Industry Perspective on Manufacturing in Early Development

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Early Development GMPs for Drug-Product Manufacturing of Small Molecules

An Industry Perspective (Part III)

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The authors, part of the International Consortium on Innovation and Quality in Pharmaceutical Development (IQ Consortium), explore and define common industry approaches and practices when applying GMPs in early development. A working group of the consortium aims to develop a set of recommendations that can help the industry identify...
Position Paper Highlights

• Scope
  – Solid-oral dosage forms, small molecules
  – Defined early development as Phase 1 – 2a
  – U.S. Focus initially, may expand to other regions in future

• Process
  – Review 2008 FDA Phase 1 CGMP guidance and 21 CFR 211 requirements
  – Conduct short survey to understand application of CGMP across companies
  – Provide industry perspective on CFR requirements related to manufacturing Investigation Drug Products in early development

• General Conclusions
  – Flexibility needed as product and process knowledge is limited in early development
  – Changes should be expected, scientifically justified and documented
  – Quality systems and risk-based decision making assure patient safety
  – FDA Phase I guidance recognizes the need for flexibility, but lacks specifics
  – IQ survey shows high variability in approach to application of GMPs in early development
Objectives

- Initiate dialog between industry and regulators to reach common understanding of stage appropriate CGMP
- Facilitate development of new drug products
- Ultimately bring the best drug products to patients as quickly and cost-effectively as possible
CFR Requirements

• Quality Systems
• Facilities and Equipment
• Raw Materials
• Batch Documentation and Execution
90% have different systems for commercial and R&D
50% have different requirements for early development
IQ GMPs in Early Development

*Relationships between material properties, process parameters and quality attributes are being developed.*

*CTS manufacturing is also development.*

*Process are not validated. Deviations should be expected and simply documented*
Quality Systems

• Most critical aspect of quality in early development is subject safety.
• Recommend use of Quality Risk Management tools to ensure subject safety is not compromised
Risk Management Tools in Early Development

Process Flow Map and Risk Analysis for Site Preparation

- **Process**: Released Active Blend
- **Subject Risks**: Product quality, Incorrect formula, Content uniformity – variable dose, Incorrect/Variable Dose
- **Controls**: Released Active Granules, Weigh/Sieve Ingredients, Blend Ingredients, Weigh Unit Dose, Program Tab Press Settings, Compress Layer 1, Compress Layer 2, Weigh and Visually inspect each tablet, Finished Tablet

**Adequacy of the specified blending process to provide content uniformity** will be confirmed by the tablet content uniformity test results from both the lab and the site pilot runs, using identical equipment and process for blending and tablet compression.
Facilities

• Traditional Pilot Plant manufacturing and release
  – Follows same quality systems, controls and requirements for all phases

• GMP area within a laboratory setting
  – Small-scale GMP applications such as preparation of radioactive substances of ADME

• On-site Dose Preparation (extemporaneous formulation)
  – An effective method to prepare early phase CTS for small single site studies
  – Underutilized approach for formulation optimization of more advanced dosage forms
    ■ Example – “on-site preparation” of extended release tablets to explore prototype formulations with varying release rate
    --Significant savings can be realized without compromising patient safety
    ■ IQ Extemporaneous Formulations Working Group
Extemporaneous Formulation

- Significant potential to speed formulation optimization
- 6 months or more for complicated formulations
- Significant savings of API and development resource costs
Equipment

• No differences in equipment requirements for early development
• Equipment may be simpler less automated but basic qualification, maintenance, calibration and cleaning requirements do not change
• Opportunities to simplify how CGMP requirements are met in early development
Raw Materials

- Buildings and Facilities
- Control of Materials
- Receipt and Approval
Raw Material Receipt and Approval

• Specifications
  – Compendial
    • Any compendia is acceptable (USP/NF, EP, JP)
  – Non-compendial
    • Vendor specification or Food Chemical Codex should guide specification setting
Raw Material Receipt and Approval

• Testing

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<tr>
<th>Question</th>
<th>% Response</th>
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<tr>
<td>In early development, does your company repeat vendor testing for excipients used in CTS manufactures?</td>
<td>10%</td>
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<td>70%</td>
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<td>20%</td>
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– If vendor is qualified, no need to repeat testing
– Qualification must occur before product release
  • Process should depend on stage of development and risk assessment
  • Could range from a questionnaire to a site audit
• Approval for Use

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<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Sometimes</th>
<th>Routinely</th>
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<tbody>
<tr>
<td>In early development, does your company manufacture GMP clinical trial supplies (CTS) prior to full release of the API?</td>
<td>40%</td>
<td>50%</td>
<td>10%</td>
</tr>
<tr>
<td>In early development, does your company manufacture CTS prior to completion of full release testing of excipients?</td>
<td>40%</td>
<td>30%</td>
<td>30%</td>
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– Ideally materials should be tested and released prior to starting manufacture

– Manufacturing “at risk” is acceptable as long as the risk is with the manufacturer and not the patient
Batch Documentation and Execution

• Batch record requirements:
  – Name Strength, Description
  – Quantitative composition (per unit)
  – Batch size, Manufacturing instructions

• Record should allow replication of the process

• Executed record must be approved by Quality.
  – Survey showed 100% also pre-approved

• Document room clearance prior start
Batch Documentation and Execution

• Hold Times
  – In early development there should be no requirement to establish hold times
  – Release testing confirms quality during early development – supports establishing hold time later
Batch Documentation and Execution

• Change Control
  – Changes to raw materials and processes are inevitable in development
  – Control is not needed as in late stage and commercial validated processes.
  – Changes simply need to be documented
Batch Documentation and Execution

• Yield
  – Yield should be calculated to further process understanding and enable optimization
  – Minimum tolerances should not apply
Conclusions

• Organizations must recognize process understanding is very limited at Phase 1 – 2a
• Quality systems must ensure patient safety but also need flexibility to handled unplanned changes
Conclusions

- Underutilized approaches exist to quickly and efficiently answer formulation questions related to bioavailability, pharmacokinetics or target release rates for CR formulations.
- More discussion on risks/benefits of these approaches is warranted.

Breakout Session: Extemporaneous Formulation
Conclusions

• Documentation of manufacturing should be phase appropriate. Early phase should not be overly prescriptive so as to restrict process changes or discourage sampling.

• Changes should be expected and be quickly reviewed and approved by qualified personnel.

Breakout Session: Risk management in DP Manufacturing with Emphasis on Batch Documentation/Execution.
Closing Remarks

• FDA Guidance considers early development as Phase 1
• Industry working groups consider Phase 1 – 2a more appropriate
  – Phase 2a clinical studies are still small and closely monitored
  – Logical break point at POC
  – Maximizes utility of guidance
• Applicability of Phase 1 Guidance ambiguity
  – Clearly applies to a Phase 1 study on a new entity
  – Significant debate on applicability to Phase 1 studies on new formulations

• If the spirit of the guidance is to foster phase appropriate CGMP, it should apply to Phase 1 studies on all new formulations
## IQ Member Company Survey

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<td>In early development, does your company manufacture CTS prior to completion of full release testing of excipients?</td>
<td>Never: 40%</td>
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<tr>
<td>In early development, does your company repeat vendor testing for excipients used in CTS manufactures?</td>
<td>Never: 10%</td>
</tr>
<tr>
<td>In early development, does your company require a vendor laboratory audit to accept materials on vendor CoA?</td>
<td>Yes: 30%**</td>
</tr>
<tr>
<td>Does the quality unit pre-approve CTS batch records?</td>
<td>Yes: 100%</td>
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<td>Do you feel your company's approach to handle deviations that occur during early development CTS manufacturing provides adequate flexibility?</td>
<td>Never: 60%</td>
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<td>Is a CAPA program applied to all early phase manufacturing exceptions?</td>
<td>Never: 55%</td>
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<tr>
<td>Is the quality system/requirements for R&amp;D different than what is used in commercial production?</td>
<td>Never: 90%</td>
</tr>
<tr>
<td>Is the quality system/requirements for early development CTS different than later stage (Phase 2b and beyond) development?</td>
<td>Never: 50%</td>
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