Major changes and extensions in the pharmacopoeias

Rainer Turek

Regional Business Development, EMEA

Outline

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United States Pharmacopoeia, USP–NF 2022, Issue 3 Chapter 621: Chromatography (Official Date Dec. 1, 2022)

- Unites States Pharmacopoeia
  - Changes in <621> Chromatography
  - <1220> Analytical Procedure Life Cycle

European Pharmacopoeia, 11.0 (Official Date Jan. 1, 2023)

- European Pharmacopoeia
  - Changes in 2.2.46 Chromatographic Separation Techniques
  - Addition of 5.26 Implementation of Pharmacopeial Procedures

USP <621> & EP 2.2.46 | Harmonization

Parameter	Currently effective	Effective soon[1]
CHANGE METHODS		
Changing HPLC methods to UHPLC condition	Permitted for isocratic Not allowed for gradients	Permitted for isocratic and gradients
CALCULATIONS		
Theoretical Plates	Tangent width reporting as plate count	Half-Height width reporting as plate number
Resolution & Relative Resolution	Tangent width	Half-Height width
Tailing factor	No formula change but renamed, harmonized, and now reported as Symmetry Factor	
S/N Calculation	5 times the peak width at half height	20 times the peak width at half height

(1) Effective by 01/DEC/2022 in USP and 01/JAN/2023 in EP

USP <621> & EP 2.2.46
Change HPLC methods to UHPLC condition

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	Alliance	Arc	ACQUITY	Arc	ACQUITY		
Waters THE SCIENCE OF WHAT'S POSSIBLE	HPLC	HPLC	Arc	Premier System	H-Class PLUS	Premier System	I-Class PLUS
Particle Size (Optimized for)	3.5-5 µm	3.5-5 µm	2.5-5 µm	2.5-3.5 µm	<2 µm	<2 µm	<2 µm

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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Parameter	Value
Stationary Phase	… no change of the identity of the substituent…
Column dimension and particle	… the particle size and/or length of the column may be modified provided that the ratio of the column length (L) to the particle size (dp) remains constant or in the range − 25 per cent to + 50 per cent of the prescribed L/dp ratio…
Column Internal diameter	… In absence of a change in particle size and/or length, the internal diameter of the column may be adjusted. Caution is necessary when the adjustment results in smaller peak volumes due to a smaller particle size or smaller internal column diameter, a situation that may require adjustments to minimize extra-column band broadening by factors such as instrument connections, detector cell volume and sampling rate, and injection volume. When the particle size is changed, the flow rate requires adjustment, because smaller-particle columns will require higher linear velocities for the same performance (as measured by reduced plate height). The flow rate is adjusted for both the change in column diameter and particle size using the following equation…

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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Parameter	Value
Flow rate	Isocratic: … in the absence of a change in column dimensions, an adjustment of the flow rate by ± 50 per cent is permitted… Gradient: … Flow rate is adjusted for changes in column diameter and particle size using the following equation …
Gradient time points	… A change in column dimensions, and thus in column volume, impacts the gradient volume, which controls selectivity. Gradients are adjusted to the column volume by changing the gradient volume in proportion to the column volume. This applies to every gradient segment volume…
Temperature	Isocratic: ± 10 °C, where the operating temperature is specified, unless otherwise prescribed Gradient: Column temperature: ± 5 °C, where the operating temperature is specified, unless otherwise prescribed
Wavelength (nm)	No adjustment permitted
Injection Volume	.. When the column dimensions are changed, the following equation may be used for adjusting the injection volume: …

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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Parameter	Value
Dwell volume	… include an isocratic step before the start of the gradient program so that an adaptation can be made to the gradient time points to take account of differences in dwell volume between the system used for analytical procedure development and that actually used. It is the user's responsibility to adapt the length of the isocratic step to the analytical equipment used…
pH of the aqueous component in the mobile phase	±0.2 pH units, unless otherwise prescribed
Concentration of salts in the buffer component of a mobile phase	±10 %

Take care for methods that use strong buffers, consider the environmental conditions prior changing the method.

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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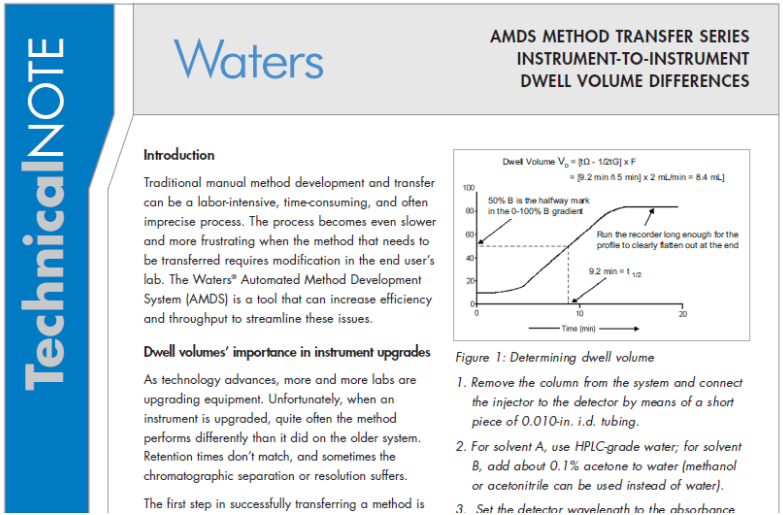
1. Recommendation

Determine the System Dwell volumes for all your instruments



TechnicalNOTE

Waters

AMDS METHOD TRANSFER SERIES
INSTRUMENT-TO-INSTRUMENT
DWELL VOLUME DIFFERENCES

Introduction

Traditional manual method development and transfer can be a labor-intensive, time-consuming, and often imprecise process. The process becomes even slower and more frustrating when the method that needs to be transferred requires modification in the end user's lab. The Waters® Automated Method Development System (AMDS) is a tool that can increase efficiency and throughput to streamline these issues.

Dwell volumes' importance in instrument upgrades

As technology advances, more and more labs are upgrading equipment. Unfortunately, when an instrument is upgraded, quite often the method performs differently than it did on the older system. Retention times don't match, and sometimes the chromatographic separation or resolution suffers.

The first step in successfully transferring a method is

Figure 1: Determining dwell volume

1. *Remove the column from the system and connect the injector to the detector by means of a short piece of 0.010-in. i.d. tubing.*
2. *For solvent A, use HPLC-grade water; for solvent B, add about 0.1% acetone to water (methanol or acetonitrile can be used instead of water).*
3. *Set the detector wavelength to the absorbance*

Waters can help you to setup custom fields (13 fields) to automatically calculate the dwell volume, following the guidelines (USP).

Validation service is also available.

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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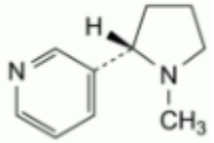
2. Adjust the column length and particle size according to L/dp.

The column must match the description of the pharmacopoeia.
The column must be available in the desired particle size and dimensions.

General Notices apply to all monographs and other texts.
See the information section on general monographs.

Nicotinum

Practical Information	Test(s)	Brand Name/Information
	related substances	waters XTerra RP18 is suitable



Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R (5 µm).

Organosilica polymer, amorphous, polar-embedded octadecylsilyl, end-capped. *1150600.*

Synthetic, spherical hybrid particles containing both inorganic (silica) and organic (organosiloxanes) components, chemically modified at the surface by the bonding of polar-embedded octadecylsilyl groups. To minimise any interaction with basic compounds, they are carefully end-capped to cover most of the remaining silanol groups.

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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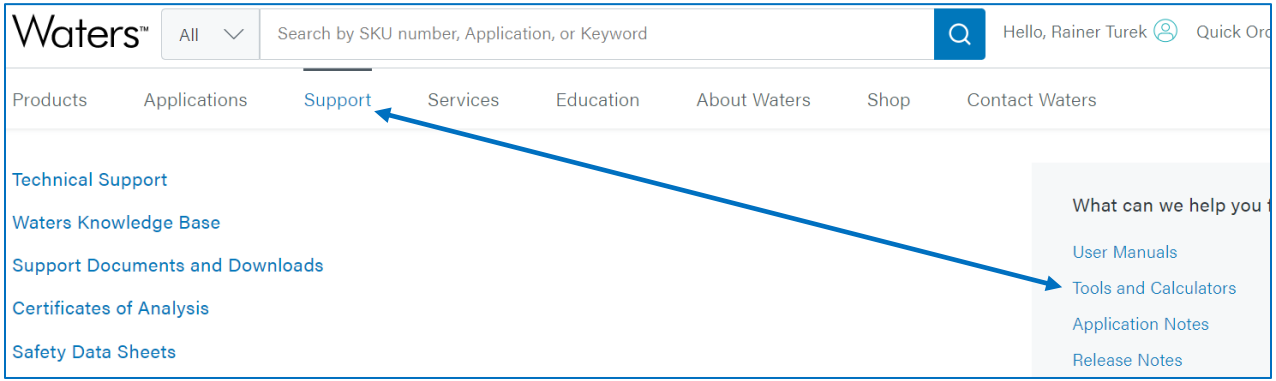
2. Adjust the column length and particle size according to L/dp.



Microsoft Edge
Web Browser

The **tools located here help you to identify the right column**, to **do the maths** (L/dp) with the column calculator, and much more…

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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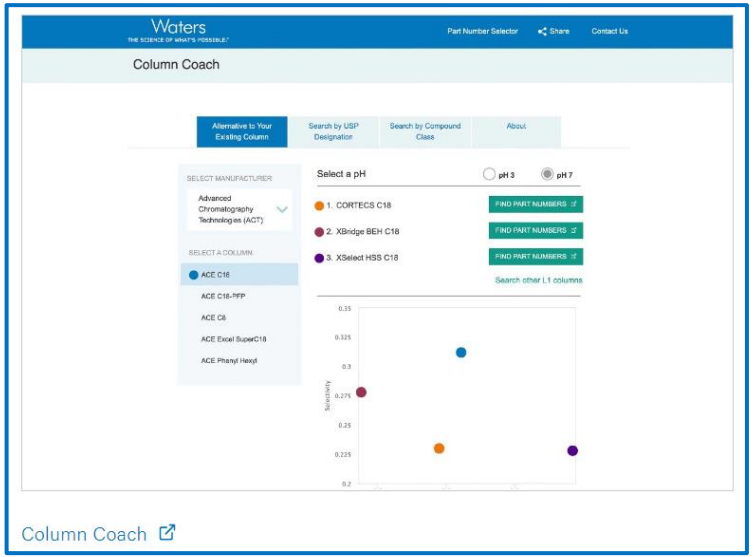
2. Adjust the column length and particle size according to L/dp.



Various columns benchmarked

Home > Products >
Chromatography Consumables & Supplies > Columns >
Column Comparison Chart

Select Your Manufacturer:

Advanced Chromatography Technologies (ACT)
Advanced Materials Technology (AMT)
Agilent Technologies
GL Sciences
Imtakt Corporation
Macherey-Nagel
MAC-MOD Analytical
MilliporeSigma
Nomura Chemical Company
Phenomenex
Restek
Shiseido
Shodex
ThermoFisher Scientific
Tosoh BioScience
YMC
Zirchrom Separations

Advanced Materials Technology (AMT)

Column Name	Bonded-Phase	Waters Closest Selectivity Column	Waters Recommended UPLC Column	Waters Recommended HPLC Column	Waters Recommended Preparative Column
Halo AQ-C18	C18	CORTECS T3	CORTECS T3	CORTECS T3	Atlantis T3 OBD
Halo Biphenyl	Phenyl	Spherisorb ODSB	CORTECS Phenyl	CORTECS Phenyl	XBridge BEH Phenyl OBD
Halo C18	C18	SunFire C18	CORTECS C18	CORTECS C18	XBridge BEH C18 OBD
Halo C8	C8	Nova-Pak C8	CORTECS C8	CORTECS C8	XBridge BEH C8 OBD
Halo ES-CN	Cyano	ACQUITY UPLC CSH Fluoro-Phenyl XSelect CSH Fluoro-Phenyl	ACQUITY UPLC HSS CN	XSelect HSS CN XSelect HSS CN XP	Spherisorb CN OBD
Halo HILIC	Silica	CORTECS HILIC	CORTECS HILIC	CORTECS HILIC	Atlantis HILIC OBD
Halo Peptide ES C18	C18	Nova-Pak Phenyl	ACQUITY UPLC BEH Peptide C18	XBridge BEH Peptide C18	XBridge Peptide BEH C18 OBD
Halo PFP	PFP	Spherisorb ODSB	ACQUITY UPLC HSS PFP	XSelect HSS PFP XSelect HSS PFP XP	XSelect CSH Fluoro-Phenyl OBD

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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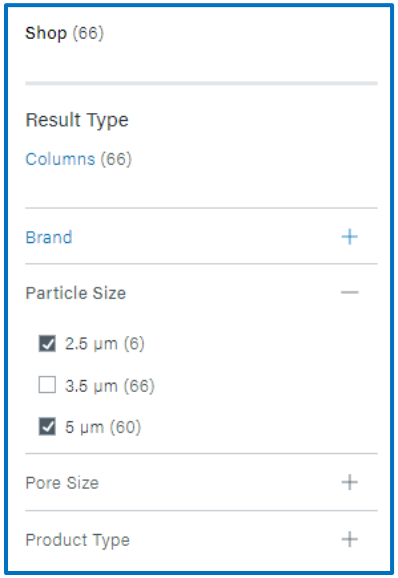
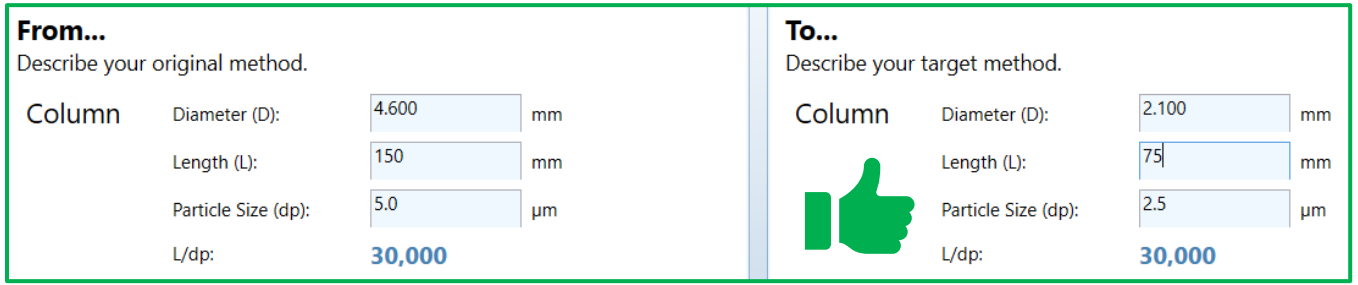
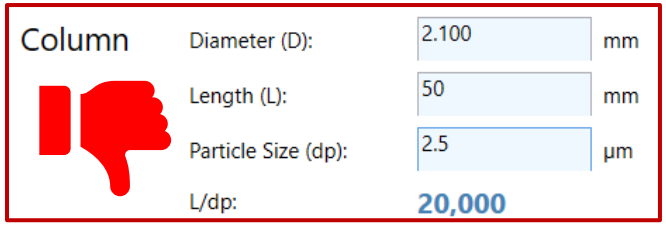
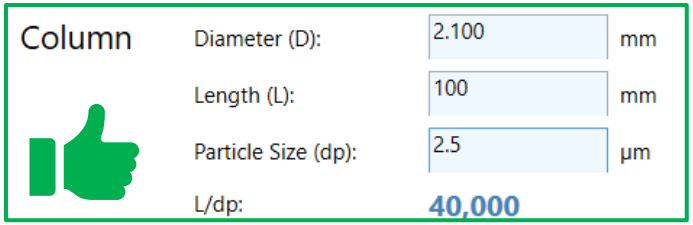
2. Adjust the column length and particle size according to L/dp.

Use the column calculator for the maths (also embedded in Empower) & visit the web-shop









USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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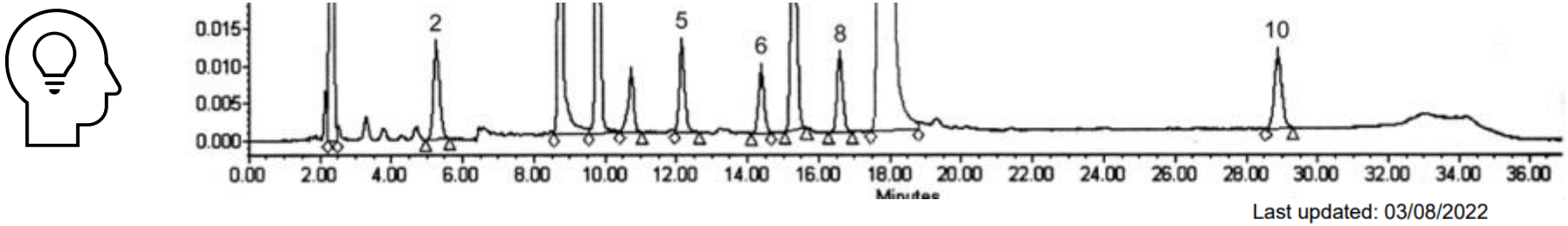
2. Adjust the column length and particle size according to L/dp.

Sometimes the pharmacopeia publishes reference chromatograms



Last updated: 03/08/2022

When peaks are close together (8-11 min), you may be best served with L/dp ≥ the original column's L/dp – trading speed for resolution.

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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3. Adjust the flow rate for changes in particle size and column diameter. Adjust the gradient time of each segment for changes in column length, diameter, and flow rate.

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 3.01	100 → 95	0 → 5
3.01 - 28	95 → 74	5 → 26
28 - 32	74 → 60	26 → 40

	Time (min)	Flow Rate (mL/min)	%A Water	%B Acetonitr	%C Methano	%D Water	Column Volumes
1	3.00	1.000	100.0	0.0	0.0	0.0	1.82
2	3.01	1.000	95.0	5.0	0.0	0.0	0.01
3	28.00	1.000	74.0	26.0	0.0	0.0	15.19
4	32.00	1.000	60.0	40.0	0.0	0.0	2.43
*							

	Time (min)	Flow Rate (mL/min)	%A Water	%B Acetonitrile	Column Volumes
1	1.00	0.417	100.0	0.0	1.82
2	1.00	0.417	95.0	5.0	0.01
3	9.33	0.417	74.0	26.0	15.19
4	10.67	0.417	60.0	40.0	2.43

The tool also provide information for the isocratic hold step to compensate dwell volume differences, computes pressure, etc.

USP <621> & EP 2.2.46
Changing HPLC methods to UHPLC condition

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Variable	Original Conditions	Adjusted Conditions	Comment
Column length (*L*), in mm	150	100	User's choice
Column diameter (*dc*), in mm	4.6	2.1	User's choice
Particle size (*dp*), in µm	5	3	User's choice
L/*dp*	30.0	33.3	(1)
Flow rate, in mL/min	2.0	0.7	(2)
Gradient adjustment factor (t_{G2}/t_{G1})	—	0.4	(3)
Gradient conditions	—	—	—
B (%)	Time (min)	Time (min)	
30	0	0	—
30	3	(3 × 0.4) = 1.2	—
70	13	[1.2 + (10 × 0.4)] = 5.2	—
30	16	[5.2 + (3 × 0.4)] = 6.4	—

1. An 11% increase within allowed *L*/*dp* change of –25% to +50%
2. Calculated using $F_2 = F_1 [(dc_2^2 \times dp_1)/(dc_1^2 \times dp_2)]$
3. Calculated using $t_{G2} = t_{G1} \times (F_1/F_2) [(L_2 \times dc_2^2)/(L_1 \times dc_1^2)]$

Column temperature: ±5° C, where the operating temperature is specified, unless otherwise prescribed

Further adjustments in procedure conditions (mobile phase, temperature, pH, etc.) may be required, within the permitted ranges described under *System Suitability* and *Adjustment of Chromatographic Conditions* in this chapter.

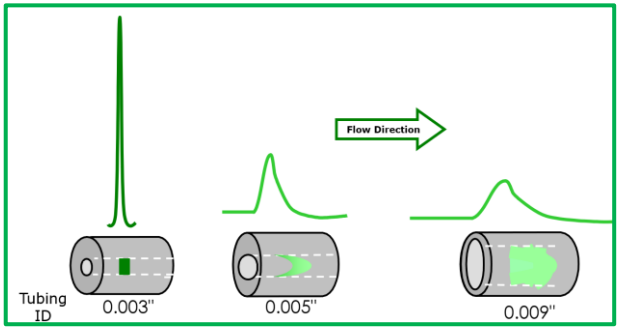
Everything

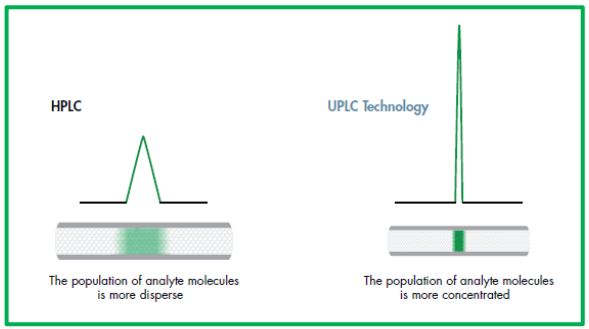
is

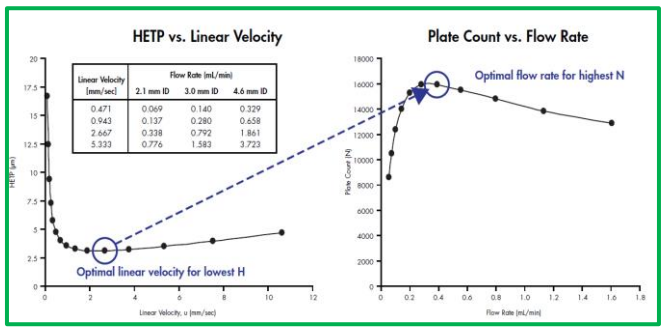
exactly

explained

Waters THE SCIENCE OF WHAT'S POSSIBLE™	Alliance	Arc	ACQUITY	Arc	ACQUITY		
	HPLC	HPLC	Arc	Premier System	H-Class PLUS	Premier System	I-Class PLUS
Particle Size (Optimized for)	3.5-5 µm	3.5-5 µm	2.5-5 µm	2.5-3.5 µm	<2 µm	<2 µm	<2 µm
Flowpath	1	2 (2x HPLC)	2 (3.5-5 µm + 2.5-3.5 µm column optimized)	1	1	1	1
Tubing	0.010“	0.010”	0.005”	0.005”	0.004”	0.004”	0.003”







…running the right column on the right system will give best results…

USP <621> & EP 2.2.46 | Harmonization

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Parameter	Currently effective	Effective soon[1]
CHANGE METHODS		
Changing HPLC methods to UHPLC condition	Permitted for isocratic Not allowed for gradients	Permitted for isocratic and gradients
CALCULATIONS		
Theoretical Plates	Tangent width reporting as plate count	Half-Height width reporting as plate number
Resolution & Relative Resolution	Tangent width	Half-Height width
Tailing factor	No formula change but renamed, harmonized, and now reported as Symmetry Factor	
S/N Calculation	≥ 5 times the peak width at half height	20 times the peak width at half height

(1) Effective by 01/DEC/2022 in USP and 01/JAN/2023 in EP

USP <621> & EP 2.2.46 | Calculations within Empower

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"The system suitability and acceptance criteria in monographs have been set using parameters as defined below. With some equipment, certain parameters, such as the signal-to-noise ratio and resolution, can be calculated using software provided by the manufacturer. It is the **responsibility of the user to ensure that the calculation methods used** in the software **are equivalent to the requirements** of the *US Pharmacopeia* and to **make any necessary corrections if this is not the case**."

USP <621>

USP <621> & EP 2.2.46
Calculations within Empower

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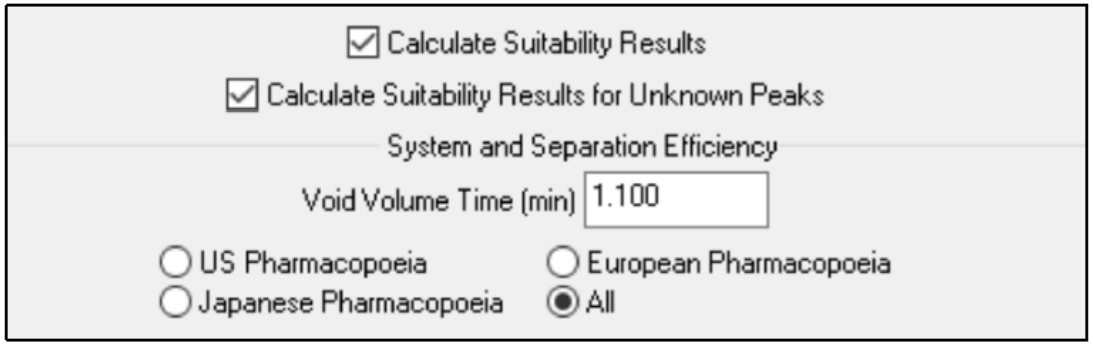
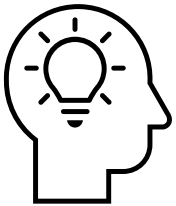
Formula used by Empower is impacted by the pharmacopeia selection



Chinese pharmacopoeia supported in Empower version 3.7 or later



I. Press **[F1] within Empower** to open the help menu, preferably inside a processing method.

II. Lookup for "**Verifying System Performance**" to display the formula used by Empower for your selection (US, EP, JP, ChP, All) and to what field it is reported.

USP <621> & EP 2.2.46 | Calculations within Empower Resolution (R_s)

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The resolution between peaks of two components (*Figure 1*) may be calculated using the following equation:

$$R_S = \frac{1.18\left(t_{R2} - t_{R1}\right)}{W_{h1} + W_{h2}}$$

$$t_{R2} > t_{R1}$$

t_{R1}, t_{R2} = retention times of the peaks
W_{h1}, W_{h2} = peak widths at half-height

Empower uses H-H width calculation in the field “USP Resolution (HH)” and the field Resolution (for EP and JP).

Empower uses the tangent width in the field “USP Resolution” an should therefore not be used any longer.

When using all pharmacopoeia or the filed “Relative Resolution” additional measures are needed.

USP <621> & EP 2.2.46 | Calculations within Empower
Relative Resolution (R_s) field & All Pharmacopoeia selection

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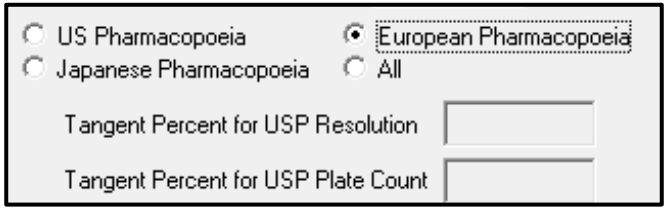
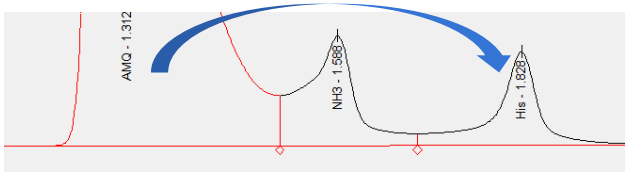
ALL or ChP will use the tangent approach



EP, JP and USP will use the H-H approach

Relative Resolution



	Name	Component Type	Peak Label	Retention Time (min)	RT Window (min)	Peak Match	3D Channel Name (Description)	Channel	Y Value	X Value	Fit	Weighting	Internal Std	RT Reference	Rel RT Reference	RRT	Rel Resol Reference	R
1	AMQ			1.310	0.150	Closest			Area	Amount	Linear thru Zero							
2	NH3			1.588	0.150	Closest			Area	Amount	Linear thru Zero							
3	His			1.829	0.150	Closest			Area	Amount	Linear thru Zero						AMQ	

USP <621> & EP 2.2.46 | Calculations within Empower
Relative Resolution (R_s) field & All Pharmacopoeia selection

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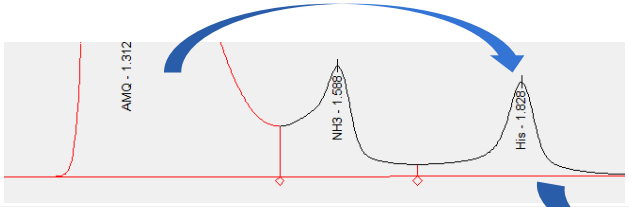

EP, USP or JP must be selected to report using the H-H calculation

	Name	Component Type	Peak Label	Retention Time (min)	RT Window (min)	Peak Match	3D Channel Name (Description)	Channel	Y Value	X Value	Fit	Weighting	Internal Std	RT Reference	Rel RT Reference	RRT	Rel Resol Reference	R
1	AMQ			1.310	0.150	Closest			Area	Amount	Linear thru Zero							
2	NH3			1.588	0.150	Closest			Area	Amount	Linear thru Zero							
3	His			1.829	0.150	Closest			Area	Amount	Linear thru Zero						AMQ	

Relative Resolution

	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	mmolAmount	Units	Peak Type	Peak Codes	Resolution	USP Resolution	USP Resolution (HH)	Rel. Resol.
1	AMQ	1.312	4505947	66.24	1402063	BV	25.000	25000000.000	pmoles	Found	S29				
2	NH3	1.588	118657	1.74	25446	VV	25.000	25000000.000	pmoles	Found	S29 S05 S07 S08 S09 S06	2.78	3.24	2.78	
3	His	1.828	87522	1.29	21734	VV	25.000	25000000.000	pmoles	Found	S29 S05 S07 S06	2.44	2.88	2.44	6.86
4	Ser	2.697	122608	1.80	27347	BV	25.000	25000000.000	pmoles	Found	S29 S05 S07 S06	10.34	10.16	10.34	

USP <621> & EP 2.2.46 | Calculations within Empower
Relative Resolution (R_s) field & All Pharmacopoeia selection

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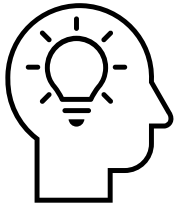
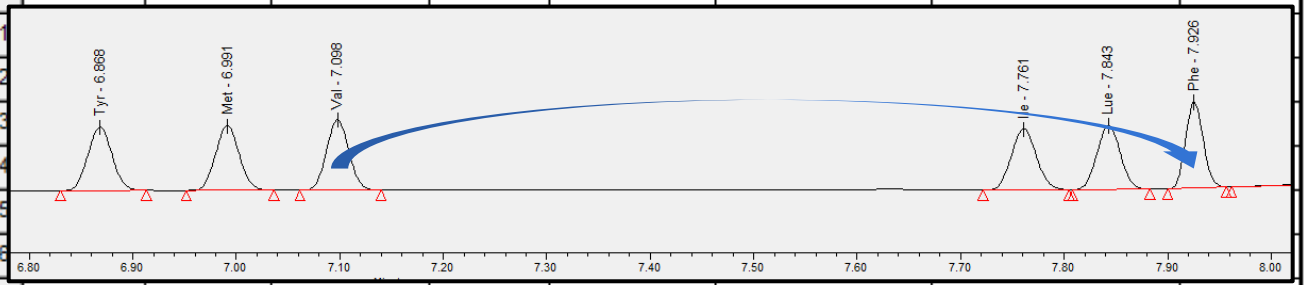


If you must use the **ALL or ChP** selection the **HH approach is not determined**
-> **use of a custom field required**
-> **to obtain a result using H-H calculations**

$$R_S = \frac{1.18\left(t_{R2} - t_{R1}\right)}{W_{h1} + W_{h2}}$$
$$t_{R2} > t_{R1}$$

lookup details in record "CRI-4304" at support.waters.com

	Name	Retention Time (min)	Width @ 50%	Resolution	USP Resolution	USP Resolution (HH)	Relative_Resolution_HH	Rel. Resol.
10	Ala	4.857	0.0377202940		6.98	7.11		
17	Val	7.098	0.0235382944		2.53	2.58		
18	Ile	7.761	0.0266709943		15.31	15.58		
19	Lue	7.843	0.0246719820		1.85	1.89		
20	Phe	7.926	0.0185677079		2.21	2.26	23.20	23.20



USP <621> & EP 2.2.46 | Calculations within Empower
Plate Count / Plate Number

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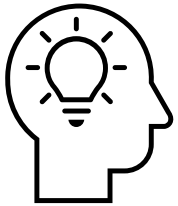
$$N = 5.54 \left(\frac{t_R}{W_h}\right)^2$$

t_R = retention time of the peak corresponding to the component
W_h = peak width at half-height (h/2)

Empower fields
EP Plate Count and JP Plate Count

USP Plate Count
uses the tangent approach.

You may compute a custom field to report USP_Plate_Number, see CRI-4304 at support.waters.com for instructions



In the Empower report method, consider to rename the field as "Plate number"

USP <621> & EP 2.2.46 | Calculations within Empower
Symmetry Factor / Tailing Factor

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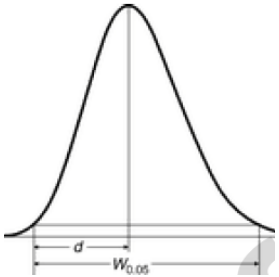
No change to formula

$$A_s = \frac{W_{0.05}}{2d}$$

$W_{0.05}$ = width of the peak at one-twentieth of the peak height
d = distance between the perpendicular dropped from the peak maximum and the leading edge of the peak at one-twentieth of the peak height



<u>Empower fields</u>
USP Tailing
Symmetry Factor (for EP and JP)
ChP Tailing Factor

USP <621> & EP 2.2.46 | Calculations within Empower Signal-to-Noise

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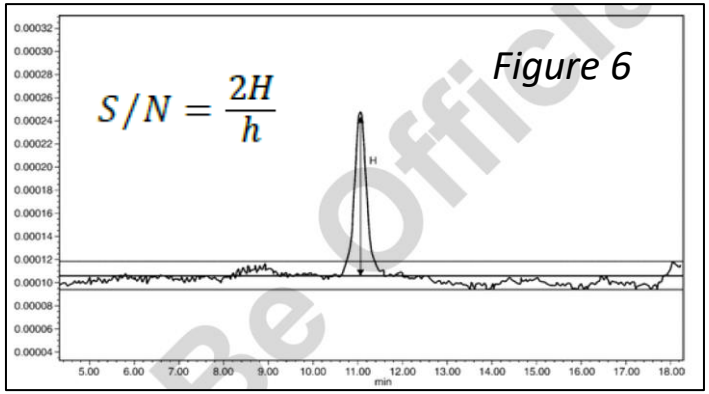
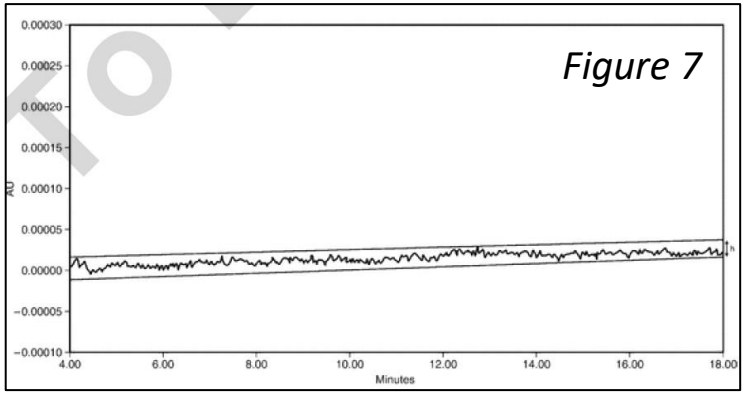
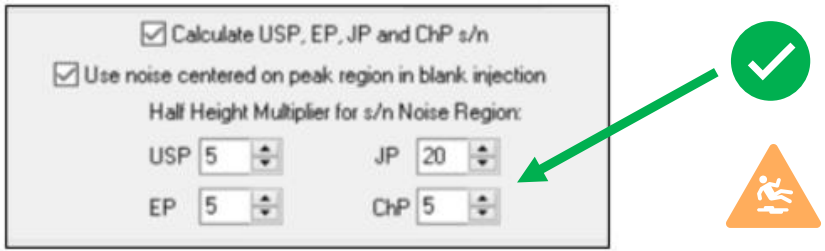




H = height of the peak (*Figure 6*) corresponding to the component concerned, in the chromatogram obtained with the prescribed reference solution, measured from the maximum of the peak to the extrapolated baseline of the **signal observed over a distance equal to 20 times the width at half-height**

h = **range of the noise** in a chromatogram obtained **after injection of a blank** (*Figure 7*), **observed over a distance equal to 20 times the width at half-height** of the peak in the chromatogram obtained with the prescribed reference solution and, if possible, situated equally around the place where this peak would be found

If a baseline of 20 times the width at half-height **is not obtainable** because of peaks due to the solvents or reagents, or arising from the mobile phase or the sample matrix, or due to the gas chromatographic temperature program, a **baseline of at least 5 times** the width at half-height is **permitted.**



Set the correct multiplier in the process method.

USP <621> & EP 2.2.46 | Calculations within Empower Summary - Calculations

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When the Pharmacopoeia in the processing method is set to:					
	United States Pharmacopoeia (USP)	European Pharmacopoeia (EP)	Japanese Pharmacopoeia (JP)	Chinese Pharmacopoeia (ChP)[1]	All
These Empower fields use the desired width @50% (HH) peak height approach:					
Resolution	USP Resolution (HH)	Resolution	Resolution	ChP Resolution (HH)[2]	-USP Resolution (HH) -Resolution -ChP Resolution (HH)
Plate Number	While the USP Plate Count field is determined using the width @ tangent approach, the EP Plate Count field is determined when the Pharmacopoeia is set to 'USP' and the EP Plate Count uses the width @ 50% height approach	EP Plate Count	JP Plate Count	ChP Plate Count (HH)	-EP Plate Count -JP Plate Count -ChP Plate Count (HH)
Symmetry Factor	USP Tailing	Symmetry Factor	Symmetry Factor	ChP Tailing Factor	-USP Tailing -Symmetry Factor -ChP Tailing Factor
Relative Resolution is determined using the desired width @ 50% (HH) peak height approach:					
	Yes	Yes	Yes	No	No

1: available in Empower 3.7.0 and above; 2: ChP Resolution (HH) formula are not harmonized with USP

USP <621> & EP 2.2.46 | Calculations within Empower Remedation

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Probably these require an update:

- Processing Methods
- Report Methods
- Displayed Views and View Filters
- Custom Fields

Waters will not change built-in formula in Empower due to data integrity.

- All existing system suitability fields will remain and will still be calculated using the same formulas as in Empower 3.7.0. This provides backwards compatibility with legacy data and custom fields.
  - New fields are proposed for new calculations for future Empower versions.
  - Default multiplier (for S/N) will be set to 20.

European Pharmacopoeia | Addition of chapter 5.26 Implementation of Pharmacopeial Procedures

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*This general chapter is published for information. It **provides guidance** on setting up an **approach for the implementation of analytical procedures** given in monographs of the Ph. Eur. (or 'pharmacopoeial procedures'hereinafter).*

The approach set out below is valid only when used in accordance with the principles laid down in the General Notices (including a suitable quality system).

*The term "**implementation**" is used to describe the **overall activities performed**, whereas "**verification**" is used exclusively to refer to the **experimental activities**.*

European Pharmacopoeia | Addition of chapter 5.26 Implementation of Pharmacopeial Procedures

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As the first step of the implementation process, an assessment is performed prior to the first use of the pharmacopoeial procedure in the implementing laboratory. The purpose of this **assessment** is not to evaluate the intrinsic capability of the procedure, but to determine **whether there are any factors associated with the complexity of the procedure and the actual conditions** of its use **in the implementing laboratory that may affect the performance** of the procedure.

If such factors are identified, an experimental verification is the second step to evaluate the analytical procedure performance characteristics (APPCs), such as accuracy and precision, that are considered relevant.

The publication of a revised monograph requires re-evaluation of the implementation of the concerned analytical procedure.

European Pharmacopoeia | Addition of chapter 5.26 Implementation of Pharmacopeial Procedures

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The aim of the pharmacopoeial procedure implementation assessment is to **identify any critical factors** related **to the actual conditions** of use **in the implementing laboratory** that may affect the performance of the procedure.

Such factors may include, but are not limited to, the following:

–the composition of the article under test;
–the complexity of the sample preparation;
–the reagents required to run the procedure;
–the laboratory equipment required to run the procedure;
–the laboratory environment.

European Pharmacopoeia
Addition of EP chapter 5.26 plus USP <1220>

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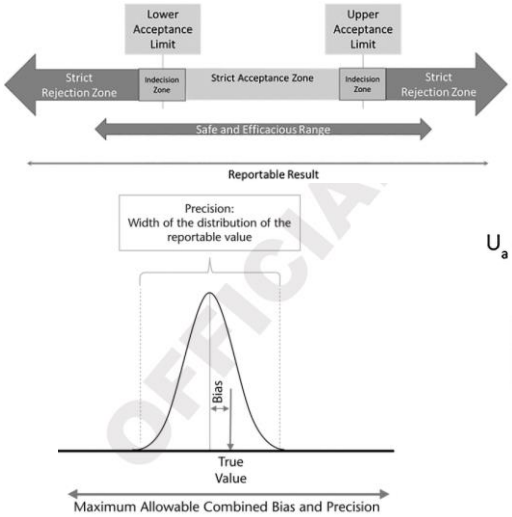
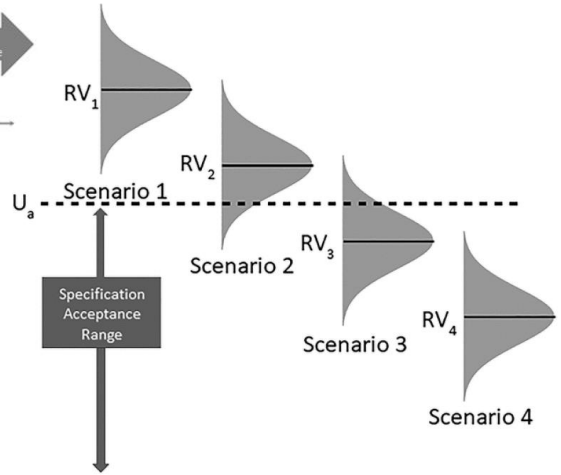
USP <1220> Analytical Procedure Life Cycle
also advises to conduct a similar assessment, during stage 1 (Procedure Design), for CQAs, to verify/validate them (Procedure Performance Qualification) and continuous monitoring (Ongoing Procedure Performance Verification).





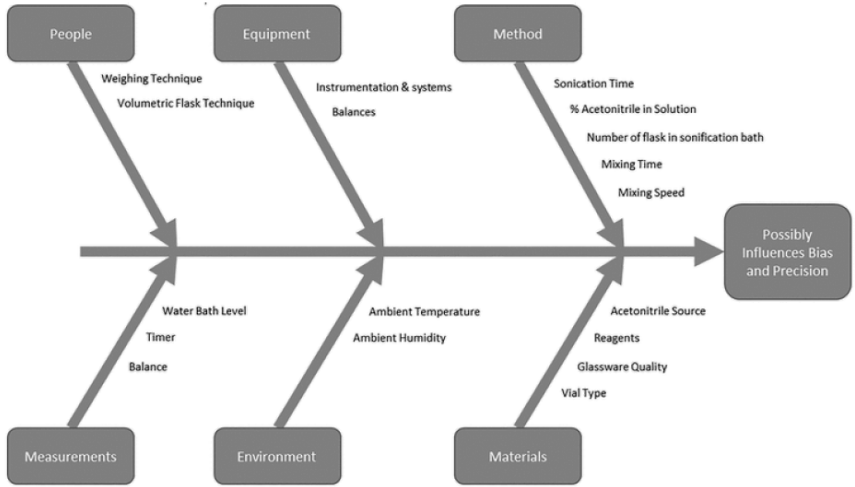


Figure 7. Ishikawa diagram used to identify potential variables.

European Pharmacopoeia
Addition of EP chapter 5.26 plus USP <1220>

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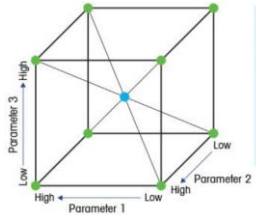
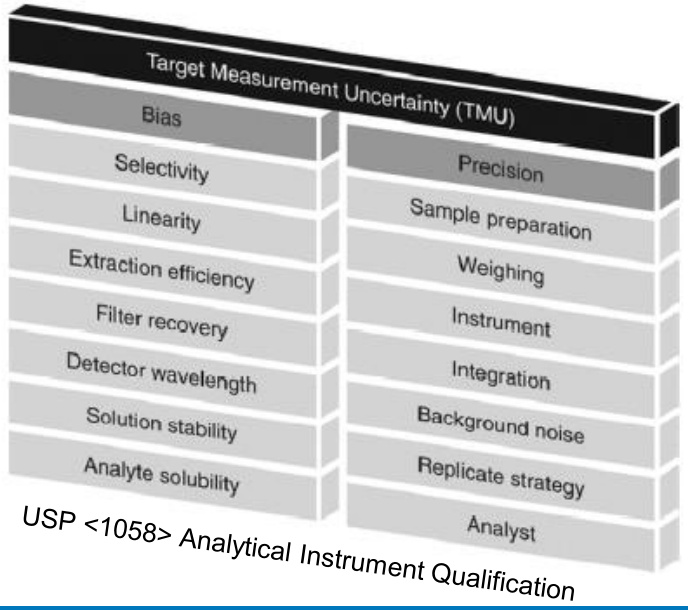
S-Matrix®

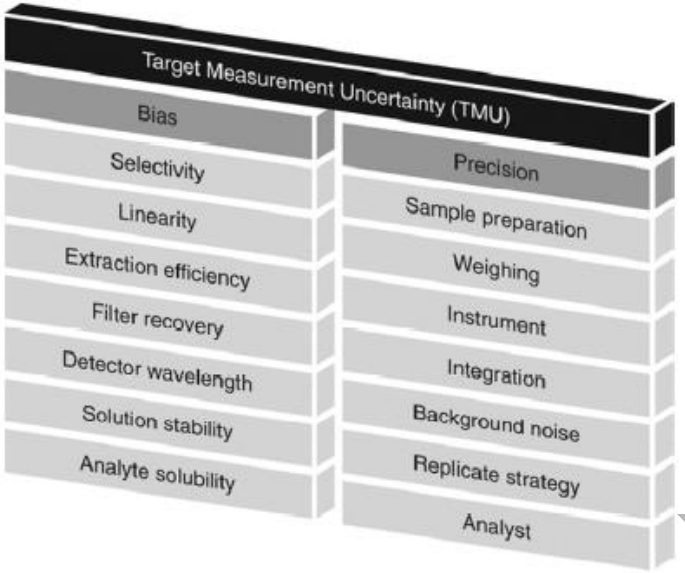


FACTORS			RESPONSES	
Temperature (°C)	Start Material (mmol)	Catalyst (°/-)	Product Yield (%)	Impurity (%)
80 (-1)	25 (-1)	2 (-1)	82	0.11
100 (+1)	25 (-1)	2 (-1)	79	0.13
80 (-1)	50 (+1)	2 (-1)	86	0.09
80 (-1)	25 (-1)	4 (+1)	82	0.11
100 (+1)	50 (+1)	2 (-1)	92	0.09
100 (+1)	25 (-1)	4 (+1)	97	0.05
80 (-1)	50 (+1)	2 (-1)	96	0.07
100 (+1)	50 (+1)	4 (+1)	81	0.10

Optimum Value



USP <1058> Analytical Instrument Qualification



Donepezil method (USP) improved

European Pharmacopoeia | Addition of chapter 5.26 Implementation of Pharmacopeial Procedures

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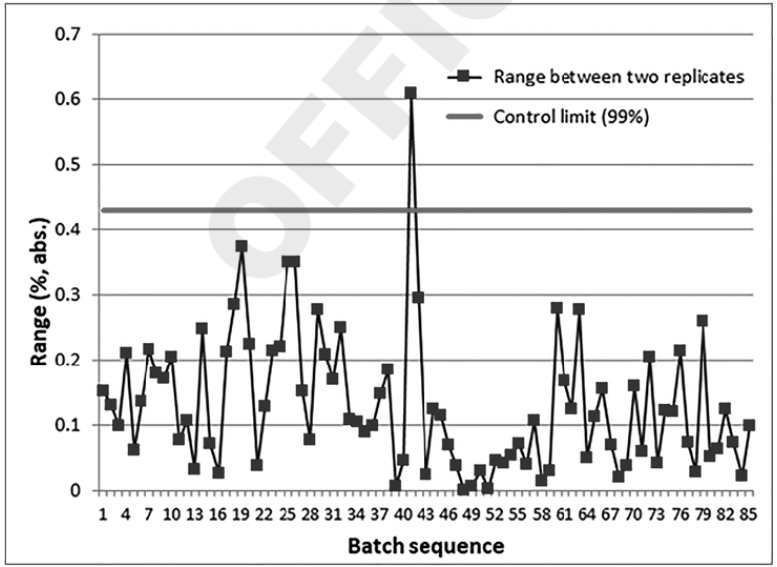
USP <1220> Analytical Procedure Life Cycle

heat map capturing a qualitative risk assessment related to sample preparation and HPLC setup steps from ananalytical procedure. Impact levels are strong (red), medium (amber), and minor(green).

Analytical Unit Operation	Analytical Factor or Variable	Identified Potential Risk	RISK HEAT MAP		Analytical Control Strategy
			Accuracy	Precision	
SAMPLE & REAGENT PREPARATION	Humidity of the laboratory	Moisture absorption by the sample can lead to incorrect weighing or degradation			Monitor environmental controls
	Analyst skill	Incorrect sample preparation; weighing & volumetric dilutions			Training program and records
	Sonication time	Lack of dissolution of the sample or degradation			Establish limit or conditions during development
	Composition of the solvent mixture used in sample preparation	Lack of complete dissolution of the sample			
INSTRUMENT & SYSTEM SET UP	% composition of the solvent in the mobile phase	Column performance, peak shape & retention times			Gravimetric preparation, SSTs
	Column temperature				Establish operation within limits during instrument/ system qualification; SSTs to confirm performance
	Batch of column packing material				Establish variability during Stage 1 and design SSTs
	Quality of the solvent	Baseline drift and ncise are wavelength dependent and may affect the peak shape			Specify required grade and transmittance characteristics
	Cleaning	Peaks from previous Injections			Establish cleaning protocol, SST



European Pharmacopoeia | Addition of chapter 5.26 Implementation of Pharmacopeial Procedures

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Assessment Outcome

if **no factors are identified as critical**, the **procedure** may be **used** in the implementing laboratory **without any specific verification experiments** to demonstrate its suitability under the actual conditions of use

if **factors are identified as critical**, the procedure may be used in the **implementing** laboratory provided **a set of verification experiments** evaluating the impact of identified critical factors on selected APPCs is performed to **demonstrate the suitability** of the analytical procedure **under the actual conditions** of use

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Intended use / APPCs	Identification	Testing for impurities		Assay - content/potency - dissolution (measurement only)	Other quantitative tests
		Limit test	Quantitative test		
Accuracy	○	○	○	◗	◗
Precision					
- Repeatability	○	○	●	●	●
- Intermediate precision	○	○	◗	◗	◗
Specificity/Selectivity	◗	●	●	●	◗
Sensitivity	○	●	●	○	◗
Linearity	○	○	○	◗	◗
Range	○	○	○	◗	◗
Robustness	○	○	◗	◗	◗

In some cases, the tests prescribed for the purpose of verifying the suitability of analytical procedures in an individual monograph and/or relevant general chapter can be used as a partial or full verification of the corresponding APPCs.

- ● *signifies that this characteristic should be experimentally verified.*
- ◗ *signifies that this characteristic should be experimentally verified, if impacted by critical factors from the actual conditions of use in the implementing laboratory.*
- ○ *signifies that this characteristic is typically not relevant for purposes of verification.*

Thank you for listening !

Additional resources are available at

www.waters.com & www.support.waters.com

This presentation will be made available to you as download after VICE2022 is finished.

Accompanying documents: USP <621>, USP <1220>, USP <1058>, EP 2.2.46, EP 5.26.

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