Validation of an Automated Method

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Discussion Topics

- Why Automate?
- System Qualification
- Why is Additional Validation Required?
- Types of Automation
- Evaluating Best Automation for your Needs
- Validation Components
- What Needs to be Validated?

Why Automate?

- Increase Analyst Productivity
- Work outside of normal hours
- Quicker result turnaround
- Increase Accuracy and Precision
- Audit trail of events
- Perform tests not possible manually

System Qualification

System Qualification

Prior to Validating a Method, the system must first be qualified for use

- IQ
- OQ
- PQ/MQ?

Qualification of the system is not validation for all products

Should Automated Systems be Qualified with PVT?

Per USP PVT Lot certificates, automation should be avoided so that no bias is introduced to the PVT

PVT is possible with automation, however, you must first validate the automation for use with prednisone

In our opinion, PVT should be performed on the Dissolution Apparatus only and performing PVT on automation is not value added.

System Qualification

In lieu of a “PQ” for the automated system, each formulation should be validated on the automation to ensure that accuracy and precision are maintained and no bias is induced.

Why is Additional Validation Required?

Potential Impacts of 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

Types of Automation

Types of Automation

Automation falls into different catagories based on the extent of the automation

- Single Step
- Single Process
- Multi-process
- Full Automation

Single Step Automation

Single step automation is the simplest and easiest to validate. It involves a single aspect of the dissolution process. Validation is none – little.

- Mechanical Qualification Tools
- Dosage Delivery Modules
- Vessel Washing Stations
- Electronic Notebooks
- Media Prep/Degassing

Single Process Automation

Single Process Automation involves automating multiple steps which make up an overall process. Validation tends to be easy – moderate

•Autosampling

Multi-Process Automation

Multi-Process Automation controls several aspects of the dissolution test – usually sampling and analysis.

Complexity of Projects is Moderate.

•Online UV

•Online UV Fiberoptics

•Online HPLC

Full Automation

Full Automation refers to automation of the complete dissolution test from media preparation to sampling, or even final analysis.

These comprise several steps and validation projects are typically lengthy and reserved for high-throughput QC work.

Evaluating the Best Automation For Your Needs

What Level of Automation Is Appropriate For You?

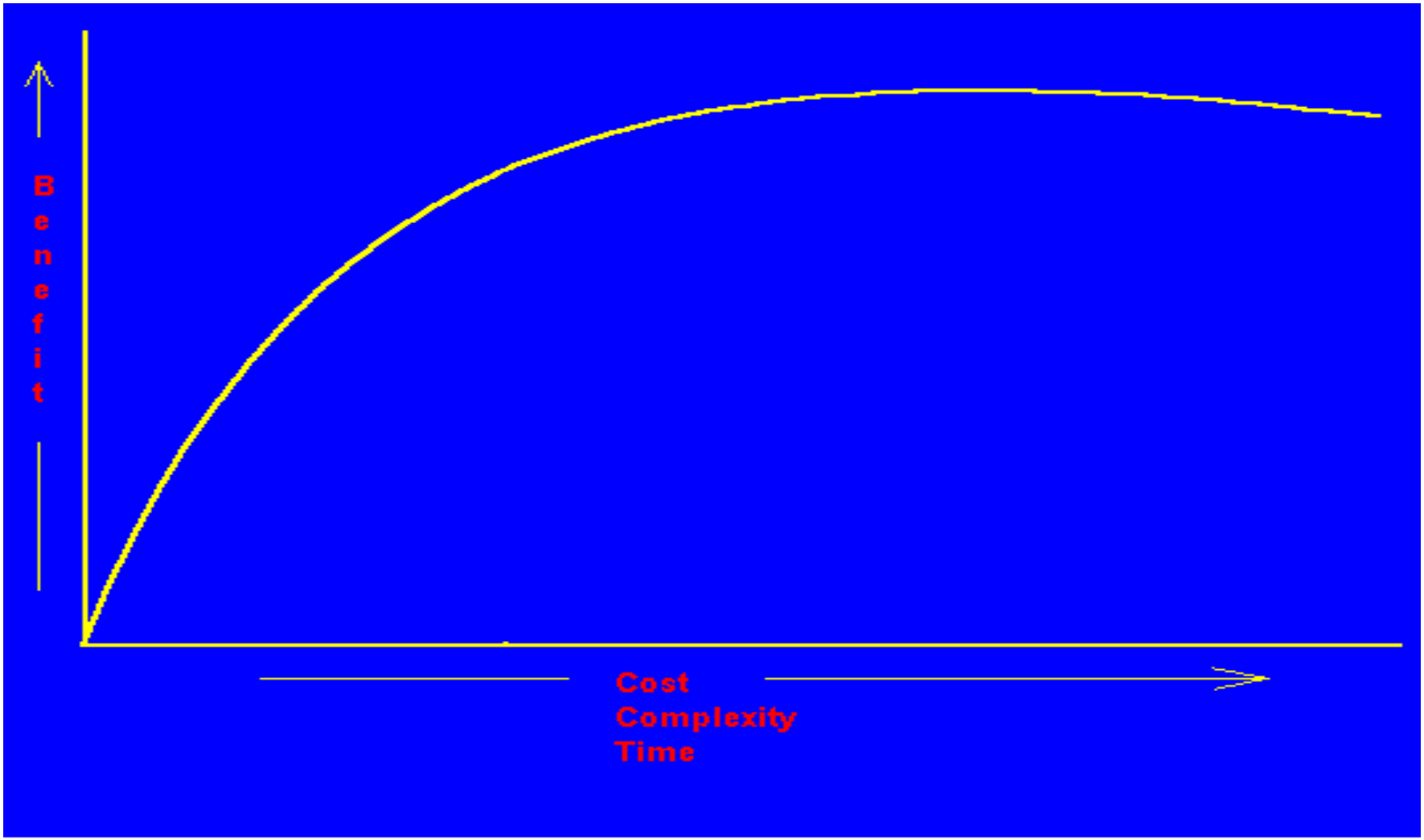
Advantages of Automation

- Less Analyst Time per run
- Increased Productivity
- Quicker data
- Increased Precision
- Increased Accuracy(?)
- Audit Trail of Activity
- Reduced Errors
- Poor Stability Samples

Challenges of Automation

- Higher cost
- Increased Validation Time
- Fewer Compatible Samples
- Increased Training Requirements
- Increase Upkeep
- Potentially Higher Vibration and Evaporation

Automation Value Curve



Questions to ask when determining automation

- Will this be used for 1 or multiple projects?
- Will analysis of samples be both UV and HPLC?
- What level of filtration is required?
- Use paddles and baskets? Non-App 1 and 2?
- Any special considerations (low volume, media change, stability issues, media replacement, etc.)

Single Step Automation

Single Step Automation

Single step automation can be used to:

•Remove a bottleneck in the lab (media prep/degassing, vessel washing)

•Improve accuracy of a step (dosage delivery)

•Improve Regulatory Compliance (Mechanical Qualification Station)

•Record Relevant Lab Data or Operate Instruments (e-notebooks, Dissolution Workstation)

Single Step Validation

Validation of single step approaches is often very simple, as they are only performing a single action, and potential impacts are limited

- Media Prep – Verify pH, etc.
- Media Degassing – Check w/ dissolved gas meter
- Vessel Washing – Carryover study
- Dosage Delivery – Timer check
- Qualification Stations – Routine Manufacturer Calibration
- Electronic Systems – 21 CFR part 11 checks

Single Process Automation

Autosamplers

Advantages

- **Automates most labor intensive step in most cases**
- **Improved accuracy (time, sampling position, force)**
- **Versatile (UV and HPLC)**
- **Allows simultaneous pull of all positions**
- **Simple**

Autosamplers

Disadvantages

- **Potential Contamination/Carryover issues**
- **Resident Probe Effect**
- **Missed sample pulls**
- **Filter and media limitations**

Autosampling

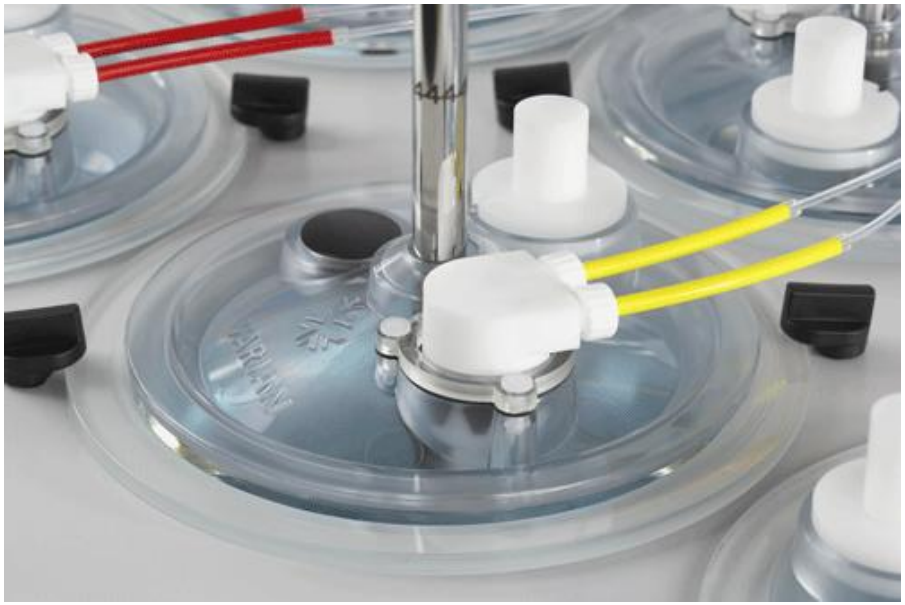
Autosampling is the most frequent example of single process automation

Controls the timing, sampling, filtration, and post-timepoint cleaning

Autosampling is often the largest efficiency gain in a laboratory

Most beneficial when dealing with 3+ timepoints

Automated Manifold or Resident Probe?



Pump Type

There are 2 general types of pumps associated with Fraction Collectors/Autosamplers, and the pump should be chosen based on:

- Filtration Required
- Media type (surfactants)
- Time Point Frequency
- Volume Accuracy

Pump Selection Chart

Pump	Peristaltic	Syringe	Syringe + Filter Changer
Filters	10um+ (2um+ w/ modifications)	2um+	0.45um+
Min. Timepoint	90s	5 min	7 min
Accuracy	+/-0.5mL	+/-0.2mL	+/-0.3mL
Recalibration	Weekly	6 mos.	6 mos.
Challenges	Less pull force; rare adsorbance issues	Surfactants/ Difficult formulations	Surfactants/ Difficult formulations

Validation Requirements

In addition to the validation of the manual sampling method, validation of the autosampler should include:

- Tubing Adsorbance check
- Filter Evaluation
- Cleaning Validation
- Automated vs. Manual Sampling Evaluation

Tubing Adsorbance

The Tubing Should be evaluated in the same way as filters for adsorbance

- Take sample of standard with manual cannula
- Take sample through sampling system
- Results should agree within 1%

Filter Evaluation

If Same Filter is Used:

•Add filter to tubing adsorbance study

If Different Filter is Used:

•Perform new filter validation for efficiency, adsorbance, and leachability

How Do I Validate A Filter?

3 Factors Should Be Tested:

•Efficiency – does it remove undissolved drug?

•Leachability – does it leach a coeluting peak?

•Adsorbance – does the filter hold drug?

Validating a Filter

Efficiency:

Take 3 samples with filter

Sample 1 – scan immediately

Sample 2 – sonicate 5 minutes and read

Sample 3 – sonicate 10 minutes and read

If <1% increase, filter is acceptable

Leachability:

Take filtered sample of blank media

If there is a peak >1% of standard response then a different filter is needed or a pre-rinse

Validating a Filter

Adsorbance:

Filter standard in small aliquots, 1mL at a time and analyze individually. When you reach 99% recovery, filter has been properly filtered.

Method will need to define amount to waste

Aliquot	% Recovery
1st mL	94%
2nd mL	96%
3rd mL	98%
4th mL	99%
5th mL	99%

Cleaning Validation

- Perform Dissolution Run
- Perform System Clean
- Sample Dissolution Media after clean
- <1% response of standard in the blank is typically acceptable
- If carryover is at or near 1%, modify cleaning method

Cleaning Methods

- Always use “Clean System” or equivalent
- For cleaning out buffers, salts, sugars, etc. use DI Water (up to 60C)
- For cleaning out sticky/filmy/gummy residues use alcohol

Cleaning Extended Release Products

Extended Release Products tend to have both water soluble elements and non-water soluble elements, so you must clean for both:

- Clean system 1x HOT DI Water
- Clean system 1+x MeOH or EtOH
- Clean system 1x with DI Water

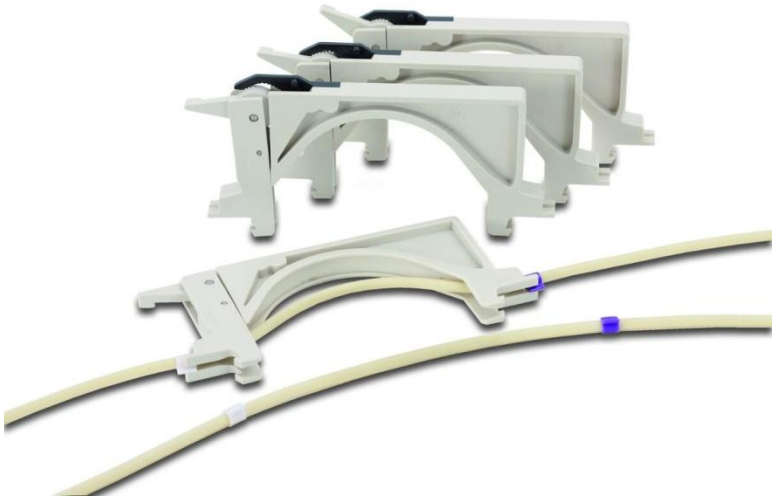
Keeping Systems Clean

Tubing tends to be very inert, but needs to be replaced from time to time:

•Teflon tubing – every 1-2 years

•Peristaltic tubing – every 6-12 months

If there is persistent carryover, replace peristaltic tubing first and try a different chemistry tubing



Sampling Comparison

First, you must ensure that sampling lines are fully wetted prior to sampling and fully emptied post sampling. Priming time will vary based on filter, media viscosiity, etc.

Hint:

Time how long it takes sample to come back through return cannula and add 15 seconds or a few mL

For purge, reverse flow and see when only sputters come from cannula and add 5 seconds or a few mL

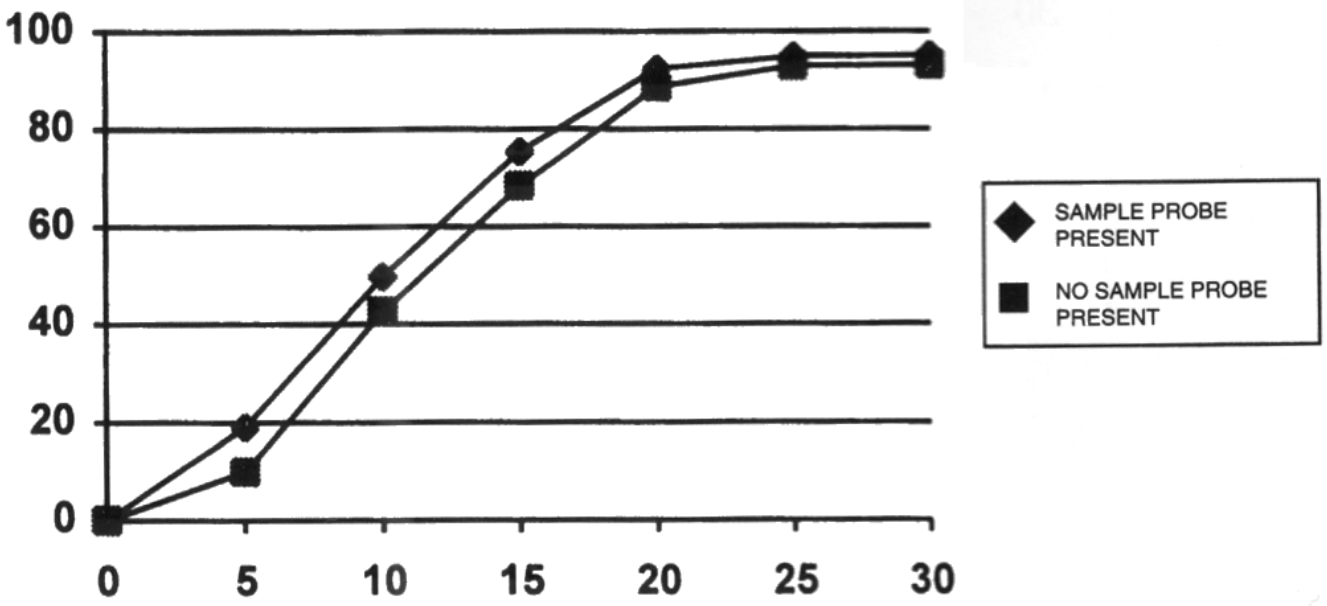
Sampling Comparison - Hydrodynamics

Depending on Sampling Approach, you may or may not need to perform additional validation after this step

•Automated Manifold – no additional validation typically required

•Resident Probes – requires f2 analysis

The Resident Probe Effect



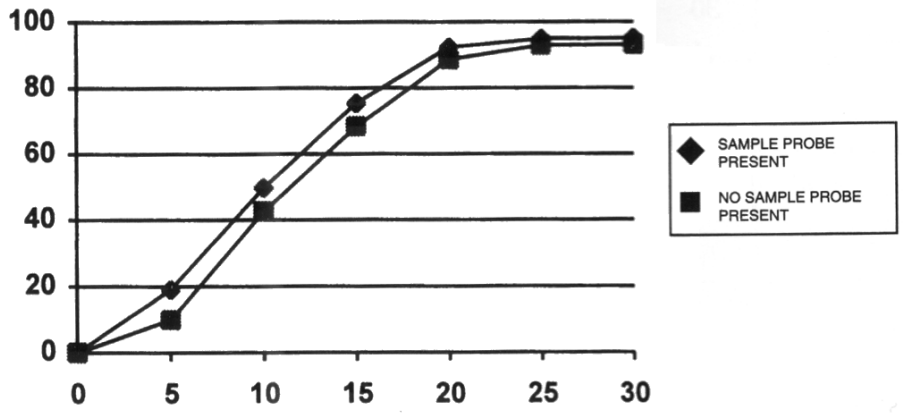
Resident Probes can greatly alter hydrodynamics and alter results vs. manual methods

Higher % Dissolved and more variability

Validation Resident Probe Effect

For each method:

- Perform n=12 dissolution manually
- Perform n=12 dissolution w/ automation
- Compare mean of n=12 data and obtain f2 value
- f2 must be greater than 50, perhaps higher



Total time to Validate Autosampler

For non-resident probe ~1 hour per method, can generally add a few samples to other analyses being performed during method validation

For resident probe 1 hour + 4 dissolution runs

Multi-Process Automation

Multi-process Automation

- Online UV w/ cell changer
- Online UV w/ single cell and valve
- Online UV w/ fiberoptics
- Online HPLC w/ injector

Online UV measurement

Advantages

- Same advantages as with an autosampler
- Real time analysis of samples
- Reports information immediately
- Full log of activities

Online UV measurement

Disadvantages

- Limited to UV analysis
- Similar disadvantages as autosampler
- No sample archival (unless autosampler is inline)
- Analyst training
- Validation time
- Possible timing restraints with multiple baths

Validation Requirements for Online UV/HPLC Approaches

- Mirror the same validation requirements of the 8000
- If analytical finish is different than what is used for manual sampling, this would need to be validated as well
- Additional validation and method development required for fiberoptic analysis

Analytical Finish Validation

If a different analytic finish or instrument is used, the following should be re-evaluated:

- LOD/LOQ
- Range
- Linearity
- Specificity (if changing techniques)

Carryover/Cleaning Check

Generally, checking for carryover and cleaning are performed the same as with an autosampler

For UV systems with a single cell and valve sampling, validation will need to be done to ensure there is <1% cross contamination between samples

New Methods of Automated Analysis

Fiber Optic Advantages

No machinery, pumps, flow cells, manual sampling/Analysis in real time

Brings spectroscopy to the vessel

Eliminates cross contamination

Provides more data-points

Fiber Optics

<u>Fiber Optic Considerations</u>

Excipient interference

Bubbles

Drying on optical surfaces

Sticky residues

Cell path length

Blanking and standardizing each probe

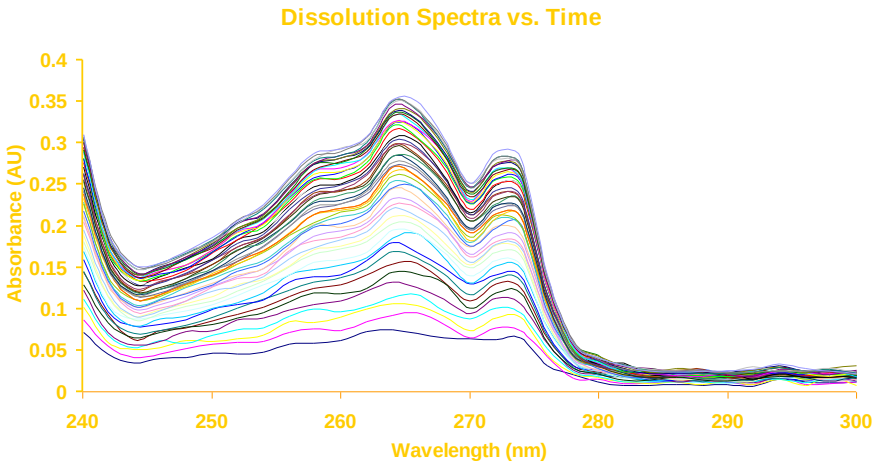
Validation

Fiberoptic Validation

For Fiberoptics, there is no filter used and a different analytical finish so multiple things need to be validated

- Apparent Dissolution vs. Filtered Dissolution
- LOD/LOQ
- Range
- Linearity
- Deaeration
- Resident Probe evaluation

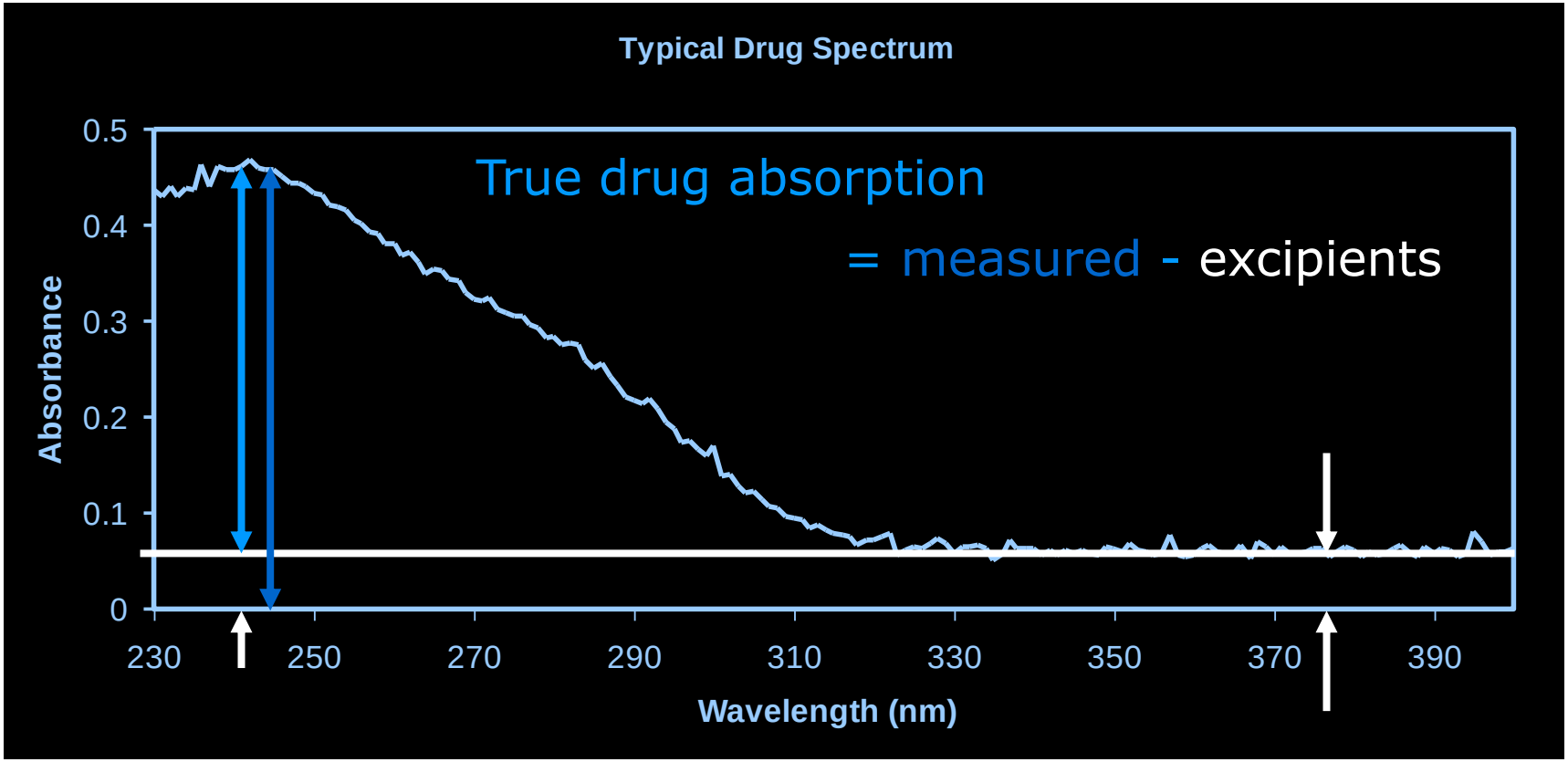
Fiberoptic Validation – Apparent Dissolution



Fiberoptics contains no filters, so your total absorbance is made up of:

- Dissolved Drug Absorbance
- Undissolved Particles
- Excipients
- Media
- Fiberoptic Probes

Baseline Correction



Baseline Correction

Baseline correction can account for most undissolved particles and other interferences, but does not work in all situations.

- Colloidal particles
- Reflecting/Diffracting Particles

Validation should be done to show that filtered samples give them same result as baseline corrected fiberoptic data

Fiberoptic Validation - Deaeration

Deaeration is Critical in Fiberoptics

Bubbles cannot be optically corrected for

Upcoming Webinars

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

Developing Methods for the Apparatus 3 and 7 – July 11th

Small Volume Dissolution Methodology – August 22nd

Online UV Dissolution Method Development – October 3rd

Fiberoptic UV Dissolution Method Development – December 5th

Thank You!

Questions?

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