Strategic Considerations
for
Successful Analytical Method Transfer

Analytical Method Development, Validation and Transfer

Conference, September 14 & 15, Prague

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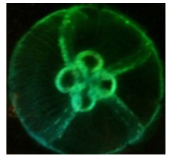
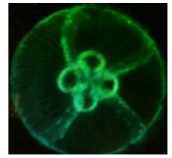
Roche Kulmbach GmbH



Overview

- Definition of Method Transfer
- Method Transfer and Validation - When to Re-Validate?
- Practical Considerations for Pre & Post Analytical Method Transfer
  - Planning for a Method Transfer
    - Contractual communication
    - Technical communication
    - Responsibilities
- Contemplating failure: Case studies
- Preparing protocols for successful method transfer
- Considerations for adopting a global company document



What is method transfer?

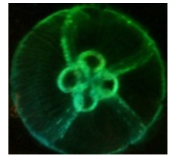
Method transfer is the process of transferring a validated analytical method from a sending laboratory to a receiving laboratory, after demonstrating experimentally that it also masters the method.

From: Rozet et al., JChrB, 877 (2009) 2214-2223 (Review)

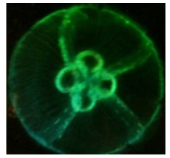
- Protocol driven study with pre-determined acceptance criteria
- Demonstration of a laboratory‘s proficiency in running a particular method
- Verification of a method‘s suitability for it‘s intended use

From: Saffell-Clemmer & Nail, BioPharma Solutions, Webinar presentation 2007

What is method transfer?



- 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



Has emphasis on Method Transfer increased?

- Increase in outsourcing and subcontracting (contract manufacturing, use of CROs)in the pharmaceutical industry

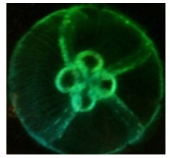
- Increase in importance of biologic / biopharmaceutical products
- Biologic / biopharmaceutical products require:
  - More complex methods
  - Multiple orthogonal methods
  - Appropriate procedures to control development

- Expected to be in accordance with:
  - Good business practice
  - Regulatory guidance

Regulatory Guidance

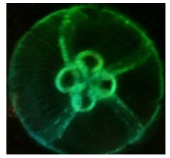
- **No Detailed Official Guidance Exists for Method Transfer. Instead Rely on ICH and FDA Guidance on Method Validation**

  - 21 CFR Part 211.194
  - US FDA. Guidance for Industry, ICH Q2(R1)
  - US FDA. Guidance for Industry: Bioanalytical Method Validation, 2001
  - US FDA. Guidance for Industry: Analytical procedures and Method Validation
  - EMA. Concept paper/ reccommendations on need for a (CHMP) guidline on the validation of bioanalytical methods. 2009



Types of Method Transfer

- **Comparative testing**
  - Involves two or more laboratories
  - Preapproved protocol
  - Predetermined acceptance criteria
- **Covalidation between two laboratories**
  - Receiving laboratory is involved in Validation (e.g: interlaboratory qualification)
  - Validation report as proof of transfer
- **Method validation/re-validation**
  - Receiving laboratory repeats some or all validation experiments
- **Transfer waifer**
  - No comparative data required
    - Receiving laboratory is using same or similar method
    - Or Method is common and well established (pH, Density)
  - Formal documentation justifying the waiving of experimental evidence is required



Re-validate or not?

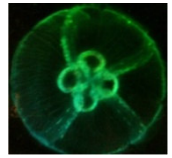
A Re-Validation is Necessary,

- whenever a method is changed, and the new parameter lies outside the operating range
  - Column Temp 41°C , Operation Range 30-40°C
- if the scope of the method has been changed or extended
  - Change of sample matrix / operating conditions
- if instruments with new characteristics are used, not covered by the initial validation
  - New HPLC pump delay of 0.5 mL vs. a validated delay of 5 mL
- if system suitability tests, or results of sample analysis, lie outside preset acceptance criteria and where the source of the error cannot be traced

From: Validation of Analytical Methods and Procedures, Author: Dr. Ludwig Huber

Practical Considerations for Pre-Method Transfer

- An open and responsive communication between sending and receiving site is essential for any method transfer



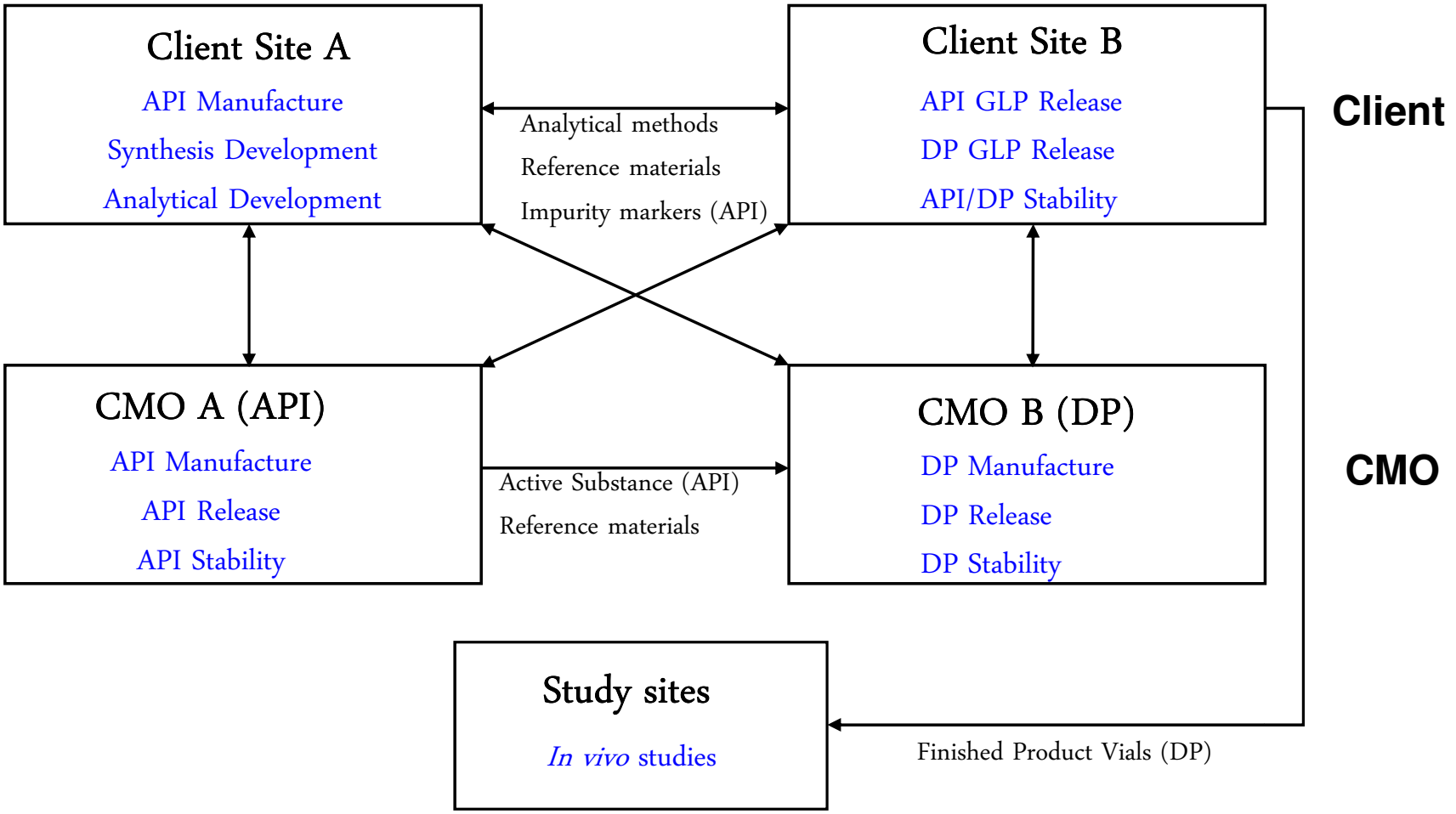
Practical Considerations for Pre-Method Transfer

Communication / Responsibilities:

- Single contact person for all methods into receiving company/site
- Single contact person for all methods from sending company/site
- Scientific teams to communicate early and frequently
  - Thorough evaluation of the method at the sending site prior to drafting the transfer protocol
  - Determine early, if any clarification to the method procedure is needed
- Evalute site specific issues
  - Instrumentation
  - Reagents
  - Data collection systems

Practical Considerations for Pre-Method Transfer

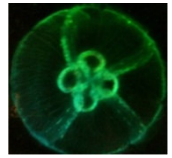
- Method Transfer involves multiple pathways of communication



Practical Considerations for Pre-Method Transfer

Information to Provide from the **Sending** Laboratory:

- **Pre-approved Transfer Protocol:**
  - Describes the General Transfer Process
  - Clearly Defines Responsibilities (at sending and receiving site)
  - Provides Specific Acceptance Criteria
  - Lists Methods
  - Provides Categorization of Method
    - API, Raw material, In-process, stability or final product
    - ID, Potency, purity/related substances or residue analysis
  - Describes Materials and Samples
    - Light-sensitive, adheres to plastics
  - Provides Batch/Lot Numbers
  - Includes Certificates of Analysis
  - Describes Instrumentation and Parameters

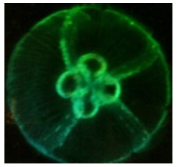


Practical Considerations for Pre-Method Transfer

Materials to Provide from the **Sending** Laboratory:

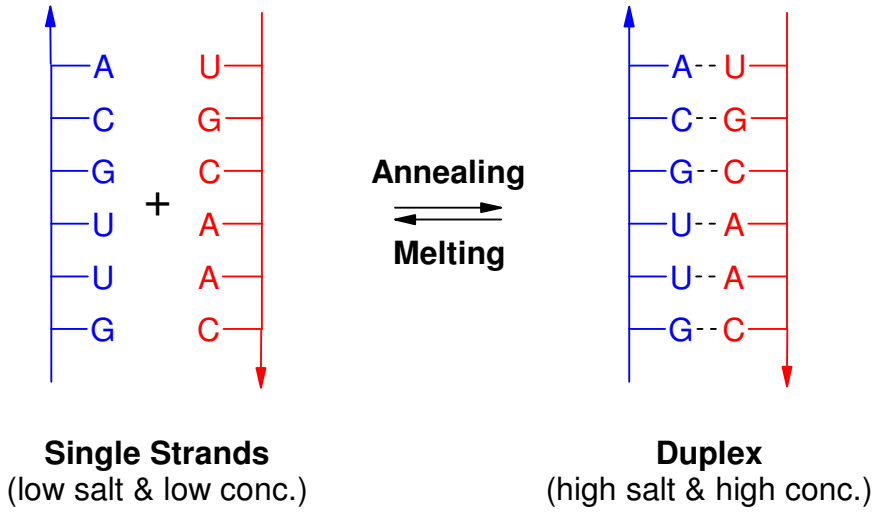
- Method
  - System Suitability Parameters
  - Rationale for Chosen Parameters
  - Step-by-Step Directions
  - Tips and Tricks
  - Safety Considerations
- Validation Report
- Reference Standards
- Samples for Evaluation
- Difficult to Purchase Supplies

Contemplating Failure:



Contemplating Failure :

Case study: UV-Spectroscopy

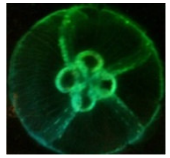


Single Strands
(low salt & low conc.)

Duplex
(high salt & high conc.)

- RNA-Duplex is stabilized by buffer salts.
- Duplex has lower absorbance than monomers.
- Sample measurements using water vs. dilution using buffered saline.

	Extinction Coefficient determined in Water (CRO)	**Extinction Coefficient** determined in Water (Client)	**Extinction Coefficient** determined in 1 x PBS (Client)
siRNA-Luc	389,000	365,000	294,900
	132 %	124 %	100 %

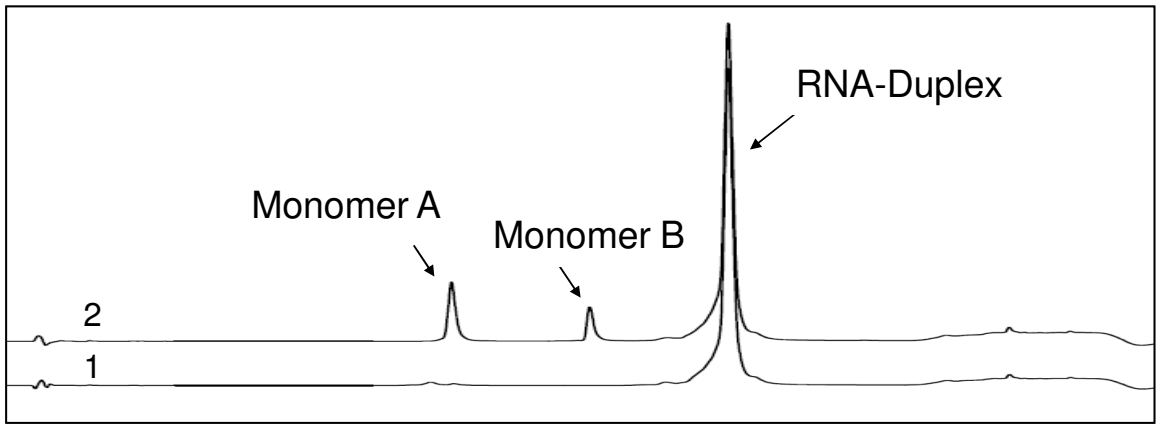


Contemplating Failure:

Case study: Ion-Pair Reversed-Phase Chromatography

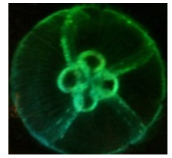
RNA-Duplex is stabilized by buffer salts.

Sample dilution using water vs. dilution using saline caused dissociation of the Duplex.



Effect of sample preparation on non-denaturing IP-RP.

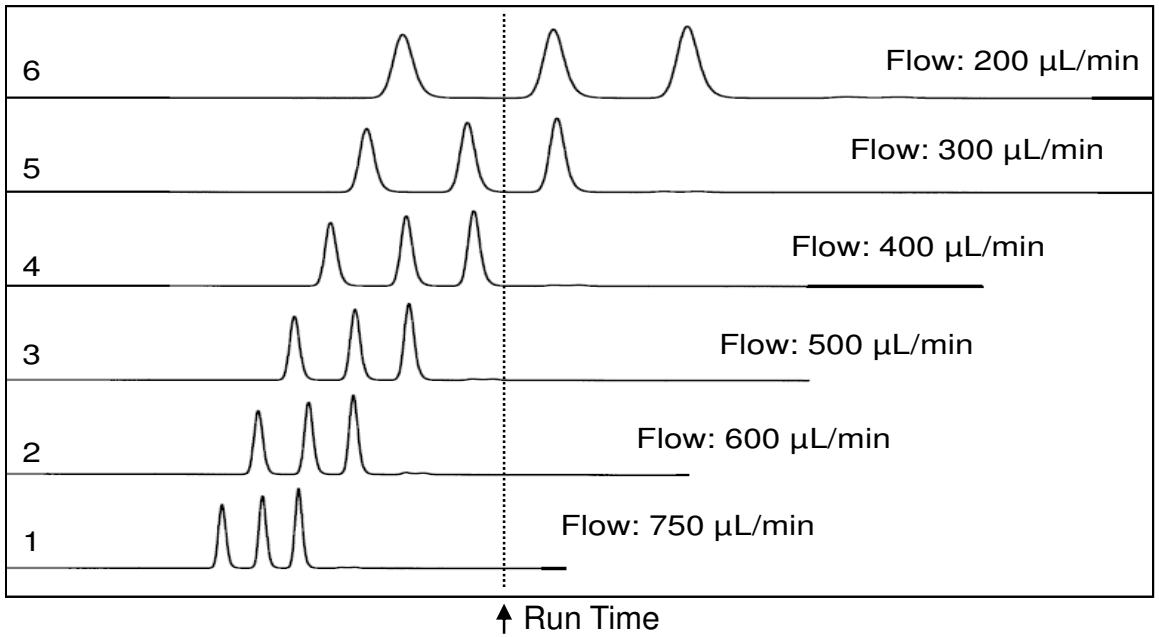
Sample in saline (trace 1) and sample in water (trace 2).



Contemplating Failure:

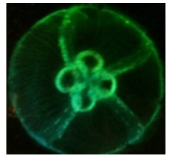
Case study: Size exclusion chromatography

Due to column pressure limits of the instrument at the receiving laboratory, HPLC flow rate was decreased, but chromatography time was held constant



Effect of different flow rates on SEC separation.

Trace 1: Flow = 750 µL/min; Trace 2: Flow = 600 µL/min; Trace 3: Flow = 500 µL/min; Trace 4: Flow = 400 µL/min; Trace 5: Flow = 300 µL/min; Trace 6: Flow = 200 µL/min.



Contemplating Failure:

Seemingly Irrelevant Differences Can Cause Method Transfer Failure:

- HPLC Systems
- Method of Sampling (e.g. Needle Rinse)
- RT vs Ambient
- Method of Pipetting
- Automatic Liquid Handling Systems
- Reagents
- Storage of Reagents
- Plate-Washers
- …

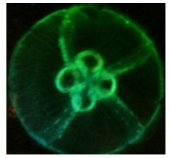
Contemplating Failure: Practical Considerations

Table 4
How to handle a problem assay (either as donor or recipient)

1. Discuss difficulties calmly, using chromatograms, calculations, etc.
2. Discuss method to ascertain if it was followed without change
3. Reassay some samples in both laboratories to verify if procedure is faulty
4. Transfer a tested column
5. Transfer a tested mobile phase
6. Transfer, if possible, other equipment
7. Transfer an analyst
8. Redevelop the method

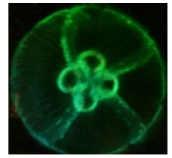
J.J. Kirschbaum, "Interlaboratory Transfer of HPLC Methods: Problems and Solutions," *J. Pharm. Biomed. Anal.* **7** (7), 813–833 (1989).

- Documentation of results
  - Report that summarizes all experiments and results
  - Address situations where acceptance criteria were not met
    - Prepare „Memorandum Document", incl. Background/Results/Conclusion/Recommendations
  - Follow policy to handle failure, describe effect on transfer
  - Investigation into failed results should be performed and documented



Considerations for a global company document

- Common Documents and Procedures Facilitate Method Transfer
  - Method Transfer Protocol
    - Describes Work and Procedures to be followed
    - Gives details about product and methods
    - Prepared Pre-Transfer
  - Method Transfer Report
    - Summarizes Results and Deviations
    - Prepared after performing experiments



Considerations for a global company document

Method Transfer Protocol (Example Structure):

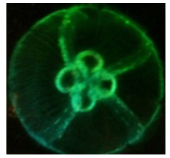
- Title / Header
- Summary (Description of experimental work, purpose and evaluated parameters)
- Description of method (Equipment, Parameters)
- Evaluation of Specificity (Incl.: Acceptance Criteria)
- Evaluation of Linearity (Incl.: Acceptance Criteria)
- Evaluation of Limit of Quantification (LOQ) (Incl.: Acceptance Criteria)
- Evaluation of Precision (Intermediate Precision) (Incl.: Acceptance Criteria)
- Signatures

Considerations for a global company document

Method Transfer Report (Example Structure):

- Title / Header
- Objective (Stating purpose and evaluated parameters)
- Description of Method (Equipment, Parameters)
- Results for Speciticity
- Results Linearity Determination
- Results ...
- Deviations and Exeptions
- Conclusions
- Appendix: Formulas and Calculations

Steps Towards Successful Method Transfer



- Discussion Initiated
- Method and Validation Reviewed
- Laboratory Evaluated
- Transfer Protocol Written
- Transfer Protocol Approved
- Experimental Data Generated
- Transfer Report Written
- Transfer Report Approved
- Transfer Complete

Summary

- Open and Responsive Communication
- Responsibilities Agreed On and Assigned
- Pre-Determined Expectations
- Clearly Documented and Communicated Technical Details
- Pre-Transfer Evaluation by Experienced Technical Staff at Receiving Site
- Technical Contact Availible at Sending Site (for troubleshooting)