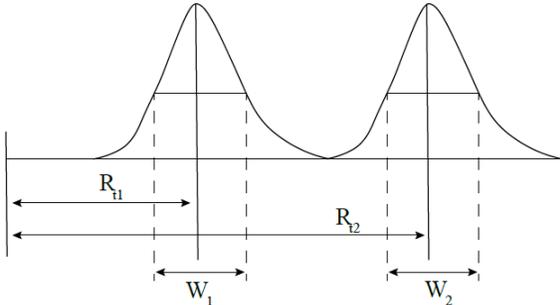
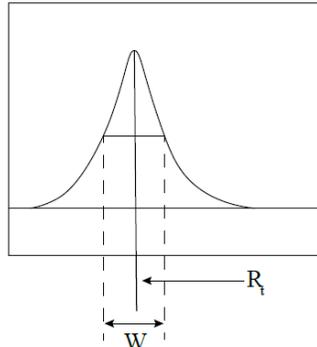


Navigating Future US Pharmacopoeia changes in Empower

The US Pharmacopoeia, Chapter 621 Chromatography, is being updated. Effective December 2022, the USP has changed the formulas for Resolution and Plate Count and has also updated the guidance for Signal-to-noise ratio. Other changes are defined but do not directly impact the use of Empower.

These changes call for using the width at 50% height approach (rather than the width at tangent approach) for the determination of Resolution (R) and Plate Count (N or Plate Number). The future definition of Signal-to-noise ratio defines the range of the noise to be observed over a distance equal to 20 times the width at 50% height of the peak. This represents a change from the previous guidance of a distance of greater than or equal to 5 times the width at 50% height of the peak.

<p>Resolution as defined by USP as of December 2022 is determined using these Empower fields:</p> <ul style="list-style-type: none"> • USP Resolution (HH) • Resolution • ChP Resolution (HH)¹ 	<p>Plate Number as defined by USP as of December 2022 is determined using these Empower fields:</p> <ul style="list-style-type: none"> • EP Plate Count • JP Plate Count • ChP Plate Count (HH)
<div style="text-align: center;">  </div> $R = \frac{1.18(R_{t2} - R_{t1})}{(W_2 + W_1)}$ <p>Where:</p> <p>R = Resolution (EP and JP) and USP Resolution (HH)</p> <p>R_{t1} = Retention time of the first peak</p> <p>R_{t2} = Retention time of the second peak</p> <p>W₁ = Width of the first peak at 50% peak height</p> <p>W₂ = Width of the second peak at 50% peak height</p>	<div style="text-align: center;">  </div> $N = 5.54 \left(\frac{R_t}{W} \right)^2$ <p>Where:</p> <p>N = Plate count (the number of theoretical plates in a chromatographic column)</p> <p>R_t = Retention time</p> <p>W = Peak width at 50% of peak height</p>

Based on feedback from USP, it is Waters' understanding that these changes apply to both existing and future methods, noting that USP Chapter <621> applies specifically to compendial methods, however, may also be applied to other methods.

Waters is investigating how to incorporate these changes in Empower without affecting legacy calculations and legacy data. As we determine a plan forward, this article will be updated. Until the anticipated changes in Empower occur, please use the *Additional Information* below to determine an interim solution if you use these calculations in your procedures.

¹ ChP Resolution uses Width @ 50%, but it uses different constants in the formula (2.0/1.17 for ChP Resolution vs. 1.17 for USP Resolution (HH) and Resolution) so the calculated value will be different than the USP Resolution (HH) and Resolution values.

This request is documented as CRI-4304.

ADDITIONAL INFORMATION

Resolution, Relative Resolution and Plate Count

The updated calculations required by the USP for Resolution (including Relative Resolution) and Plate Count (Plate Number) are calculated and available in Empower.

When the Pharmacopoeia in the processing method is set to:					
	United States Pharmacopoeia (USP)	European Pharmacopoeia (EP)	Japanese Pharmacopoeia (JP)	Chinese Pharmacopoeia (ChP) ²	All
These Empower fields use the desired width @50% peak height approach:					
Resolution	USP Resolution (HH)	Resolution	Resolution	ChP Resolution (HH) ³	-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)
Relative Resolution is determined using the desired width @ 50% peak height approach:					
	Yes	Yes	Yes	No	No

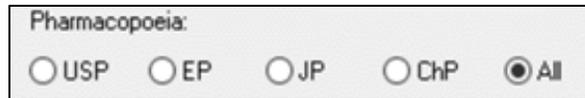


Figure 1: Pharmacopoeia choice in the Empower processing method (Suitability tab)

Given the matrix above, it is possible to generate results for Resolution, Relative Resolution, and Plate Number using the width @ 50% peak height approach. To do so, choose 'USP' for Pharmacopoeia and use the USP Resolution (HH), Relative Resolution, and EP Plate Count fields.

² ChP Resolution (HH) and ChP Plate Count (HH) are available in Empower 3.7.0 and above.

³ ChP Resolution uses Width @ 50%, but it uses different constants in the formula (2.0/1.17 for ChP Resolution vs. 1.17 for USP Resolution (HH) and Resolution) so the calculated value will be different than the USP Resolution (HH) and Resolution values.

However, it is not possible to generate results for Resolution, Relative Resolution, and Plate Number using the width @ 50% peak height approach while using Pharmacopoeia selections of 'ChP' or 'All'. For example, when 'All' is selected, multiple Resolution and multiple Plate Number values are determined as desired, however Relative Resolution is not.

To resolve this issue, custom fields can be created for Plate Count (Plate Number) and/or Relative Resolution. Refer to the sections for *Custom Fields* in this document for details.

Signal-to-Noise

The future definition of Signal-to-noise ratio defines that the range of the noise be observed over a distance equal to 20 times the width at 50% height of the peak. This can be accomplished in Empower by setting the Half Height Multiplier for s/n Noise Region parameter to 20. This must be changed from the default value which is 5 for the USP s/n field.

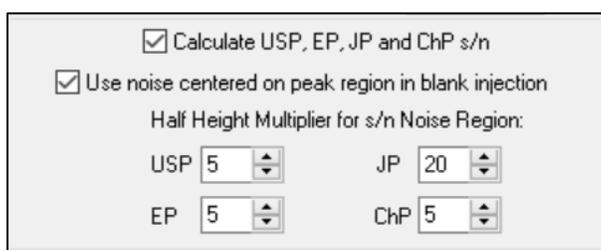


Figure 2: Half Height Multiplier parameter in the Empower processing method (Suitability tab) which defines the distance for which to measure noise for s/n

Update Views and Reports

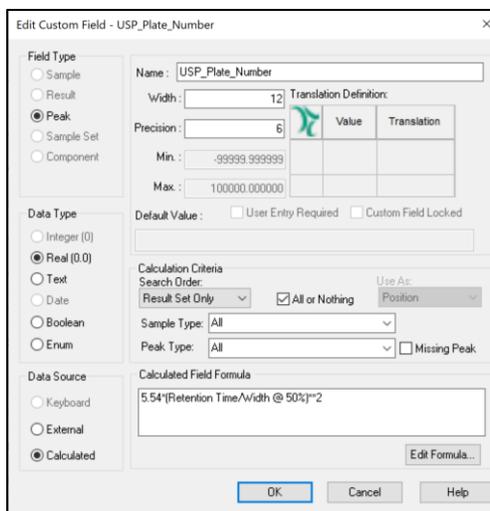
If you are transitioning to use the new USP guidance, existing reports, views and view filters may need to be updated to include the appropriate fields. It may also be necessary to consider if any custom fields using the legacy fields for Resolution and/or Plate Count are present and need updating.

Custom Field for Plate Count/Plate Number

When the Pharmacopoeia setting is 'USP' or 'ChP', the width at tangent approach is used by Empower to determine Plate Count⁴. If you are using 'USP' or ChP and have a desire to identify Plate Count using the width at 50% height approach, a custom field may be created. To calculate the updated determination of Plate Count, create a Peak Type custom field using the following formula:

$$5.54 * (\text{Retention Time} / \text{Width @ 50\%}) ** 2$$

⁴ 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. Using EP Plate Count may be a viable workaround for you as it allows you to avoid creating, validating, and copying a custom field to all current and future projects.



Waters recommends that custom fields are appropriately validated as fit for purpose before putting into routine use.

Custom Field for Relative Resolution

When the Pharmacopoeia setting is 'All' or 'ChP', the width at tangent approach is used by Empower to determine Relative Resolution. If you are using 'All' or 'ChP' and have a desire to identify Relative Resolution using the width at 50% height approach, a custom field may be created. To calculate the updated determination of Relative Resolution, create a Peak Type custom field using the following formula:

$$1.18 * ((\text{Retention Time}) - \text{CCompRef1}[\text{Retention Time}] / (\text{Width @ 50\%} + \text{CCompRef1}[\text{Width @ 50\%}]))$$

In the processing method, define the CCompRef1 field as the component for your Relative Resolution Reference.

Waters recommends that custom fields are appropriately validated as fit for purpose before putting into routine use.

