

Transferring Dissolution Methods

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Agenda

- Prerequisites of a Method Transfer
- Transferring a Method to Automation
- Transferring a Method to Another Lab
- Determining Appropriate Transfer Type
- Assessing Potential Differences between Sites

USP <1224> Transfer of Analytical Procedures

Discusses appropriate procedures for transferring an analytical procedure:

- Types of Transfers of Analytical Procedures
- Elements Recommended for the Transfer of Analytical Procedures
- Preapproved Protocol
- Analytical Procedure
- Transfer Report/Qualification of Receiving Unit

Prerequisites to Method Transfer

- Dissolution Method must be Validated
- SOP signed off
- Training in place for SOP
- Preapproved Protocol Written

Validated Dissolution Method

- Must be validated for manual dissolution
- Key parameters validated:
 - Filters
 - Degassing Technique
 - Stability of samples and standards
 - Analytical finish



Standard Operating Procedure

Defines:

- Dissolution Procedure
- Sampling Procedure
- Analytical Finish
- Any special considerations:
 - Drawings/Descriptions of items such as handmade sinkers
 - Special Preparation techniques
 - Stability issues
 - Robustness issues

SOP – Flexibility

SOP should be written with flexibility to accommodate changes to method over time/transfers:

- Do not use “...or equivalent”
- “...or another validated” is much more acceptable

Examples of items that may change over life of method are filters, LC columns, dissolution units, etc.



Preapproved Protocol

Mutually agreed upon Documented Protocol covering:

- Objective and Scope
- Responsibilities of transferring and receiving units
- Materials/Instruments to be Used
- Analytical Procedure
- Experimental design
- Acceptance Criteria for all tests



Transferring a Method to Automation

Transferring to Automation

Automation can lend itself very well to dissolution, however, one must ensure that the results are comparable to a manual method and no bias is induced.



Potential Sources of Bias

Care should be taken to identify which aspects of the automated method would handle the test/sample differently from a manual method:

- Hydrodynamic Impact from Probes
- Tubing adsorption/leaching/carryover
- Filtration differences
- Analysis differences
- Cleaning Validation

Survey the Automation for Changes

Transferring a method to automation will require partial revalidation of elements. It is important to review the automation and determine any potential bias that could be created and review it.



Validation of an Automated Method

Previous webinars on developing and validated methods for automated dissolution are available at:

<http://www.chem.agilent.com/en-US/Training-Events/eSeminars/dissolution/Pages/default.aspx>

- Validation of a Semi-Automated Dissolution Method
- Online UV Dissolution Method Development
- Fiberoptic UV Dissolution Method Development

Transferring a Method to Another Lab

Transferring a Method to Another Lab

- Types of Transfers
- Method Training
- Lab Assessment
- Pre-transfer Testing
- Is Partial/Full Revalidation Required?
- Preapproved Protocol and Transfer Testing
- Transfer Report – Pass or Fail?

Types of Transfers of Analytical Procedures

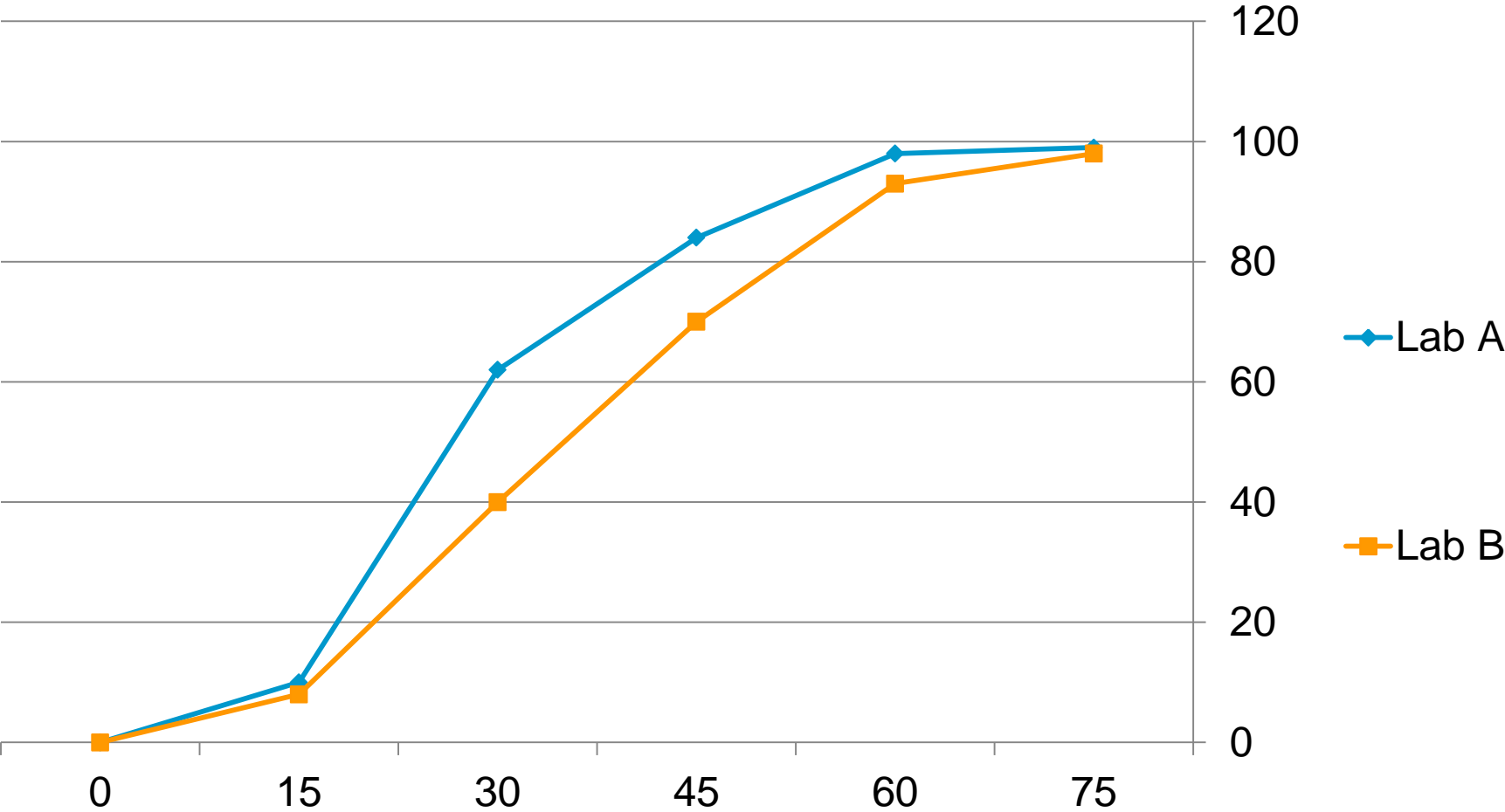
- Comparative Testing
- Covalidation Between 2+ Laboratories
- Revalidation or partial revalidation
- Transfer Waiver

Comparative Testing

Analysis of predetermined number of samples of the same lot(s) by both the sending and receiving units

- Sending unit may use data from validation study – intermediate precision
- Dissolution data can be compared by f2 analysis or comparison of % dissolved at key time points.
 - n=12 for each lot/site for comparison
 - Variability should also be checked <10% at mid/late timepoints, <20% at early points

Comparison of Data Sets



Covalidation

- Recipient lab tests validation alongside transferring unit
- Assesses reproducibility of method
- Possible if multiple sites are starting method at the same time

Revalidation or Partial Revalidation

- Assess potential items from validation protocol which could be affected by the transfer
- Revalidate entire protocol, or only potentially impacted items

Transfer Waiver

It may be possible in certain circumstances to avoid a method transfer if:

- Product is similar enough to one which is already being tested at recipient lab
- Procedure is similar enough to one which is already being used at recipient lab
- If method is in USP-NF and unchanged (but would need verification per USP <1226>)
- If trained personnel are moved to the recipient site

Recommendations for Dissolution Transfers

A partial revalidation along with comparative testing of several formulation lots appropriate to ensure recipient lab is qualified:

Amount of revalidation depends on a lab assessment of equipment at the recipient lab compared to the transferring laboratory.

At a minimum, comparative testing is highly recommended.

Method Training

Training should be hands-on for method transfers, if possible.

Training options are:

- Training chemist in your facility
- Sending someone to train at their facility
- Both

Training approach depends on method complexity, 2nd lab's experience level, and previous history with the lab

Training a Chemist at Your Facility

The most common training method is hosting someone from the other lab

It is important that:

- Chemist does the work hands-on
- An assessment is done of any elements where technique is important
- Conversation covers potential differences between sites



Training a Chemist at Your Facility

Limitations:

- Method will be trained to new lab by someone new to method
- Specific questions regarding method may not be answered at 2nd site
- A good assessment of 2nd site isn't performed

Sending a Trainer

Sending a trainer is a better approach to transferring a method:

- Can run samples, if needed, at new facility
- Directly train key method users
- Will be able to directly view lab, and assess areas of concern

Lab Assessment

Prior to transferring the method, the receiving lab should be reviewed to ensure:

- Units are calibrated for use
- Units are qualified
- Lab is compliant and properly trained overall
- Additionally, differences in equipment and procedures should be assessed

Equipment Differences to Be Considered

- Dissolution Units
 - Brand/Model differences
 - Vessels
 - Level of Automation
- UV
 - Linear range
 - LOD/LOQ
 - Specificity
- HPLC
 - Same as UV
 - Pressure

Procedure Differences to Be Considered

- Media Preparation
- Media Degassing
- Filtration Differences



Dissolution Unit Differences

- All dissolution units must meet USP/FDA/ASTM requirements
- Results for dissolution samples are generally the same
- Some differences may exist however, and have occasionally caused differences in results
 - Vessel type
 - Bath vs. Bathless
 - Level of Automation
 - Sampling Location/Resident Probes



Dissolution Vessels

1L Dissolution vessels are defined in USP as 160 – 210mm height and 98-106mm diameter, and is cylindrical with a hemispheric bottom

- Hand blown
- Vessel manufacture is key
- Proper attachment device
- Condition and Cleanliness



Statistics for Vessel Attachment based on Lab Services and Internal Data

Vessel Type	% Pass Rate	% CV	Mean
Easealign glass	92%	5.2%	32
TruCenter	100%	4.3%	33
Generic	57%	6+%	34
Mixed set	33%	6.3%	33
TruAlign	100%	4.4%	33

Dissolution Vendor Differences

- USP Range for vessels is very wide
- Vessel Quality is key to low %RSD
- Differences in vessel dimension “target” within USP range does differ – and has occasionally led to different results
 - 1 vendor known w/ vessels on short + wide end of range
 - 1 vendor known w/ vessels on tall + narrow end of range

Bath vs. Bathless

Bathless units require media to be stirred prior to starting run to equilibrate media

This may lead to skewed results for certain formulations such as:

- Disintegrating products (Prednisone PVT)
- Film covered dosage forms or other sticky dosage forms

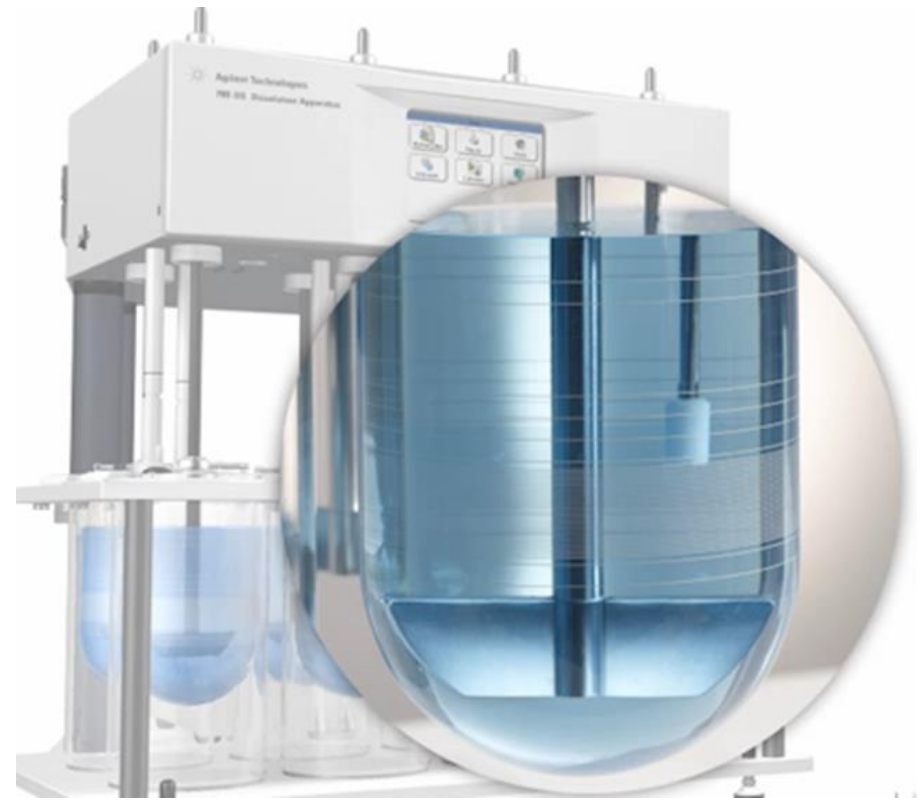


Level of Automation

Automation, if any, should be validated and compared to the manual results

Some automated systems sample in non-optimal ways

- Resident Probes – Hydrodynamic Disturbances
- Hollow shaft sampling – removes sample from poorly stirred zone, may not be representative



UV and LC Differences

UV and LC Specifications should be compared between units, especially for:

- Linear Range
- Noise
- Photometric Range
- Baseline Flatness



Procedure Differences

Some different procedures for dissolution in general may cause differences:

- Media Preparation
- Media Degassing
- Filtration
- Sample/Standard Storage Conditions
- Sample Introduction



Media Preparation

Media prep can be done manually, or with automation. If automated, the media prep should be validated.

Some labs may be inexperienced with preparation of media with enzymes – and this should be addressed for any capsule shell formulations

Pouring and Measuring Media may also be areas of concern.



Media Degassing

Baseline method for comparison should be:

USP Method: Heat media to 41°C, vacuum filter through 0.45µm filter, continue to pull vacuum for 5 additional minutes.



Media Degassing Options – with Validation

Acceptable Methods

- USP Vacuum Filtration Method (default unless another approach is validated)
- Helium Sparging
- Automated Degassing
- Superheating
- Not Degassing At All

Unacceptable Methods

- Nitrogen Sparging
- Sonication

Filtration

Filter should be defined in dissolution method, but may need to make sure the same filter, or one which is validated to be equivalent is used.

Centrifugation is **not** a replacement for filtration



Lab Assessment Complete

- What changes in equipment/procedures were noted?
- What is the experience level of the lab in handling new methods?
- How close is the method/product to something being tested at this facility?

Based Upon Assessment

One of the following protocols should be done:

- Comparative Testing
- Covalidation Between 2+ Laboratories
- Revalidation or partial revalidation
- Transfer Waiver

Most Common Options

Comparative testing is acceptable when the recipient lab has good dissolution experience, and no specific concerns are noted.

Generally will test ~3 lots of material which were tested during original validation

- F2 analysis comparison
- Comparison of Results at Specific Timepoints

Revalidation

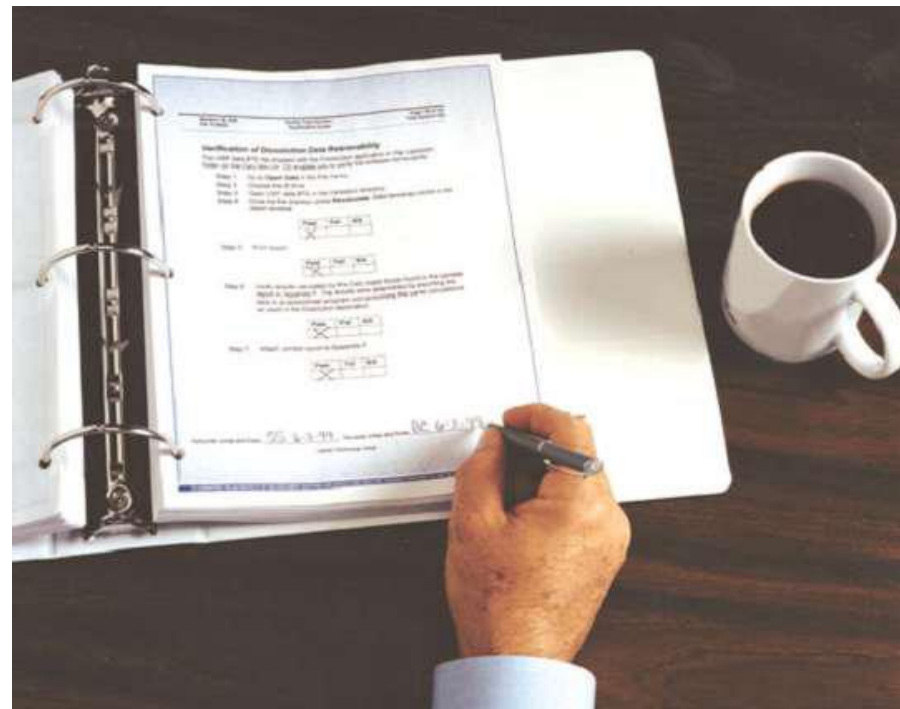
A partial revalidation is performed on impacted elements in addition to comparative testing if differences are noted:

- Linearity
- Range
- Precision of Standard or Spiked Placebo preps

Preapproved Protocol

Mutually agreed upon Documented Protocol covering:

- Objective and Scope
- Responsibilities of transferring and receiving units
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Transfer Report

- Compares results to the preapproved protocol
- If criteria is met, receiving unit is qualified to run the procedure
- Deviations need to be documented and properly justified
- If failure occurs:
 - Full investigation
 - Remedial steps
 - Re-perform failing aspects

Dissolution Exchange

<http://dissolution.chem.agilent.com/>

New Dissolution Focuses website which is a one-stop location for information



The image shows a screenshot of a website titled "Dissolution 1-on-1". The main heading is "Dissolution 1-on-1" in orange and white, followed by the subtitle "Self-paced training resource for dissolution testing". Below this is a thumbnail of a presentation slide with a table of contents. At the bottom of the screenshot, there is a speaker icon and the text "Please turn on your speakers or use headphones for this presentation." The Agilent Technologies logo is visible in the bottom right corner of the screenshot.

- Online course on dissolution fundamentals
- FAQs
- Dissolution Hotline
- Dissolution Discussion Group
- Previously recorded webinars on various topics including MQ
- Upcoming Talks

Questions?

Ken.Boda@Agilent.com or Dissolution.Hotline@Agilent.com

Next Webinar:

Troubleshooting Differences Between Labs

May 1st, 11am EST