



# Power Up Your Analytical Method Transfer

Webinar – May 16<sup>th</sup> 2007

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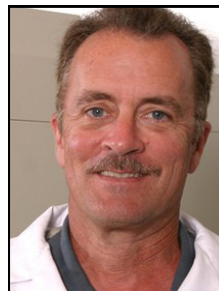
## Speaker:



**Wendy Saffell-Clemmer**  
Manager II  
Pharmaceutical Research & Development

Ms. Wendy Saffell-Clemmer, is recognized as an expert in the field of analytical methods of parenteral products and is a frequent presenter at the annual IBC Bioprocess International and AAPS Biotech conferences. Ms. Saffell-Clemmer authored and contributed to key publications on analytical methods including BioPharm International and Pharmaceutical Technology. She earned her M.S. in Physical Chemistry from Northwestern University and her B.S. in Chemistry from the University of Virginia. Ms. Saffell-Clemmer currently manages a group of 13 scientists responsible for the development, validation and transfer of all chemical analytical methods in Bloomington. Prior to joining Baxter, she held a number of positions with Eli Lilly & Company.

## Moderator:



**Dr. Steven L. Nail, Ph.D.**  
Senior Baxter Research Scientist  
Pharmaceutical Research & Development

Dr. Nail is widely recognized as one of the world's leading experts in lyophilization science, technology, formulation design, and processing, with over three decades of experience in the field. He currently serves as adjunct professor at Purdue University in West Lafayette, Indiana, and previously held teaching positions with the Industrial and Physical Pharmacy division and is active in AAPS and PDA organizations. Additionally, he is chairperson for the United States Pharmacopoeia, Industrial Panel of Experts. Dr. Nail is a member of several journal editorial advisory boards and has contributed to over 50 publications, authored numerous chapters in pharmaceutical textbooks, and co-edited *Development and Manufacture of Protein Pharmaceuticals*.

# Course Outline

- **Definition of Method Transfer**
- **Planning for a method transfer**
  - **Contractual Communication**
  - **Technical Communication**
- **Regulatory Expectations**
- **Types of Method Transfers**
- **Case Studies**

# What is Method Transfer?

- Protocol driven study with pre-determined acceptance criteria
- Demonstration of a laboratory's proficiency in running a particular method
- Verification of a method's suitability for its intended use.



# Method Transfer and Validation

- Method Transfers are closely related to Validation
- More challenging because multiple laboratories and companies are involved
  - Different approaches to Validation and Transfer
  - Different expectations of what is an acceptable validation
  - Different instruments and facilities
- Balancing Act
  - Adapt method to new facility/instrument
  - Meet new facility validation requirements
  - Maintain validated state of method

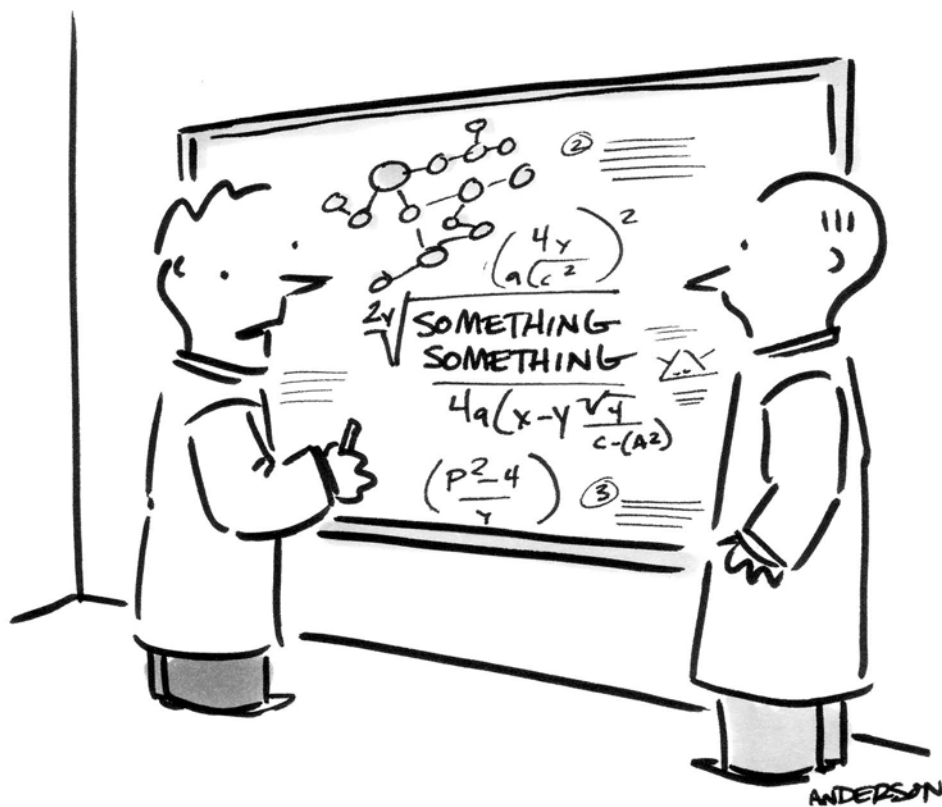


# Why more interest/emphasis on Method Transfer?

- **Increase in outsourcing**
  - **Contract Manufacturing**
  - **Use of CROs**
- **Increase in biologic products**
  - **More complex methods**
  - **Multiple orthogonal methods often required**
- **Regulatory trends**
- **Great emphasis on Technical Transfer in General**
- **Good business practice**

# An Exact Science?

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"It's an inexact science."

## Method Transfer is not Rocket Science

The most important ingredient to any method transfer is open and responsive communication between the transferring organization and the receiving site.



# Communication – Contractual Details

- Confirm details about the Product and Method before finalizing the transfer protocol
  - Product
    - Formulation
    - Strength
  - Method
    - Assay Category
    - Intended Use (In-process, Release, API)
    - Specification for results



# Communication – Technical Details

- Small Technical Issues Frequently cause delays in Method Transfers
  - Lack of Documentation of Important Details in Procedure
  - Lack of Robustness
- Not well documented in SOPs or Validation Documents
  - HPLC Column Temperatures – Room Temperature vs Ambient?
  - HPLC Methods – Needle Rinse Used?
  - ELISA Methods – To Tap or Not to Tap

## To Tap or not to Tap?

- Direct ELISA for ID of a Monoclonal Antibody API
- During method transfer all system suitability and acceptance criteria were met
  - Positive Samples Passed the ID Test
  - Negative Samples Failed the ID Test
- OD values obtained were lower than typically observed by the client
  - OD values of positive controls at CMO were 1.0
  - OD values expected by client were 3.0.

## To Tap or Not to Tap?

- All Reagents were Stored and Diluted according to Method
- Incubation Times and Temperatures were within method parameters
- Used an automatic plate washer for washing of ELISA plates and evacuation of wells following wash step.
- During Transfer - No visible fluid remained in wells, analysts did not tap the plate upside down.
- A side-by-side comparison of two plates, one tapped and one not tapped resulted in Positive control OD values of 3.0 and 1.0 respectively.
- Tapping plates is common practice, and is something the transferring lab should communicate during transfer.

# Communication

- Lack of Robustness
  - Parameters documented in the Method may not have been fully validated.
  - Example
    - Temperature Storage range for an antibody was –20 to –80 C
    - Method evaluation results were acceptable when antibody was stored at –70C.
    - When the antibody was moved to –20C storage for transfer work in another laboratory, results were unacceptable.
  - Problem was determined and solved only with help of technical experts at the transferring laboratory.

# Preparation for a method transfer

- **Materials**
  - Method
  - Validation Report
  - Reference Standard
  - Samples for Evaluation
  - Difficult to purchase supplies
- **Information**
  - Technical Contact
  - Intention of Method
    - API, Raw Material, In-Process, Stability, or Final Product
    - ID, Assay/Potency, Purity/Related Substances, or Residue Analysis
  - Method Performance Expectations
    - Specifications
  - Details about product
    - Light Sensitive, Sticks to Plastic
  - Details about method
    - Specific Instrument?

# Regulatory Guidance on Method Transfer



U.S. PHARMACOPEIA

Very little guidance specific to  
Method Transfer!

# Regulatory Guidance on Method Transfers?

## 21 CFR Part 211.194

### §211.194 Laboratory records.

(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

(2) A statement of each method used in the testing of the sample. The ~~statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested.~~

~~(If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods,<sup>1</sup> or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.~~

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# Regulatory Guidance on Method Transfers?

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# No detailed Guidance on Method Transfers

- Instead, rely on ICH and FDA Guidance on Method Validation
  - Guidance for Industry, Q2(R1) Validation of Analytical Procedures: Text and Methodology  
<http://www.ich.org/LOB/media/MEDIA417.pdf>
  - Guidance for Industry, Bioanalytical Method Validation  
<http://www.fda.gov/cder/guidance/4252fnl.pdf>
  - Guidance for Industry, Analytical Procedures and Method Validation – Chemistry, Manufacturing, and Controls Documentation, US Food and Drug Administration Center for Drug Evaluation and Research, Draft Guidance, August 2000.  
<http://www.fda.gov/cder/guidance/2396dft.pdf>

# Types of Method Transfers

- Verification - documented evidence that a previously validated method performs as intended under actual conditions of use.
- Qualification – a method transfer conducted such that only the receiving laboratory performs testing.
- Comparative - a method transfer conducted in which the test solutions are assayed by the transferring and receiving laboratories.
  - Criteria for comparison is consistent with the acceptance criteria from the analytical method validation.
- All types of transfers involve repeating specific performance characteristics from the method validation.

# Categories of Assays

- Suggested performance characteristics are dependant on assay type:

Categories of Assays	
Category	Definition
Category I	Analytical methods for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.
Category II	Analytical methods for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These methods include quantitative assays and limit tests.
Category III	Analytical methods for determination of product performance characteristics (e.g., dissolution, drug release).
Category IV	Identification tests

# Comparative Testing Criteria

Examples of Comparative Transfer Criteria								
USP Category	Category I (Assay)		Category II (Quantitative)		Category II (Limit)		Category III (Performance)	Category IV (Identification)
Laboratory	T	R	T	R	T	R	NA	NA
Performance Characteristics								
Accuracy	N	N	N	N	N	N		
Precision	Y	Y	Y	Y	N	N		
Linearity	N	Y	N	Y	N	N		
Specificity	N	Y <sup>1</sup>	N	Y <sup>1</sup>	N	Y <sup>2</sup>		
Sensitivity or LOQ	N	N	N	Y	N	N		
Comparison of results <sup>3</sup>	Y		Y		N			

1. With respect to sample diluent, if applicable
2. No response to appropriate blank(s), Positive response with analyte present
3. For example, percent difference between assay results from both laboratories

T = Transferring Laboratory    R = Receiving Laboratory

N = Testing not suggested    Y = Testing suggested

NA = Not Applicable to side-by-side testing design

# Qualification Transfer Criteria

Examples of Qualification Transfer Criteria					
USP Category	Category I (Assay)	Category II (Quantitative)	Category II (Limit)	Category III (Performance)	Category IV (Identification)
<b>Performance Characteristics</b>					
Accuracy	Y	Y	N	N	N
Precision	Y	Y	N	Y	N
Linearity	Y	Y	N	N	N
Specificity	Y <sup>1</sup>	Y <sup>1</sup>	Y <sup>2</sup>	N	Y <sup>2</sup>
LOQ	NA	Y	N	N	N

1. With respect to sample diluent, if applicable
  2. No response to appropriate blank(s), Positive response with analyte present
- N = Testing not suggested  
 Y = Testing suggested to be performed by receiving lab  
 NA = Not Applicable

# Validation Review

- As per 21 CFR Part 211.194 the laboratory must be able to present the location of data that “establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested.”
- The method transfer can be used to fill in validation gaps
- Examples
  - Sample Stability
  - Mobile Phase Stability
  - Robustness Studies



# Transfer Waivers



- Experimental Evidence may be waived in certain situations
  - The same or similar method is used for other similar samples
  - The method is a well established compendial procedure (General Chapter)
  - The method is a common one which lacks specialized technique and is well characterized for a variety of formulations.
    - pH
    - Density
- Formal documentation explaining and justifying the waiving of experimental evidence is required.

Surprises?

“A surprise in research is called a discovery”

“A surprise in development is called a disaster”

# How does BPS minimize surprises?

- Reorganization of method transfer process in 2005
- All method transfers occur through development group
  - Development group also performs Method Validations
  - Single path for all methods into company
  - Method validations for potential method transfers are reviewed and assessed against the site Validation Procedure
  - Gaps in client provided method validation can be filled during the transfer.

# How does BPS minimize surprises?

- Methods are given a thorough laboratory evaluation in the development laboratory prior to drafting the Transfer Protocol
  - Evaluate any site specific issues
    - Instrumentation
    - Reagents
    - Data Collection Systems
    - Personnel/Technique
  - Confirm that acceptance criteria can be met
  - Determine if any clarification to Method Procedure is needed and contact technical representative if needed

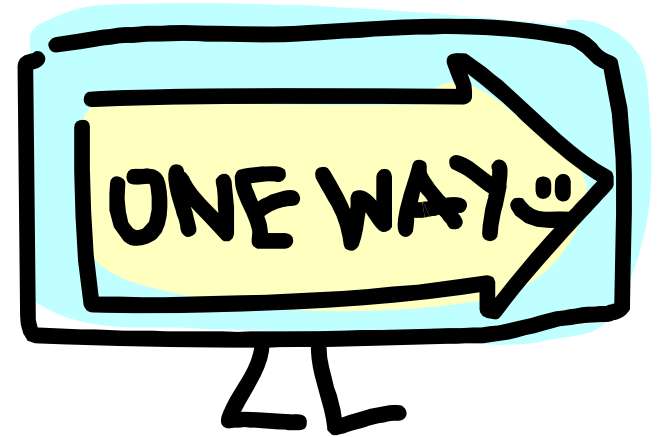


# How does BPS minimize surprises?

- The Research Associate who performs the evaluation is responsible for the transfer
  - Draft SOP
  - Draft Protocol
  - Train QC Analysts
  - Write Transfer Report
- Some or all of the protocol in the QC laboratory under actual conditions of use.

# Method Transfer Steps

- Discussions Initiated
- Review of Method and Validation
- Laboratory Evaluation
- Transfer Protocol Written
- Transfer Protocol Approved
- Experimental evidence from a transfer study generated
- Transfer Report Written
- Transfer Report Approved
- Transfer Complete.



## Case Study – Gas Chromatography (GC)

- Client Provided a Method for a Commercial Product
- The Client did not wish to make any changes to the method
  - Changes would require resubmission to the FDA
  - The product had been on the market for more than 30 years
- The Client method was designed for a significantly older model of GC
  - Inlet Flow and Pressure were not specified
  - A Packed Column was used
  - A Column Flow Rate was not specified

## Case Study - GC

- Changing the packed column to a capillary column was not an option
- Settings for Inlet Flow, Inlet Pressure, and Column Flow are required for operation of modern GCs
  - Research Associate consulted Instrument Manual for suggested settings
  - Obtained a lot of rejected material
  - Rejected material was analyzed on the new GC with suggested settings and results were compared to results generated on the client's older model GC.
  - Results were comparable

# Case Study - ELISA

- Client provided a validated method for an ID ELISA
  - SOP and Validation report were reviewed and were detailed.
- Research Associate evaluated the method in the Development Laboratory
  - Assay failed to meet transfer criteria 3 times!
  - Investigated Plates
  - Investigated Pipets
  - Client requested that the associate demonstrate her ability to pipet using food coloring

# Case Study - ELISA

- Troubleshooting with client
  - Laboratory analyst mentioned that they they use the plate washer to shake to plate before reading
  - Led to Discussion of Plate Washer Settings
  - Needles set to bottom and side of each well
  - Neither shaking or needle settings were mentioned in the method procedure
- When specific settings used all criteria was met.



## In Conclusion, Successful Method Transfers...

- Maintain the Validated State of the method and meet all regulatory requirements
- Minimize surprises!
  - Open and Responsive Communication
  - Pre-determined expectations
  - Clearly documented and communicated technical details
  - Pre-transfer evaluation by experienced technical staff at receiving site
  - Technical contact available at troubleshooting at transferring site

# Question and answer session

Please submit your questions in the Q&A box on your screen

# Thank You for Attending!

The slide deck will be emailed to you today



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Contract Pharma, New Brunswick, NJ .....	September 18-19, 2007
ICSE, Milan, Italy- Booth#16C76 .....	October 2-4, 2007
AAPS, San Diego, CA- Booth 307 .....	November 11-15, 2007

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