Regulatory Perspective on Analytical Method Validation During Product Development

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Outline

1. Analytical method development
2. Life cycle management of analytical methods
3. Method qualification vs. method validation
4. Regulatory considerations for changes to analytical methods during early clinical phases
5. Case studies and lessons learned
Analytical Methods

• In scope for this talk
  – methods that assess physico-chemical properties of a product (e.g.: primary, secondary, tertiary structure), glycosylation, charge, size variants, post-translational modifications, process-related impurities (MS, CEX, IEC, HILIC, IEF/cIEF, RP, SEC-HPLC, SDS/CE-SDS) during clinical development

• Out of scope
  – biological assays (BA, BE, PK, immunochemical assays)
  – product lifecycle and analytical methods post-approval
  – biosimilars
Method Lifecycle
(similar concept to process validation)

Stage 1 – Assay Design: The assay is defined during this stage based on knowledge gained through development activities.

Stage 2 – Assay Qualification: During this stage, the assay design is confirmed as being capable of producing reproducible results suitable for the specified purpose. Scientifically sound work in progress.

Stage 2 ½ - Formal Assay Validation Study: The assay is tested against specific acceptance criteria set to verify that the performance characteristics of the final method are suitable and reliable for the intended applications.

Stage 3 – Continued Assay Verification: Ongoing assurance is gained during routine production that the assay remains in a state of control (system suitability, assay suitability, trending of results, OOS, etc.).

Courtesy of Sarah Kennett
Method development vs. clinical development

**Pre-Clinical**
- Selection
- Development
- Optimization

**Phase 1**
- Qualified methods
- Set preliminary release/stability acceptance criteria

**Phase 2**
- Optimization/qualification
- Refine lot release criteria
- Set validation acceptance criteria
- Define/initiate assay validation parameters

**Method**
- Develop
- Implement
- Qualify
- Validate
- Review
- Optimize

**Post-Licensure**
- Trend analysis
- Performance review
- Methods replacement

**Phase 3**
- Full assay validation (strongly recommended for phase 3)
Qualification vs. Validation

• Assay Qualification:
  Determining whether an assay is suitable for its intended purpose
  – Limited pre-determined performance criteria

• Assay validation
  Assuring the assay is suitable for its intended purpose on a routine basis.
  – Pre-defined assay performance criteria.

Note: development of sensitive and precise assays for characterizing the product as early as possible. Why?

To support manufacturing changes. If changes to quality attributes occur (e.g., new manufacturing facility, new container closure system), the more that is known about the quality attributes the better able one can assess the risk to the safety and efficacy of the product.
Analytical Method Qualification

- Qualification studies will identify/refine method performance capabilities such as specificity, linearity, accuracy, precision, robustness, stability etc. where applicable
- Provides a sufficient foundation for the development of a scientifically sound validation protocol
- Limited pre-determined method performance specifications
- A method cannot fail qualification; it gets re-optimized until it can achieve acceptable performance or it is rejected for the intended application
Analytical Method Validation

• Validation trials are run according to an established validation protocol
• Method performance specifications are pre-established, documented, and confirmed during validation trial
• These specifications must be met by every validation trial
• A method can fail validation; if it does, assignable cause for the failure must be investigated, resolved, and the assay re-validated
What Assays Need to be Validated

• Regulatory (Compendial): Procedures used to evaluate a defined characteristic of the drug substance or drug product that are legally recognized under 21 USC 501(b) (USP/NF). Generally, will need no or only partial validation (e.g., need to be verified for use).

• Alternative (Non-Compendial): Procedures proposed by the applicant for use instead of or in addition to the regulatory analytical procedure. Generally, will need full validation.

• Stability: Procedures that can detect changes with time in the pertinent properties of the drug substance and drug product will need full validation unless they fall under regulatory.
Pre-Phase 1

• Identify the purpose of the analytical method (characterization/release) and all critical quality attributes (CQAs)

• Select the appropriate analytical method aligned with CQAs and development objectives (the method should be fit for use)

• Identify the process steps associated with the method

• Determine specification limits associated with testing of preclinical lots (initiate stability testing to support first-in-human clinical trials)

• Perform a risk assessment as to where assay development is needed and what may influence robustness and stability
Phase 1 INDs

- Analytical methods for characterization, release, and stability testing *to ensure safety*

- Inclusion of methods should be based on product knowledge, early assessment of critical quality attributes, process knowledge, risks associated with immunogenicity, mechanism of action

- Provide information on purity of the product

- During product- and process-development activities, methods should be scientifically sound (e.g., specific, sensitive, and accurate) and provide results that are reliable. FDA Process Validation Guidance, 2011
Assay Validation During Product Development

- FDA Process Validation Guidance (2011)
  - “Validated analytical methods are not necessarily required during product- and process-development activities or when used in characterization studies.”
  - “…analytical methods should be scientifically sound (e.g., specific, sensitive, and accurate) and provide results that are reliable.”
  - Clinical supply production should follow the CGMPs appropriate for the particular phase of clinical studies.

- **Interpretation:**
  Review staff focus on the adequacy of non-compendial safety tests for early phase clinical supply material
Phase 1 INDs

• Information to support analytical methods
  – Description of method
  – Results of analyses, quantitative and qualitative
    • Gels, chromatograms, electropherograms
  – Summary of information or data collected on method performance can be provided but not required
Guidance for Industry
Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies [...]

[...] Validation data and established specifications ordinarily need not be submitted at the initial stage of drug development. However, for some well-characterized, therapeutic biotechnology-derived products, preliminary specifications and additional validation data may be needed in certain circumstances to ensure safety in Phase 1.
Guidance for Industry
Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies […]

• Interpretation:
  Review staff focus on the adequacy of non-compendial safety tests for early phase clinical supply material. Depending on the method development strategy, validation data may be available and could be requested. Typically method validation data are not available and if the regulatory agency request method validation data, qualification data could be provided instead.
Expectations For Methods During Product Development

• Ensure safety of the product
• Assay provides meaningful results
• Assurance that analytical information gained in development can be reliably related to commercial manufacturing
• Determine method performance capabilities including specificity, linearity, accuracy, precision, robustness, and stability
Product Development Phase

• Product Characterization
  – Orthogonal methods to ensure product variants are identified and characterized
  – Isolate product variants to assess activity, determine potential to impact safety and efficacy

• Degradation Pathways
  – Stability indicating assays should be identified
  – Physico-chemical methods can be more sensitive to some degradation pathways than activity/bioassays

• Comparability Analyses
  – Methods selected should take into consideration stage of development and the extent of manufacturing changes
Information to support methods during development

• Description of method

• Summaries of method performance can be provided (typically not required)
  – Can be useful to support investigations into unexpected quality results
  – When introducing novel methods not previously utilized for product characterization or control

• Validation of analytical methods not typically required or expected during development
Guidance for Industry
INDs for Phase 2 and 3 Studies

• Phase 2

[...] The analytical procedure used to perform a test and to support the acceptance criteria should be indicated (e.g., HPLC). A complete description of the analytical procedure and supporting validation data should be available on request.

Interpretation:
Depending on the method development strategy more validation data could be available and, if needed, should be available upon request. If method validation was not performed yet, relevant qualification data should be available.
Product Development (Phase 3 Studies)

• Validation of analytical methods is expected during this stage of product development

• Validation reports for release and stability methods not required to be submitted to the IND
  – Biological assay e.g. immunogenicity assays validation could be requested during IND stage

• Analytical methods are used for:
  – Support manufacturing development, characterization studies, release testing of clinical batches, stability testing, comparability
Product Licensure

- Support for inclusion/exclusion of methods in the control strategy
- Detailed method descriptions for release and stability methods
- Validation reports for release and stability methods (FDA Method Validation Guidance, 2015)
  - Specific for type of sample (in-process, release)
  - Appropriate samples for stability indicating methods
- Characterization methods
  - Information to support the method is fit for the intended purpose
Analytical Method Transfer During Product Development

• Comparative testing: Both originating and receiving labs participate in method transfer exercise. Results are compared to pre-defined acceptance criteria

• Co-validation: The receiving laboratory participates in the initial method validation activities

• Method validation or revalidation: Complete or partial validation is performed by the receiving laboratory
Retain samples

- Manufacturing changes are common in Biotech
- Should link critical quality attributes to those found in the clinical trial material
- Make sure retain samples are stored under appropriate conditions to ensure stability (e.g.: -70°C)
- Retains are critical during analytical assay development - as technologies improve they may detect things not seen with older assays. Retain samples allow you to determine if they were always present.
- Retain samples used in comparative studies should include samples that represent, when possible, pivotal clinical trial material
Case Study #1: Method Transfer During Product Development

• Phase 2/3 IND amendment – new site for drug substance manufacturing and DS and DP testing
• Transfer of several stability-indicating purity (RP-HPLC, SEC-HPLC, SDS-PAGE) and potency assays was found unacceptable
• Transfer data only included evaluation of the main peak/band and did not include aged or spiked samples to demonstrate that the transferred methods are capable of detecting and quantifying impurities at comparable levels between the sites
• The clinical study continued as sufficient material was available; new material was used after successful site transfer was demonstrated
Case Study #2: Change in Analytical Method During Development

- Late phase of clinical development – change in purity method used for quality control testing (release, stability)
- New testing site but no method transfer data (new method validation data provided)
- Old method used for:
  - Release, stability (including PPQ lots) and in-process testing
  - Proposed commercial specifications
- New method proposed for commercialization
- The sponsor was advised to perform a bridging study using release and stability samples (including accelerated and forced degradation conditions)
- Lack of the bridging data led to a delay in product approval
Case Study #3: Method Transfer During Product Development

- Phase 2 IND, type B meeting – changes to drug substance manufacturing process (new MCB, scale and purification process) and new testing site
- The sponsor planned to use the new material during the phase 2; however, new testing site was introduced around the same time and no bridging data was available
- Not enough product to initiate the phase 2 studies
- The sponsor was advised to provide transfer of analytical procedures data along with comparability data for phase 1 and phase 2 clinical materials before the initiation of the phase 2 clinical study.
Case Study #4: Phase 1 Potency Assay Provided Highly Variable Results

- New IND – The proposed antigen binding ELISA potency assay used for release and stability testing of drug substance and drug product is not in sufficient control to ensure a consistent measure of potency of the product.

- Due to issues with the potency assay and with the potency acceptance criteria, the IND was placed on partial hold, allowing the use of the current lot of DP in the proposed clinical trial but requiring additional information prior to allowing the use of subsequent lots.
Case Study #4 (continued)

- Two separated testing sites were used for DS release and stability and DP release and stability testing.

- In the IND submission the sponsor referred to a “validated potency assay”. FDA Information Request (IR): “Provide the potency assay validation protocols used to generate the variation, repeatability, and intermediate precision data[...].”

- Method qualification data from one testing site and validation data from the other testing site were provided and reviewed by the FDA. After assay optimizations the results were consistent and the hold was lifted.
Summary

• Development and validation of the analytical procedures used for testing product quality during product development is a continuous and evolving process and different strategies are available

• FDA strongly recommends validating analytical methods by phase 3; FDA can request assay validation data at any stage of product development but validation data are not required to be submitted until BLA

• Early assay development provides many benefits (e.g., greater understanding of the products critical quality attributes allows more effective product development)

• Retention samples should be collected and appropriately stored to allow for comparative studies