



Analytical Method Validation in Early Drug Development – US FDA Perspective

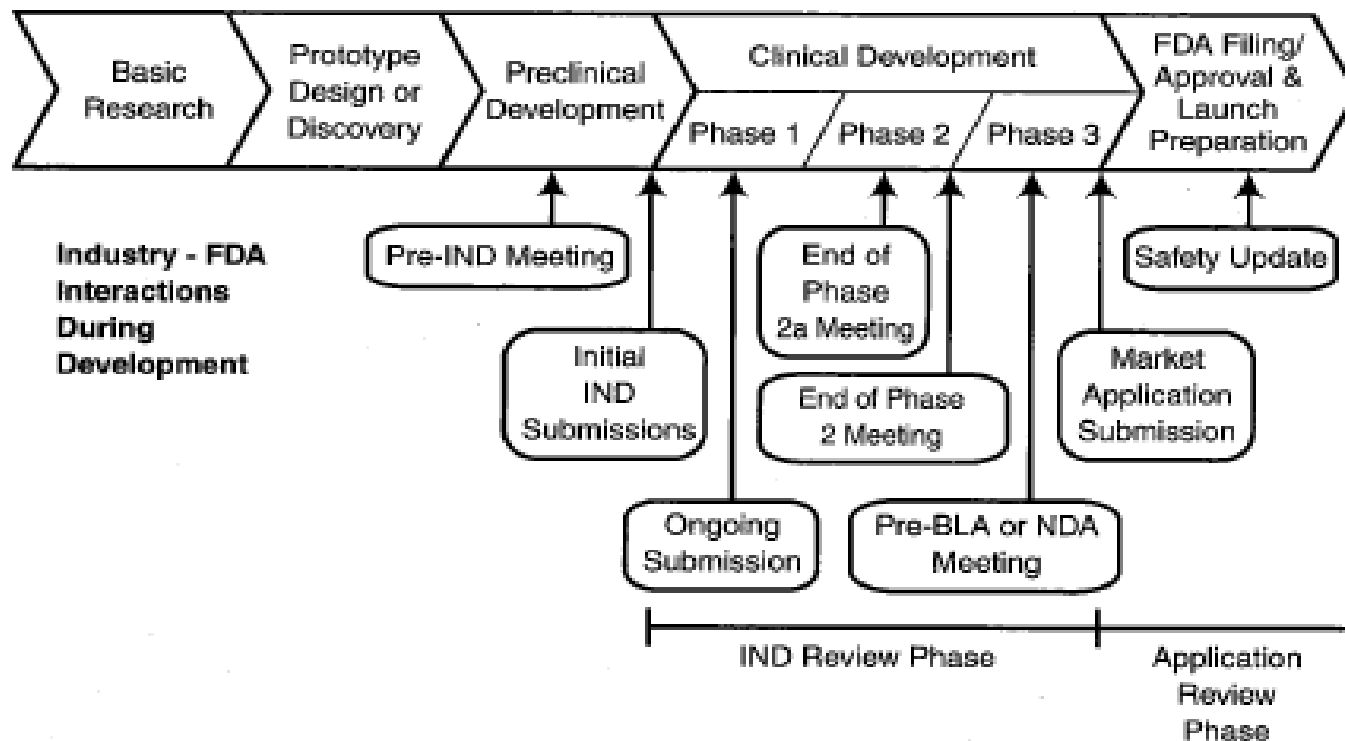
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Early Development
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Discussion Topics

- Background
- Share thoughts from CMC Reviewers and Investigators on
 - Method Validation
 - Documentation
 - Data Storage

Industry-FDA Interactions



Pharmacokinetics

Acceptance

**In-Process
PAT**

Release

Analytical Procedures



Cleaning Validation

Stability

Expiration Dating Period

21 CFR 312.23(a)(7)

- Amount of information on analytical procedures and methods validation necessary will vary with the phase of the IND
- Sufficient information to ensure proper identification, quality, purity, strength, and/or potency

Analytical Validation

- Validation is not a one-time study to fulfill agency filing requirement
- Perform during development of the analytical procedure and with procedure changes
- Extent of validation depends on the application stage and type of procedure
- Procedure dependent
- Appropriate validation parameters should be addressed

Validation vs. Qualification

- Based on the concepts of analytical validation in previous slide, the need to differentiate between qualification and validation as used for IND vs. NDA/BLA/ANDA test procedures is unnecessary
- Qualification is commonly used in “qualification of critical equipment and ancillary systems” with activities for DQ, IQ, OQ and PQ as in ICH Q7, Section XII.C (12.3) Qualification

ICH Q7

- “analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated” per ICH Q2R1, “they should be scientifically sound”*.
- Test procedures should be reliable to support clinical studies
- Use appropriate parameters and sound scientific judgment

* ICH Q7, Section XIX.H (19.8) Laboratory Controls

Validation Parameters

- IND is to evaluate safety of the product
- The API manufacturing process and the dosage form may be evolving/improving
- The validation parameters may be reduced during early development with gradual addition as the IND proceeds to an ANDA/BLA/NDA
- Validation data should be retained to link analytical procedures used in early phase/pivotal clinical studies to commercial product

The objective should be a procedure to produce reliable data to support clinical studies

Specificity & Accuracy

- Understand the API and the potential degradation pathway
- Parent compound should be resolved from process and degradation impurities
- Process impurities may change due to change in manufacturing process
- Dosage form may change during development
- Specificity aims for compound of interest to be totally resolved from all other compounds

Specificity & Accuracy cont'd

- Accuracy aims to be on target
- Accuracy of the assay could be compromised
 - if API not resolved from process & degradation impurities in the drug substance
 - If compound of interest not resolved from impurities and excipients in the drug product

Specificity and accuracy should be addressed

Precision

- Aim for tightness of data generated for reliability
- Includes repeatability, intermediate precision and reproducibility
 - Injection repeatability is a measure of the performance of the equipment
 - Analysis repeatability is a measure of the performance of the method as handled by the analyst

Both required to support reliability of method

Precision cont'd

- Intermediate precision to minimize variation on different days, analysts, and equipment
- Reproducibility to minimize variation between laboratories or locations

During the development stage, the data are collected by limited personnel. Thus, these are not necessary studies

Quantitation Limit (QL) & Detection Limit (DL)

- Apply to impurities method
- QL defined as the lowest concentration of analyte that can be determined with acceptable precision and accuracy under stated experimental conditions
- DL is the lowest concentration of analyte detectable

Determined to evaluate the capability of method for impurities testing

Linearity

- The assay should be performed in the linear dynamic range of detector
- Whether assay for API or preservative, the external reference standard used should be close in concentration.
- Impurities may not be known structurally or available

Linearity is not a critical parameter in early phase

Robustness

- Defined as “a measure of the procedure’s capability to remain unaffected by small, but deliberate variations in procedure parameters”
- Performed during method development and/or validation
- The more conditions without any effect on procedure, the more robust and reliable is the procedure

Generally not important in Phase 1 and 2 studies but may become important for later, larger-scale IND studies

System Suitability Testing for Chromatographic Procedures

- USP <621> Chromatography
- Important for ensuring reliability of such procedures
- Use appropriate tests for assay and impurities procedures

Genotoxic Impurities

- Genotoxic impurities are controlled at low levels
- Testing should demonstrate that the procedure has the necessary reliability and sensitivity for the detection of these impurities at low levels

Genotoxic Impurities cont'd

Useful references include:

- Guideline on the Limits of Genotoxic Impurities (EMA guideline), June 2006 (<http://www.emea.europa.eu>)
- FDA Draft Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, December 2008
- ICH M7, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, Step 2, February 2013

Compendial Procedures

For APIs with compendial monographs, validation can be met as described in <1226> Verification of Compendial Procedures

Data Documentation

- Formal validation report with change control may not be required
- A brief summary of the validation studies is recommended to be submitted in the original IND

Data Storage

- All data collected shall be stored in a safe and secure environment
- “retain the records and reports .. for 2 years after a marketing application is approved for the drug; or, if an application is not approved .. until 2 years after ... investigational use is discontinued and FDA has been so notified”*

* 21 CFR 312.57(c)

Data Availability

- FDA inspections are considered for Treatment INDs* and
- “For cause” inspections can occur for other INDs.

* MAPP 6030.6 INDs: Processing Treatment INDs and Treatment Protocols, Attachment A: Treatment IND/Protocol Review Timetable

Data Availability cont'd

- Developmental data, though not commonly evaluated by investigator, shall be available. The sponsor shall grant FDA, upon request, “access to and copy and verify any records and reports relating to a clinical investigation”*

* 21 CFR 312.58 (a)

Summary

- Understand the API and the dosage form of the product
- Design the procedures to achieve the purpose and the claim
- The level of validation can be reduced
- Use sound scientific judgment
- Objective is to provide reliable data to support the clinical studies

Where to Obtain Guidances

CDER Home Page at

<http://www.fda.gov/cder/guidance>

References - FDA

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products (November 1995)
- INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing, and Controls Content and Format (May 2003)

References – FDA cont'd

- FDA Reviewer Guidance – Validation of Chromatographic Methods, November 1994
- FDA Draft Guidance for Industry – Analytical Procedures and Methods Validation, FR August 2000
- FDA Draft Guidance for Industry -Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, December 2008
- MAPP 6030.6 Processing Treatment INDs and Treatment Protocols

References - ICH

- Q2(R1): Validation of Analytical Procedures: Text and Methodology (November 2005)
- Q7 : Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (November 2005)
- M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, Step 2, February 2013

References - USP

USP/NF General Chapters and other references are not available through the CDER Home Page website

- USP General Chapter <621>
Chromatography
- USP General Information Chapter <1226>
Verification of Compendial Procedures

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