Extemporaneously Prepared Early Phase Clinical Trial Materials

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Agenda Topics for Discussion

- Extemporaneously Prepared Clinical Trial Materials (EP CTMs)
- PDA Technical Report
- US Guidance and Regulations
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 supervision of a pharmacist to create a customized medication dosage form in accordance with a clinical protocol.*

Drug substance  →  Clinic  →  Drug Product

* PDA Technical Report definition
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
✓ Speed access to patients through quicker testing of clinical concept
✓ Ideal for small scale studies

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Time-Line

Dev

EP

Dev

CT

Simple (e.g., drug in capsule)

DEV

CT

Complex (e.g., tablet)

API to develop formulation

EP Simple Complex

FTE/Year burn

EP Simple Complex
Disadvantages

– Only qualified 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
### GMPs…to Practice of Pharmacy

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

<table>
<thead>
<tr>
<th>GMP Manufacturing</th>
<th>Practice of Pharmacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>Quantity/batch size?</td>
</tr>
<tr>
<td>Yes</td>
<td>Commercial scale equipment?</td>
</tr>
<tr>
<td>~months+</td>
<td>How far in advance?</td>
</tr>
<tr>
<td>~Future</td>
<td>Sale: immediate or future?</td>
</tr>
<tr>
<td>Yes</td>
<td>Selling to 3rd party?</td>
</tr>
<tr>
<td>~No</td>
<td>Relationship with patient?</td>
</tr>
<tr>
<td>Yes</td>
<td>Use in Clinical Trials?</td>
</tr>
<tr>
<td>Small</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>~minutes – days</td>
<td></td>
</tr>
<tr>
<td>~Immediate</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>~Yes</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

**Federal laws**

21CFR210/211

**State laws / Local Rqts.**

USP<795>, <797>, etc.

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R. Hoffman
February 2014

IQ Consortium for Innovation & Quality
In Pharmaceutical Development
PDA Technical Report

- 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
- Published Sept. 2013
PDA Consideration: The Triad Analogy

Traditional Compounding Relationship (Triad)

Physician

Rx

Patient

Compounder

State / Local Law
Practice of Pharmacy

EP for CTM Relationship (Triad)

Investigator

Protocol

Subject

Compounder

Approved CTA & IRB
Appropriate Q Systems
PDA Paper: Covered Topics

- Scope
- Regulatory Aspects
- Quality Systems
- Facilities, Equipment, and Materials Management
- Pharmacy Manual & Preparation Record
- Clinical Trial Material Assessments
- Packaging, Labeling, and Release
- Site Selection, Qualification, Oversight & Control
PDA Group Key Areas of Discussion

- Quantity of CMC information in CTA / IND
- Sterile preparation
- Preparation at one site to be utilized at another
- EP for studies following completion of Phase 1
• 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.”
Sec. 210.2 Applicability of current good manufacturing practice regulations.

(c) An investigational drug for use in a phase 1 study, as described in 312.21(a) of this chapter, is subject to the statutory requirements set forth in 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or phase 3 study, as described in 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a phase 2 or phase 3 study or the drug has been lawfully marketed, the drug for use in the phase 1 study must comply with part 211.
Other Country Regulations

**EU**

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

**Singapore**

- No CM&C information provided to Health Sciences Authority

**Canada**

- 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
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
  – Multiple guidance documents available
• Sponsors are ultimately responsible
• Delivering drugs safely to patients must be top priority