



# Analytical Methods Transfer Considerations for Biological Products

Alfred V. Del Grosso, Ph.D.

FDA – CBER

Office of Compliance and Biologics Quality  
Division of Biological Standards and Quality Control (DBSQC)  
Lab. of Analytical Chemistry and Blood Related Products

# CBER - OCBQ – DBSQC- LACBRP

## Division of Biological Standards and Quality Control

### LACBRP/ Analytical Chemistry, Blood Related Products

- Product Control Testing
- Vaccines, Blood Products, Allergenic Extracts, Allergen Patch Tests
  - Lot Release
  - New Product Approval: Biologics License Applications (BLAs) and Supplements
- Methods Development and validation
- Qualification of CBER Standards
- Regulatory Reviews – Analytical Methods
  - BLAs, Supplements, Masterfiles, INDs

# Methods Transfer

## Relevant cGMP Drug regulations

- CFR 211.160 Change in laboratory control mechanisms shall be ... reviewed by the quality control unit ... and shall be documented at the time of performance.
- CFR 211.194 (a) (2) Suitability of all testing procedures shall be verified under actual conditions of use.

## 21CFR 601.12 Changes to an Approved Application

- 601.12 (a)(1) An applicant must inform the FDA, through submission of a **supplement** to the original license application, about changes in the product, production process, **quality controls** or labeling established in the approved license application.
- (2) Before distributing a product made using a change, an applicant must assess the effects of the change and demonstrate through **appropriate validation** and/or other clinical and/or non-clinical laboratory studies the **lack of adverse effect** of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

## 21CFR 601.12 Changes to an Approved Application

601.12(b)(3) Changes to an Approved Application

- (i) A detailed description of the proposed change
- (ii) The products involved
- (iii) The manufacturing site(s) ...
- (iv) A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, purity, or potency of the product as they may relate to the safety or effectiveness of the product

# Definition of Method Transfer

- USP <1224> Transfer of Analytical Procedures

“The transfer of analytical procedures (TAP), is the documented process that qualifies a laboratory (the receiving unit), thus ensuring that the receiving unit has the procedural knowledge and ability to perform the analytical procedure as intended”.

# Transfer Types

- R&D to QC Laboratories
- Site transfer
- QC to Contract laboratory
- Regulatory Agency to QC Lab.
  
- Methods transfer versus Method adoption
  - Method Transfer involves active cooperation between originating and receiving labs.

# Transfer Protocol

- Developed with involvement of originating and receiving labs
- Roles and responsibilities clearly defined
- Transfer study design, number of samples, parameters to be evaluated, acceptance criteria



# Transfer Protocol Components

- Equipment
  - Instrumentation used in transfer
  - Differences between laboratories
  - Any Procedural modifications
- Reference Standards used
- Acceptance Criteria
  - Explicitly state criteria to be met
    - Accuracy and variability
  - Assay acceptance criteria, including system suitability

# Transfer Protocol Components

- Personnel and training
  - Specific staff, both originating and receiving labs
  - Specific training and qualification to be performed prior to transfer
- Deviation policy and reporting
  - Unanticipated changes in protocol, failure to meet criteria.
- Definition of oversight and approval authority
  - Receiving lab management, QA oversight
  - Final approval authority

# General approaches to Transfers

- **Comparative testing**
  - Validated procedures
  - Study of assay comparability
- **Co-validation**
  - Both labs part of original validation team
- **Revalidation**
  - Receiving lab re-evaluates at least some of the analytical characteristics appropriate for the type of test
- **Transfer waiver** – simple, non-complex methods, e.g. pH, osmolality

# General approaches to Transfers

- Comparative testing / Partial Revalidation
  - Demonstration of Comparability
  - Establish suitability of method and laboratory capability through performance verification
  - Evaluation of appropriate analytical characteristics, especially precision (Repeatability / Intermediate)

# Post-Approval Change Reporting Categories

- Reporting Categories for Changes – Risk Based
  - 601.12(b)(1) **Substantial potential** for adverse effect on the product
    - Prior Approval Supplement (PAS)
  - (c) (1) **Moderate potential**
    - “Supplement – Changes Being Effected in 30 Days” CBE-30 or CBE
  - (d) (1) **Minimal potential**
    - Annual Report

# Factors in Risk Assessments

- Experience with product
  - Manufacturing, testing history, consistency
  - Relevant product specifications, test performance history
  - Analytical robustness, ruggedness over time
  - Test criticality with respect to Critical Quality Attributes (CQAs)
- Procedural complexity
  - Analytical robustness, ruggedness over time

# Factors in Risk Assessment

- Procedural consistency
  - Identical test method
  - Slight modifications to test method
    - e.g. minor adaptations to new instrumentation
    - Impact may need evaluation
  - Major modifications to test method (new procedure)
    - Full validation would be required

# Comparative Testing

- Testing of samples from same product lots by both labs. Acceptance criteria and variability are established in protocol.
- Considerations: Number of lots required
  - Risk based: Usual minimum 3.
  - Complexity and Criticality: If a statistical approach is needed a larger relevant number of samples will be required.
  - Statistical approaches and acceptance criteria.



# Approaches to Equivalency

- Comparison of Means: Testing of a defined number of batches / lots by both procedures.
  - Pre-acceptance criteria for average % difference
  - Acceptance criteria for %RSD of % difference
  - Acceptability: Relate to Product Specification and historical batch results
- Confidence Interval Method
  - Calculate confidence interval for difference in means
  - Acceptability: Compare to acceptance range as specified *a priori* in protocol

# Statistical Approaches to Equivalency

- *t*-test for statistical significance of difference in averages by two methods
  - Calculate confidence interval – Equivalence is demonstrated if it contains zero
  - Even if significant statistically, non-equivalence may meet acceptance criteria for practical requirements of method as related to quality attribute measurement and product specifications
- Reference USP <1010> Analytical Data – Interpretation and Treatment

# Co-validation

- Typical for transfer of new method from R&D
  - Receiving lab participates in evaluation of some validation characteristics, typically Intermediate precision, Quantitation limit and Accuracy

# Revalidation

- Complete or partial validation. Complete validation required if the transfer results in a substantial change in procedure, as evaluated on a risk basis.
- Partial revalidation of some validation characteristics, e.g. repeatability, intermediate precision, linearity may be appropriate along with comparative testing.

# Validation Characteristics for Receiving Lab

Method Type	Risk Evaluation	Characteristic Recommendations
Colorimetric Protein (Lowry)	Low	Precision (repeatability, IP) Linearity Accuracy
Gel Methods (SDS-PAGE)	Moderate	Precision (repeatability, IP) Linearity, LOQ Accuracy Specificity
HPLC (SEC, RPLC)	Moderate	Precision (repeatability, IP) Linearity, LOQ Accuracy, Specificity, Robustness
Potency (Immunogenicity, Cell Based)	High	Precision (repeatability, IP) Linearity, LOQ Accuracy, Specificity, Robustness

# Potential Receiving lab issues

- Instrumentation differences
  - Gradient chromatography- dwell time
- Training: analyst experience with technique
- Reagents
- Different Software
  - Data acquisition, integration parameters

# Common Issues

- Unrealistically tight acceptance criteria
  - Precision, Linearity
  - LOQ or LOD specification
    - Often instrumentation dependent
- Overly broad acceptance criteria
- Insufficient number of samples or data to establish satisfactory transfer

# Common Issues

- Failure to identify bias between labs
- Test method details – ambiguities between laboratories:
  - Minor equipment
  - Sampling or sample preparations
  - Calculations





# Guidances related to Method Changes and Transfers

## FDA

- Analytical Procedures and Methods Validation 2015
- ICH Q2(R1) – Validation of Analytical Procedures 2005
- ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process 2005
- ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management – step 1/2 - 2016

## USP

- <1224> Transfer of Analytical Procedures
- <1225> Validation of Compendial Procedures
- <1226> Verification of Compendial Procedures



# Thank you!

- Questions – Discussion?
- [alfred.del-grosso@fda.hhs.gov](mailto:alfred.del-grosso@fda.hhs.gov)