GMPs for Method Validation in Early Development: An Industry Perspective (Part II)

Pharmaceutical Technology
Volume 36, Issue 7, pp. 76-84

Henrik T. Rasmussen, Vertex Pharmaceuticals, Inc.
Industry Contributors: Analytical and QA

Donald Chambers, Merck Research Laboratories
Gary Guo, Amgen
Brent Kleintop, Bristol-Myers Squibb Co.,
Henrik Rasmussen, Vertex Pharmaceuticals, Inc.
Steve Deegan, Abbott
Steven Nowak, Abbott
Kristin Patterson, GlaxoSmithKline
John Spicuzza, Baxter
Michael Szulc, Bioden Idec
Karla Tombaugh, Merck & Co.
Mark D. Trone, Millennium Pharmaceuticals
Zhanna Yuabova, Boehringer Ingelheim Pharmaceuticals
• Rationale for reduced validation during early clinical phases (pre-phase IIb)
• Validation vs. qualification
• ICH Q2 – Differences and similarities
• Generic or general methods
• In-process testing methods
• Genotoxic Impurities
• Documentation
Considerations and Drivers for Reduced Validation

- Ensure patient safety
- Maintain suitable quality standards
- Leverage existing guidelines
- Aligned with product/process knowledge
- Improve lead-time to FIH
- Reduce development costs

Goals: Clarify expectations for Phase I – Phase IIa (i.e. during acute dosing). Harmonize inter-company approaches.
Validation vs. qualification

• Validated methods are required only for release testing and stability testing of clinical materials (drug substance and drug products) against Specifications.

• Qualified methods are reliable experimental methods intended to generate scientific understanding. Qualified methods are used for characterization of reference standards, prediction of shelf-life, etc.
Early vs. late development: Similarities

• At all development stages methods must collectively:
  – Ensure that the correct dose is delivered in the clinic.
  – Provide a known impurity (synthetic impurity and degradation product) profile.
  – Allow for evaluation of drug release and content uniformity.
  – Allow for understanding physical form
Early vs. late development: Differences

• Drug substance synthetic routes are at small scale using non-optimized chemistry. Impurity profiles may vary batch-to-batch.
• Drug product formulation and manufacturing are not representative of the commercial image and process.
• Method transferability is frequently not of major concern.
• Methods change to accommodate route and formulation revisions.
<table>
<thead>
<tr>
<th>Validation parameter</th>
<th>Identification</th>
<th>Assay</th>
<th>Impurity (quantitative)</th>
<th>Impurity (limit test)</th>
<th>Physical tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early Phase</td>
<td>Late Phase</td>
<td>Early Phase</td>
<td>Late Phase</td>
<td>Early Phase</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major component</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Forced degradation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Known impurities/excipients</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>+^1</td>
<td>+^1</td>
<td>+^3</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Precision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeatability</td>
<td></td>
<td></td>
<td>+^3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intermediate precision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limit of quantitation</td>
<td></td>
<td></td>
<td>+^3</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Limit of detection</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Linearity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main component</td>
<td>+^2</td>
<td>+</td>
<td>+^2</td>
<td>+</td>
<td>+^2</td>
</tr>
<tr>
<td>Impurities</td>
<td>+</td>
<td>+</td>
<td>+^3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Range</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method Robustness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solution stability</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Method parameter variation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Note: 1 refers to drug product analysis only. 2 is linearity derived using fewer standards than late-phase validation. 3 is determined using the API as a surrogate.
• No significant validation differences for early phase vs. late phase.

• Specificity is challenging in early phase:
  – Knowledge regarding related substances is limited
  – There are frequently a larger number of related substances
  – Related substances may change lot-to-lot
Differences: Accuracy

- Less levels and less replicates are evaluated
- Broader acceptance criteria are used (consistent with broader specifications)
- Accuracy for impurities is evaluated using the API at the impurity specification limit(s) as a surrogate.
Differences: Precision

• Injection repeatability and analysis repeatability are performed. Intermediate precision and reproducibility are not evaluated.

• Less levels and less replicates are evaluated.

• Broader acceptance criteria are used (consistent with broader specifications).

• Repeatability for impurities is evaluated using the API at the impurity specification limit(s) as a surrogate.
Differences: LOD and LOQ

- API is used as a surrogate for impurities.
- LOD and LOQ are determined as “practical limits” vs. “measured limits”.
- An acceptable signal-to-noise ratio is obtained at the lowest level of interest (i.e. S/N > 10 at the Reporting Threshold).
Differences: Linearity

• Less levels are evaluated for both API and impurities.
• Broader acceptance criteria are used (consistent with broader specifications)
• Linearity for impurities is evaluated using the API at impurity levels as a surrogate.
Differences: Robustness

• Solution stability is evaluated
• Systematic variation of method parameters is not performed.
**Generic methods**

- Are evaluated or qualified to demonstrate suitability:
  - FTIR (identification)
  - KF (water)

or

- Are validated once for parameters that are compound independent:
  - GC (residual solvents)
In-process testing methods

- Used to establish knowledge
- Not used as a control
- Testing is not against specifications

Method qualification is suitable for demonstrating method performance
Genotoxic Impurities

• Methods used for assessment are qualified
• Methods used for control against a specification are validated

Methods need to meet TTC limits: Higher control limits are possible during acute dosing studies.
• Data: Full and complete audit trail (ideally using ELN)
• Protocols: Methods are validated against pre-established guidelines (Best practices, plan outlined in ELN). Formal protocols are not necessary.
• Reports: Formal method development and validation reports are not needed. Audit trail provides details required for regulatory filings and Change Control.
• Quality Systems and oversight of validation activities are provided by Analytical Departments. QA oversight focuses on late phase activities.
Conclusions

• Due to limited knowledge in early development, scientific flexibility is required to address key issues.

• Appropriate method risks align with early clinical study designs (acute dosing, SAD, etc.), limited toxicology, broader specifications, and limited process knowledge.

• Inter-company and Regulatory harmonization will facilitate filings and accelerate drug development.