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The Impact of Automated Performance Verification in the Regulated Laboratory

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Outline

- Overview of Pharmacopeia Requirements from USP and EP
 - Required tests
 - Thermo scientific standards
- Impact of Automation
 - A tiered testing approach
 - Benefits of automation





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Pharmacopeia Overview

Recommended UV-Visible
Performance Verification Tests

Photometric Accuracy

- USP:

- “For checking the photometric scale, a number of ***standard inorganic glass filters*** as well as ***standard solutions*** of known transmittances such as potassium chromate or ***potassium dichromate*** are available.”

- EP:

- “Check the absorbance using suitable ***filters or a solution of potassium dichromate...***”
- Common testing performed with 60 mg/mL standard
- New addition of a 600 mg/mL standard for checking photometric accuracy in the visible at 430 nm

Photometric Accuracy

Standard	Includes
6 Potassium Dichromate Solutions in Perchloric Acid (UV-Vis)	6 sealed cells: Perchloric acid blank, 20, 40, 60, 80, and 100 mg/L potassium dichromate in 0.001M perchloric acid Absorbance ranging from 0.1A to 1.5A
Potassium Dichromate in Perchloric Acid Solution (UV-Vis)	2 sealed cells: Perchloric acid blank and 60 mg/L potassium dichromate in 0.001M perchloric acid Absorbance ≈ 1 A
4 Nicotinic Acid Solutions in Hydrochloric Acid (UV)	5 sealed cells: 0.1N HCl blank and 6, 12, 18, and 24 mg/L nicotinic acid in 0.1N HCl Nominal absorbance values of 0.0A, 0.25, 0.50, 0.75, and 1.0A

- NIST and NPL traceable standards are also available for existing SOPs
 - NTRM 930 and 1930

Wavelength Accuracy

■ USP:

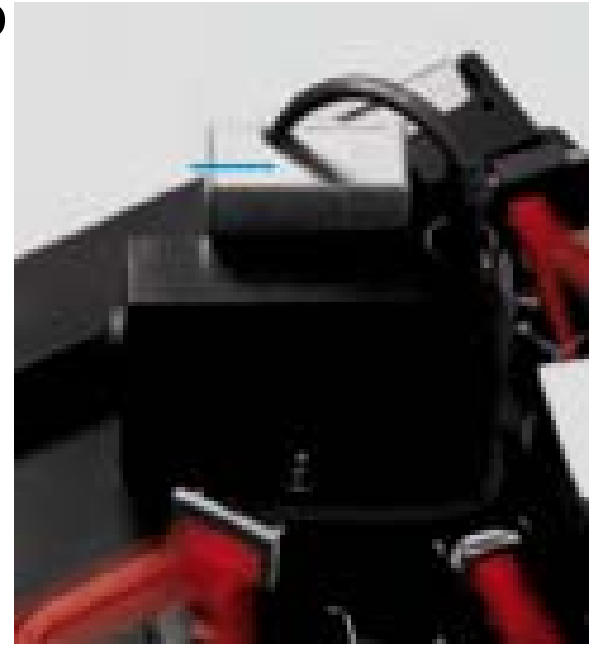
- “**The best single source of UV and visible calibration spectra is the quartz-mercury arc...**”
- “The wavelength scale may be calibrated also by means of suitable glass filters, which have useful absorption bands through the visible and UV regions.”
- “Standard holmium oxide solution has superseded the use of holmium glass.” -- New is USP 29

■ EP:

- Verify the wavelength scale using the ***absorption maxima of a holmium perchlorate solution***, the line of a hydrogen or deuterium discharge lamp, or the ***lines of a mercury vapour arc...***”

Mercury Lamp Accessory

- Primary Standard – No Calibration or Re-Calibration Necessary
- If necessary, allows a factory re-calibration to be performed without a service call
- “The best single source of UV and visible calibration spectra...”
--USP 29 First Supplement
- Useful for IQ,OQ,PQ, and RQ of instrument
- Scans of emission lines can be used to measure spectral bandwidth



Wavelength Accuracy Liquid Standards

Standard	Includes
Holmium Oxide in Perchloric Acid Solution (UV-Vis)	One sealed cell with 4% v/v solution of holmium oxide in 10% perchloric acid Empty cell holder used as blank
2 Calibrated / Traceable Glass Rare Earth Filters (UV-Vis)	One Holmium GLASS filter calibrated against NPL & NIST Primary Standards One Didymium GLASS filter calibrated against NPL Primary Standard

- Automated PV Tests use:
 - Mercury Lamp (if installed)
 - Instrument Lamp

Stray Light

- USP:

- No specification given in Section 851
- Currently under review – revision coming shortly

- EP:

- “Stray light may be detected at a given wavelength with suitable filters or solutions: for example, the absorbance of a 12 g/L solution of **potassium chloride**...and is greater than 2.0 at 198nm when compared to water as compensation liquid.”

Filter	Cut Off Wavelength
Potassium Chloride	198 nm
Sodium Iodide	220 nm
Sodium Nitrite	340 nm

Resolution

- USP:
 - No specification given in Section 851

- EP:
 - “...record the spectrum of a 0.02 per cent V/V solution of ***toluene in hexane***. The minimum ratio of the absorbance at the maximum at 269 nm to that at the minimum at 266 nm is stated in the monograph.
 - No monographs in the EP currently specify the resolution of the spectrophotometer.

ThermoFisher
S C I E N T I F I C

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Automated Performance Verification

The CVC accessory

Calibration **Validation** Carousel (CVC)

- Automates Performance Verification
- Increases Productivity
 - Each CVC has a unique Serial Number
 - Automatically Detected by Software
 - Matched to the Calibration Data
- Filters and Solutions are certified by NIST or NPL
- Does not calibrate instrument, verifies calibration



CVC Automated Tests

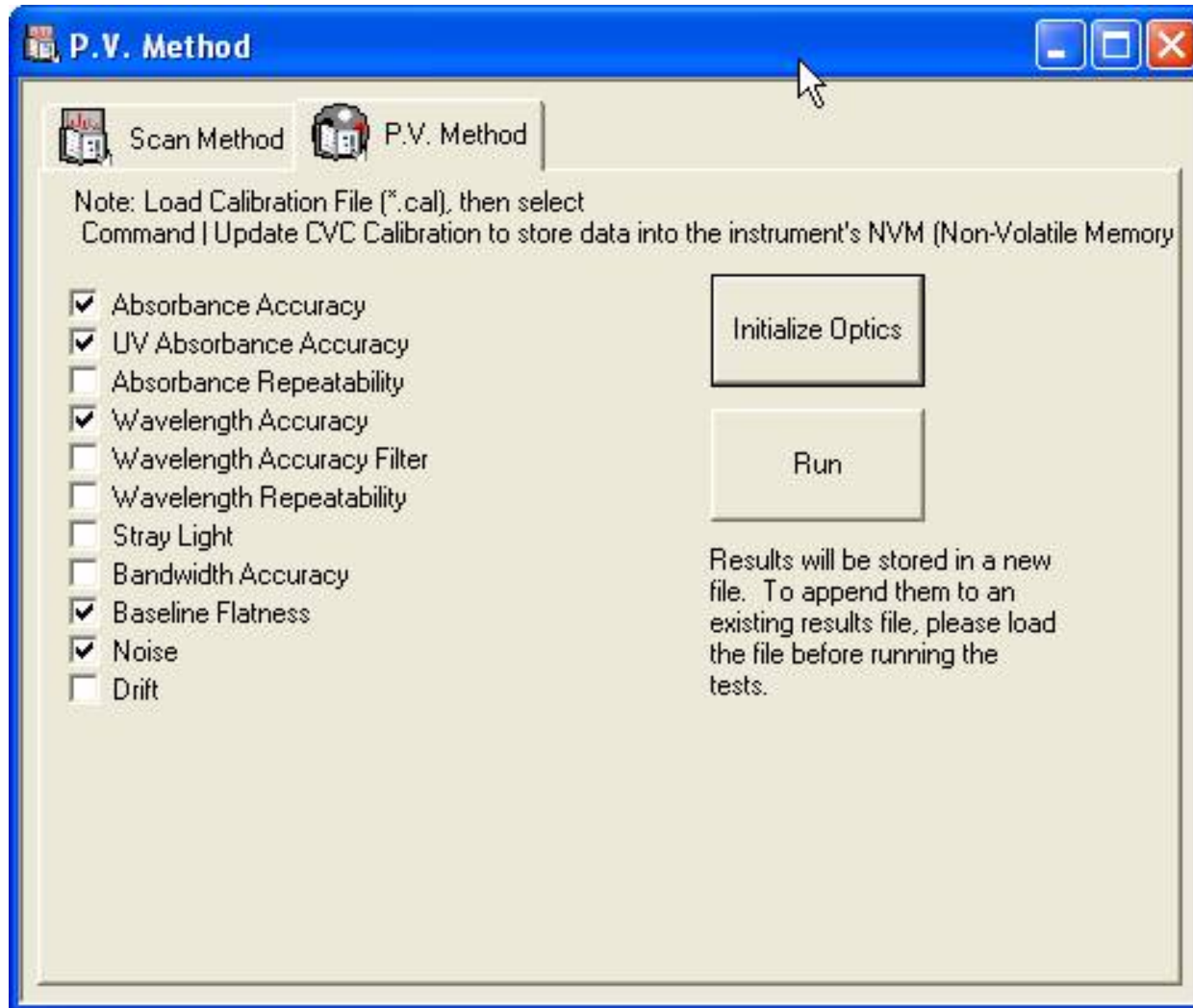
- CVC automates tests for:
 - Wavelength Accuracy
 - Photometric Accuracy
 - Stray Light
 - Photometric Noise
 - Photometric Stability or Drift
 - UV Absorbance Accuracy
 - Bandwidth Accuracy

CVC Advantages

- Automation Benefits:
 - No Matching of Standards to Data –all calibration data stored under one serial number
 - No copying of calibrated values from certificates
 - No manual entry of serial numbers
 - Eliminates transcription errors
 - Eliminates need to handle standards
 - Eliminates need to present standards manually – no errors

- Scientist or technician spends only minutes on PV (OQ) testing
 - Dramatically increases productivity
 - Allows testing time to be filled with other & more productive activities

PV Test Setup in VISION software



Instrument "Initialization" Options

Options

Batch Information Printout | Environment Information

File Load/Save Behavior | System Settings

Communications

Comms Port: COM1

Baud Rate: 9600

Note: The UV Series Spectrophotometer will only communicate at 9600 baud.

P.V. Test Setting

Optics Initialization Every: 1 day

Absorbance Display

3 4 8 Decimal places

Timer/Trigger Setting

Synchronization Start Prompt

Prompt between samples

Show table gridlines on printout

Manual calculation of UVcalc templates (F9)

Print audit trail

Disable Live Signal

Display Baseline

OK Cancel

PV Test Result Reporting

- All GLP information reported
 - CVC serial number
 - Instrument serial number
 - Date and time
 - Test result

P.V. Test Results - CVC PV test results.vre							
	Instrument ID	114005					
1							
2	Absorbance Accuracy	Pass	Test Date	8/5/2005	Test Time	12:06	
3							
4	Instrument	Hours=671			Serial No.	Calibrated	Details
5	Xe Lamp	%Life=0.5	Energy=7.0%		32408	5/20/2003	CVC
6							
7	Wavelength	Actual	Measured	Tolerance	Difference	Result	
8	(nm)	(A)	(A)	(A)	(A)		
9	546.00	0.91340	0.91490	0.01000	0.00150	Pass	

- Evaluate instrument performance and control over the wavelength and photometric axes
- Tests are representative of the requirements of most Pharmacopeias and regulatory agencies
- Tests are designed to quickly identify discrepancies in instrument performance and give a relevant and useful snapshot of instrument performance
- Tests:
 - Wavelength accuracy
 - Photometric accuracy (two separate tests)
 - Absorbance accuracy
 - UV absorbance accuracy
 - Photometric noise (noise)
 - Baseline flatness

- Examine long-term aspects of the instrument's mechanical performance
- Compromises in instrument performance arising from these tests will also be identified during Tier 1 testing
 - a major component failure that causes wavelength repeatability to fail during Tier 2 testing would also be likely to cause a wavelength accuracy failure in Tier 1 testing
- Tests:
 - Photometric (absorbance) repeatability
 - Wavelength repeatability
 - Stray light

- Evaluate instrument performance and control over the wavelength and photometric axes
- Tests are representative of the requirements of most Pharmacopeias and regulatory agencies
- Tests are designed to quickly identify discrepancies in instrument performance and give a relevant and useful snapshot of instrument performance
- Tests:
 - Drift
 - Bandwidth Accuracy

Time Savings with the CVC Accessory – Factor of ~100

PV Test Performed	Automated Standard	Total Automated Method Time (minutes)	Manual Standard	Manual Measurement Time (minutes)	Manual Calculation Time (minutes)	Total Manual Method Time (minutes)
wavelength Accuracy	Mercury Lamp	5	Holmium Perchlorate Solution	10	15	25
Wavelength Repeatability	Mercury Lamp	8	Holmium Perchlorate solution	36	32	68
Photometric Accuracy	Potassium Dichromate	2	Neutral Density Filter (Vis only)	6	20	28
UV Photometric Accuracy	Potassium Dichromate		Potassium Dichromate	2		
Photometric Repeatability	Neutral Density Filter	<1	Neutral Density Filter	4	12	16
Stray Light	220 and 340 nm filters	1	Sodium Iodide (220 nm)	4	15	19
			Sodium Nitrate (340 nm)			
Photometric Noise	Empty beam	7	Instrument (0A)	7	13	20
	Neutral Density Filter (1A)		Neutral Density Filter (1A)			
Photometric Stability (Drift)	No external standard	60	No external standard	60	10	70
Baseline Flatness	No external standard	12	No external standard	12	5	17
Bandwidth Accuracy	Mercury Lamp	3	Mercury Lamp	10	15	25
Total Time		100				288
Total Time of User		2 - 3				288

Tier 1 Comparison

PV Test Performed	Automated Standard	Total Automated Method Time (minutes)	Manual Standard	Manual Measurement Time (minutes)	Manual Calculation Time (minutes)	Total Manual Method Time (minutes)
wavelength Accuracy	Mercury Lamp	5	Holmium Perchlorate Solution	10	15	25
Photometric Accuracy	Potassium Dichromate	2	Neutral Density Filter (Vis only)	6	20	28
UV Photometric Accuracy	Potassium Dichromate		Potassium Dichromate	2		
Photometric Noise	Empty beam	7	Instrument (0A)	7	13	20
	Neutral Density Filter (1A)		Neutral Density Filter (1A)			
Baseline Flatness	No external standard	12	No external standard	12	5	17
Total Time		26				90
Total Time of User		2 - 3				90

- User spends 2 to 3 minutes doing routine PV testing (OQ) compared to 90 minutes using manual methods
 - Allows more frequent testing
 - Allows more confidence in data

Tier 2 and Tier 3 Testing Comparison

Tier 2

PV Test Performed	Automated Standard	Total Automated Method Time (minutes)	Manual Standard	Manual Measurement Time (minutes)	Manual Calculation Time (minutes)	Total Manual Method Time (minutes)
Wavelength Repeatability	Mercury Lamp	8	Holmium Perchlorate solution	36	32	68
Photometric Repeatability	Neutral Density Filter	<1	Neutral Density Filter	4	12	16
Stray Light	220 and 340 nm filters	1	Sodium Iodide (220 nm)	4	15	19
			Sodium Nitrate (340 nm)			
Total Time		<10				105
Total Time of User		2 - 3				105

Tier 3

PV Test Performed	Automated Standard	Total Automated Method Time (minutes)	Manual Standard	Manual Measurement Time (minutes)	Manual Calculation Time (minutes)	Total Manual Method Time (minutes)
Photometric Stability (Drift)	No external standard	60	No external standard	60	10	70
Bandwidth Accuracy	Mercury Lamp	3	Mercury Lamp	10	15	25
Total Time		63				95
Total Time of User		2 - 3				95

Summary

- Automated testing
 - Eliminates human error
 - Reduces time of analyst for PV or OQ testing
 - Facilitates better compliance
 - Increases lab productivity
 - Other tasks accomplished while tests are automatically performed

- Tiered Testing
 - Segregates tests by the most useful information captured
 - Saves time
 - Increases productivity
 - No time wasted on tests that are not frequently required

Additional Thermo Automation Advantages

- Windows Security integration of user access control
 - Thermo Security Administration makes global user level management simple
 - All users on all workstations managed from one location for all UV-Visible instrument worldwide
 - Extraordinary benefits only available:
 - Check server access before sending data
 - Track data changes even when control software is not running
 - Automated integration into audit trails and event records
 - One password and log-in for system and software access
 - Works for all Thermo Scientific UV-Visible, Raman, Near-IR, and FT-IR instruments