Analytical Procedures and Method Validation

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Outline

- Background: role of analytical science
- Final Guidance on Analytical Procedures and Method Validation for Drugs and Biologics

Desired State: A Mutual Goal of Industry, Society and Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.

-Janet Woodcock, October 5, 2005

- Robust, innovative analytical science is the backbone assuring high quality drugs

Use of Analytical Science in Product Control Strategy

Raw Material Testing	• Linking RM specifications to product quality attributes • Effect of variability, including supplier variations, on process is understood
In process Testing	• Real time (at-, on-, or in-line) measurements • Enable manufacturers to actively control process to minimize product variation • Set acceptance criteria based on multivariate process understanding
Release Testing	• Confirm the control of material attributes and process inputs (Design Space) • Specification based on patient needs (quality, safety, efficacy, performance)
Stability Testing	• Predictive models at release to minimize stability failures • Monitor desired product performance with time

Analytical Testing and Continual Process Improvement

Process learning does not stop at product launch!

- Product and Process Tracking and Trending
  - Find and correct process drifts before they become problems
  - Can include both routine and non-routine analysis
- Non-routine analysis
  - Evaluation of product quality on periodic and/or risk basis (e.g. upon process changes)
  - Can use non-traditional analytical techniques not typically used for routine release testing (e.g., LC-MS, NMR)
  - Performed under firm's quality system

Final Guidance for Industry issued July 2015

- Supersedes the 2000 draft guidance for industry on *Analytical Procedures and Methods Validation,*
- Replaces the 1987 FDA guidance for industry on *Submitting Samples and Analytical Data for Methods Validation*,
- Complements ICH Q2(R1) Validation of Analytical Procedures.

Guidance applies to:

- New Drug Applications (NDAs)
- Abbreviated New Drug Applications (ANDAs)
- Biologics License Applications (BLAs)
- Supplements

Guidance Contents

I/II. Introduction/ Background

III. Analytical Methods Development

IV. Content of Analytical Procedures

V. Reference Standards and Materials

VI. Analytical Method Validation

VII. Statistical Analysis and Models

VIII. Life Cycle Management of Analytical Procedures

IX. FDA Methods Verification

X. References

III. Analytical Method Development

- Choice of analytical instrumentation and methodology based on the intended purpose of the method
- Risk assessment
- DOE to understand factorial parameter effects on method performance
- Understand sources of variation

IV. Content of Analytical Procedures

- Description should be in enough detail to allow a competent analyst to reproduce the method
- FDA recognized sources can be referenced if procedure is not modified:
  - USP/NF
  - AOAC
- Essential information to be included in an analytical procedure includes…

IV. Content of Analytical Procedures: Essential Information

- Principle/Scope
  - Principles of test, target analyte and sample type
- Apparatus/Equipment
- Operating Parameters
  - Optimal settings and ranges critical to the analysis
- Reagents/Standards
  - Grade, source, state, storage controls, shelf life
- Sample Preparation
  - Procedures, replicate preparations for quantitative tests, stability and storage conditions

IV. Content of Analytical Procedures: Essential Information (cont.)

- Standards and Control Solution Preparations
  - Stability and storage conditions
- Procedure
  - Enough detail to allow a competent analyst to reproduce the method!
- System Suitability
  - Ensure system (equipment, electronics, analytical operations) will function correctly
- Calculations
  - Include representative calculations, justification for correction factors
- Data Reporting
  - Format to report results (including significant figures)

V. Reference Standards and Materials

- Suitable for use
- Characterized by orthogonal methods including routine and beyond routine testing (ICH Q6A)
- Biological products reference standard information should be in BLA and annual reports
  - Where applicable reference standards authorized by CBER must be used
  - Two tiered approach when qualifying new reference standards to prevent drift

VI. Analytical Method Validation

- Noncompendial: Follow ICH Q2(R1)
  - Specificity
  - Linearity
  - Accuracy
  - Precision (repeatability, intermediate precision and reproducibility)
  - Range
  - Quantitation Limit
  - Detection Limit
- Compendial: Verify under conditions of use

VII. Statistical Analysis and Models

- Ensure appropriate statistical methods are used (i.e. may need to demonstrate data are normally distributed)
- Statistical power and range for model development and validation should be considered
- Vary model parameters to test model robustness

VIII. Life cycle Management of Analytical Procedures

When should a method be changed or revalidated?

- Trend analysis to evaluate method performance suggests method is not optimal
- System Suitability becomes difficult to meet
- New product knowledge
- Change to product formulation or manufacturing
- Availability of new technologies

When would a comparability protocol be needed?

- Alternative analytical procedure
- Transfer of an analytical method

Alternative Analytical Procedures

NDA or ANDA: propose the alternative analytical procedure in the application during filing or put in the next annual report for approved products

BLAs: additions or revisions of analytical procedures may require a supplement

Perform a comparability study that demonstrates:

- New method coupled with additional control measures is equal or superior to the original method for the intended purpose
- New method is not more susceptible to matrix effects

IX. FDA Methods Verification

- FDA laboratory may determine whether a procedure is acceptable for QC and regulatory purposes
- FDA laboratory will send request for samples and supplies
- Laboratory results and comments will be forwarded to the product quality reviewer

IX. FDA Methods Verification: Frequent Comments to Reviewers

- Missing stability (hold time) information for prepared samples or standards
- Need for a method blank when determining impurities
- Observed relative retention time of impurities does not closely match method
- Incomplete method description
  - Mobile phase description
  - Sample preparation
  - No or minimal system suitability (SS) requirements
- Column or detector over load causes chromatography problems.

IX. FDA Methods Verification:Frequent Comments to Reviewers (cont.)

- Materials used in method have unique properties: Only some lots or manufacturers will work
- LOQ sample does not meet S/N specification for system suitability
- Method LOQ is above specification limit
- Unidentified peaks
- Resolution and/or theoretical plates difficult to meet for system suitability

Conclusions

- Analytical science plays an essential role
  - Supports product and process development
  - Enables advanced control strategies like PAT and RTRT
- The new guidance provides current thinking on development and validation of methods
- Some regulatory flexibility for analytical methods is currently available
  - USP
  - Alternative analytical methods

Thank you

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