory oversight (CTA, IRB)
- Establishes appropriate Quality System requirements
  - Draws upon USP and other regulations (e.g., Ph 1 GMPs)
  - Positions the Pharmacist in the Quality role
  - Recommendations reflect minimum Quality requirements


- Responsible quality person – usually Pharmacist in Charge
- SOPs
- Training
- Documentation
- Quality agreements / Business Agreements
- Self Inspections
- Record management
### Draft PDA Paper: Facilities & Equipment

- **Facilities**
  - Properly designed for CTM preparations
  - Potable water for washing / Purified for non-sterile preparations
  - Secure preparation, testing, and storage areas
  - Written procedures to prevent cross-contaminations

- **Equipment**
  - Appropriately designed, calibrated, and cleaned
  - Procedures in place for reusable equipment
  - Properly stored to protect from contamination
  - Qualified & checked prior to use

### Draft PDA Paper: Materials Management

- **Raw Materials**
  - Material Management procedures must be in place
  - Use of compendial raws preferred / use of reliable suppliers
  - Must be traceable

- **Acceptance Criteria**
  - CoA accepted for most raw materials
  - ID test or other methods of assurance recommended for API

- **Storage**
  - Controlled conditions per label and/or sponsor requirements
  - Monitored storage areas
**Draft PDA Paper: Preparation Instructions**

**Pharmacy Manual**
- Provided / Written by Sponsor
- Sponsor has responsibility to perform development studies to ensure proper CTM preparation and administration
- Typical Contents:
  - description of CTM
  - Beyond Use Date (BUD)
  - critical API and CTM information
  - detailed dose preparation instructions
  - labeling instructions
  - etc.

**Preparation Record**
- Written by Sponsor or prep. site, apart of CTA/IND submission
- Detailed enough to allow for reproducibility & traceability
- Master Preparation Record preferred for multiple dose preps.
- Typical contents:
  - pre and post approval
  - detailed instructions
  - raw material and equipment id
  - area for initials & calculations
  - final release
  - etc.
Draft PDA Paper: Analytical Assessment

- CTM visual examination and weight checks
- Analytical testing if required
- Use of contract laboratories, if needed
- Instrumentation must be qualified & routinely checked
- Retain samples as required by Sponsor

Draft PDA Paper: Packaging, Labeling, & Release

- Appropriate containers to ensure SISPQ
- Labels must comply with Sponsor, local, state, & federal rqts.
- Unique identifier must be used
- BUD or expiration date must be applied
- Proper storage of packaged CTM per Sponsor requests
- Release of CTM by Pharmacist in Charge or designee
  - Critical steps require second person verification
  - Must be free of any deviation or free from outstanding deviation
Draft PDA Paper: Site Selection and Due Diligence

• Site Selection
  - previous site experience
  - robust quality systems
  - adequate flexibility, capacity, capability

• Due Diligence
  - conducted by Sponsor
  - must adhere to Sponsor standards and applicable regulations as Sponsor is ultimately responsible

Draft PDA Paper: Audits and Oversight

• Audits
  - conducted by Sponsor prior to EP CTM
  - periodic audits to review lesson’s learned
  - utilize a risk-based approach

• Sponsor Oversight
  - recommend cross-functional review board at Sponsor
  - quality and/or business agreement
  - practice / demonstration runs as needed
  - real time observations (man in the plant) as needed
Draft PDA Paper: Regulatory Strategy

- CMC submission requirements vary by country
- Complete DS CTA sections must be submitted
- Description of process (P.3.3) should contain all of the key steps for preparation of the CTM
- Data from the qualification noted within section P.2 or P.5
- BUD of EP CTM should be noted (P.8) & supported by data
- Advantageous to have Preparation Record written at the time of submission

Conclusions

- EP CTM is flexible, economic, & medically useful tool
- Practice performed successfully by Pharma for many years
- Comprehensive quality systems must be in place
- Submission requirements less extensive for DP section
- PDA Technical Report outlines basic approach & requirements
- Delivering compounds safely to patients is top priority
Questions?

Contact Information

Vince Mathews: Mathews_Vince_L@Lilly.com
Richard Hoffman: Hoffman_Richard_D@Lilly.com
Kathleen Greene: Kathleen.Greene@Novartis.com

Backup Content
Clinical Trial Material (CTM) – Drug substance or drug product 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.

Compounder – A professional authorized by the appropriate jurisdiction to perform compounding pursuant to a prescription or medication order by a licensed prescriber.

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 federal and state pharmacy and drug laws, rules, and regulations.

Pharmacy Manual – A manual usually created and provided by the study sponsor that contains specific information and documentation for the pharmacist/pharmacist to properly receive, store, prepare, label, dispense and return clinical trial material and document the related activities of the pharmacist/pharmacy. 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. Many states and regions have broader definitions describing very specific activities and responsibilities that further defines the practice of pharmacy.
Draft PDA Paper Working Definitions

Preparation – a compounded drug dosage form or dietary supplement, or a device to which a compounding pharmacist has introduced a drug. This term will be used to describe compounded formulations; the term product will be used to describe manufactured pharmaceutical dosage forms.

Preparation Site – The location where extemporaneous preparations of Clinical Trial Materials (CTM) are made. This is a suitable area (e.g., pharmacy) typically associated with a hospital, Clinical Research Unit (CRU), or academic institution.

Quality Personnel – Personnel who are responsible for technically verifying quality requirements (quality control) or for assuring by investigation and review (quality assurance) that quality requirements have been achieved. For extemporaneously prepared CTMs, this is the Pharmacist in Charge or designee.

US Laws, Regulations, Guidance, etc.

- Laws
  - FD&C Act Section 503A “Pharmacy Compounding”
  - State pharmacy laws

- Regulations
  - 21CFR210 & 211 (CGMP)
  - Revised 21CFR210 (as of Sept. 2008)

- Guidance
  - Compliance Policy Guidance for FDA Staff and Industry, Chapter 4, Subchapter 460, “Sec. 460.200 Pharmacy Compounding”, May 2002
    - Comprehensive list of factors
    - Not intended to be “exhaustive”
  - Warning Letters (example: [http://www.fda.gov/cder/pharmcomp/default.htm](http://www.fda.gov/cder/pharmcomp/default.htm))
  - Guidance for Industry, “CGMP for Phase 1 Investigational Drugs”, July 2008

- USP Chapters
  - <795> - Compounding Non-sterile Preparations
  - <797> - Compounding Sterile Preparation
  - <1075> - Quality Assurance in Compounding
  - <1191> - Stability Consideration in Dispensing Practices
CGMP for Phase 1 Investigational Drugs, July 2008

- Applies specifically to Phase 1
  ✓ Material used for, or produced for Phase 2 & beyond, needs to comply with part 211
  ✓ Phase 1 material not manufactured under 211 cannot be used for Phase 2 or beyond

- Applies to small molecule, biologics, placebos

- Does not apply to human cell/tissue, device, PET, etc.

- Replaces 1991 guidance "Preparation of Investigational New Drug Products (Human and Animal)" as it applies to Phase 1 only
  ✓ still applies to Phase 2 & 3 clinical trial materials

- Allows flexibility for Phase 1 manufacturing
  - "Manufacturers should establish manufacturing controls based on identified hazards for the manufacturing setting that follow good scientific and QC principles."
  - "These recommendations provide flexibility to the manufacturers in implementing CGMP controls appropriate to their specific situation and application."
  - "...all QC functions may be performed by the same individual(s) performing manufacturing."

European Regulations

Directive 2001/20/EC (Article 13) – Clinical Trial Directive

"Member States shall take all appropriate measures to ensure that the manufacture or importation of investigational medicinal products is subject to the holding of authorisation."

"Member States shall take all appropriate measures to ensure that the holder of the authorisation referred to in paragraph 1 has permanently and continuously at his disposal the services of at least one qualified person…"


Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centers or clinics, by pharmacists or other persons legally authorised in the Member States to carry out such processes and if the investigational medicinal products are intended to be used exclusively in those institutions.

EudraLex Volume 4 (Good Manufacturing Practices Guidelines) - Annex 13

Manufacture of Investigational Medicinal Products, July 2003
Other Country Regulations

Singapore
No CM&C information provided to Health Sciences Authority
Minimal CM&C information provided in IB

Canada
Typical CM&C information provided similar US or EU submission
Policy on Manufacturing and Compounding Drug Products in Canada (POL-0051)
Health Products and Food Branch Guidance Document, Annex 13 to the Current Edition of the CGMP Guidelines Drugs Used in Clinical Trials Canada, GUI-0036