FUTURE-PROOF SOLUTIONS FOR REGULATED LABORATORIES IN THE FACE OF CHANGING USP <621> GUIDELINES

How to use UPLC technology within "allowable adjustments" to improve QC laboratory throughput

For many in the regulatory environment, the collection of standards provided by the United States Pharmacopeia and the National Formulary (USP-NF) offer guidance for quickly accessing suitable analysis methods. Through Chapter <621> Chromatography, the USP-NF provides guidelines for specific "allowed adjustments" to monograph methods to ensure consistent analysis across different chromatographic systems.

Effective August 1st, 2014, the USP-NF put into effect certain changes to "allowable adjustments" within Chapter <621> as part of USP37-NF32 S1.

This white paper discusses how to leverage the changing USP <621> guidelines within established methods, while providing options to immediately improve results and illustrate how to achieve long-term return on investment (ROI). By staying within allowable adjustments, significant benefits may be realized with only verification of the suitability of the method for its intended purpose, rather than a full revalidation.

OVERVIEW

The USP-NF <621> guidelines governing allowed adjustments to chromatographic system parameters changed as of August 1st, 2014. These changes represent a first step toward bringing modern technology into regulated and QC environments. They also create an opportunity for QC groups to adopt methods and techniques that can be sustained well into the future, beyond the lifetimes of legacy techniques.

Figure 1 lists the relevant differences between former USP <621> guidelines and their updates, most notably in the division of the previously consistent guidelines between isocratic and gradient analysis methods. While isocratic methods have been granted more relaxed parameters, gradient methods have been restricted to more directly follow established monographs or an existing approved alternative method.

This document outlines strategies to take advantage of USP <621> allowable adjustments to improve method quality and efficiency without the need to perform a full revalidation, where possible.

Variable	Allowable Adjustment per USP 621 Chromatography		
	USP36-NF31 (previous)	After Aug 1, 2014 (USP37-NF32 S1)	
	Isocratic & Gradient	Isocratic	Gradient
Particle size	-50%	Per constant L/dp or N: -25% to +50%	No changes allowed
Column length	±70%		
Flow rate	±50%	*Based on particle size and ±50%	No changes allowed
Column ID	Flexible	Flexible	No changes allowed
Injection volume	Flexible	Flexible	Flexible
Column temperature	±10 ˚C	±10 ˚C	±10 ˚C
Mobile phase pH	±0.2 unit	±0.2 unit	±0.2 unit

Figure 1. Tabulated comparison chart of allowable adjustments to USP <621>. Refer to USP website (www.usp.org) for detailed descriptions of allowances and specific guidelines on flexible allowance parameters. For full discussion of the derivation of the chromatographic parameters, please refer to the referenced Stimuli article.[2]

PRACTICAL IMPLEMENTATION OF USP <621> GUIDELINES

Under previous USP guidelines, variations in column dimensions were considered individually, as discrete parameters. For instance, a monograph calling for a 4.6 x 150 mm, 5 µm particle column could not be transferred to a 2.1 x 50 mm, 1.7 µm particle column without revalidation of the method. Even though the column length and internal diameter (I.D.) fall within accepted allowances, the difference in particle size falls outside of the former -50% guideline and therefore such transfer would require revalidation. Under the new guidelines, however, column equivalency is established in terms of efficiency (N), or a ratio between column length (L) and particle size (dp).

Isocratic method adjustments

Figure 2 demonstrates the consistency between these L/dp values for the above mentioned columns (30,000 and 29,400 respectively) for an isocratic USP method. This L/dp ratio falls well within the -25% to +50% guideline and therefore within the new acceptable allowance limits. Provided that the column chemistry L-designation remains consistent, there is no requirement in this case to revalidate the method, although it is generally good practice to do so.

Figure 2 further demonstrates how smaller particle sizes can reduce run times without compromising separation performance, resulting in almost 10-fold time savings and greater than 15-fold decrease in solvent consumption.

Sub-2-µm particle columns require a system with low dispersion capable of handling much higher back pressures, such as the ACQUITY UPLC® H-Class System, to fully realize performance gains. The ACQUITY UPLC® H-Class System has been purposefully designed to be able to run both HPLC and UPLC methods without having to change tubing, providing labs the flexibility to run all their methods on one system.

Waters also offers scalable column chemistries that provide the same stationary phase material in different particle sizes, which enable more consistent separations without changing selectivity as long as constant L/dp guidelines are followed. By using the proper tools and staying within the new <621> allowable adjustments, revalidation of existing methods may not be required as long as verification tests demonstrate that the method is appropriate for its intended use. Flexibility in the new guidelines now opens the possibility to transfer previous isocratic HPLC methods to UPLC without the time investment and hassle of revalidation, while realizing the overall laboratory efficiency and productivity gains of higher throughput assays.

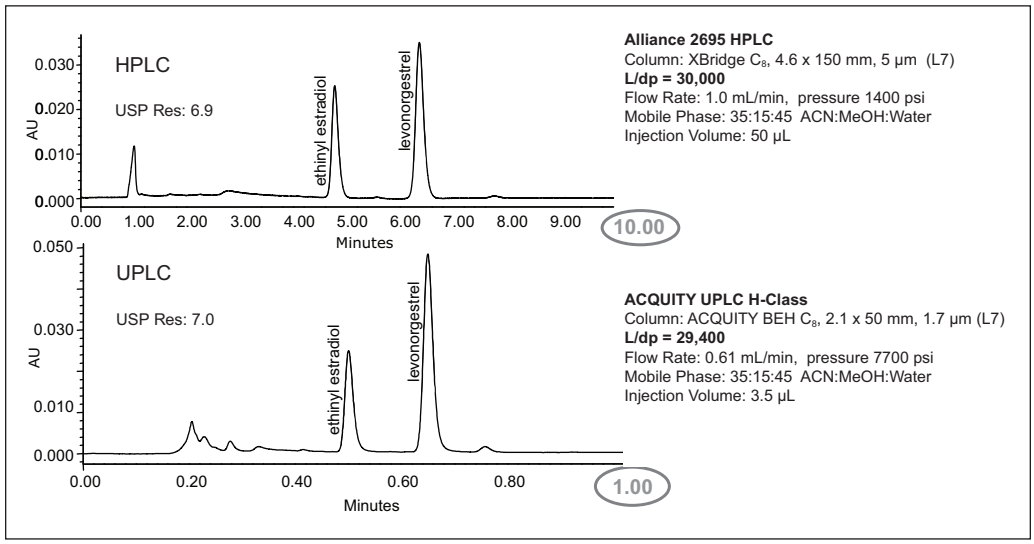

Figure 2. A USP HPLC separation transferred to ACQUITY UPLC H-Class System, keeping column L/dp constant per USP <621> Guidelines.

Column optimization with HPLC systems

Many QC laboratories have invested solely in HPLC systems. For these groups, some moderate efficiency gains can still be accomplished by implementing newer column technology with existing HPLC systems. An added benefit to using newer column technology is that the quality of newer columns is generally higher than legacy columns, leading to more robust separations across batches. Columns that use hybrid particles such as bridged ethyl hybrid (BEH) and charged surface hybrid (CSH™) offer wider operating pH ranges, resulting in longer column lifetimes.

Figure 3 demonstrates the transfer of an isocratic method within <621> guidelines, reducing a 5 µm particle size column method down to a 2.5 µm particle size column on an HPLC system. Run time and solvent consumption are cut in half and an evaluation of tailing, resolution, and %RSD all meet criteria described in the monograph. In this case, full revalidation of the method is not required and efficiency gains can be immediately realized simply by switching the column.

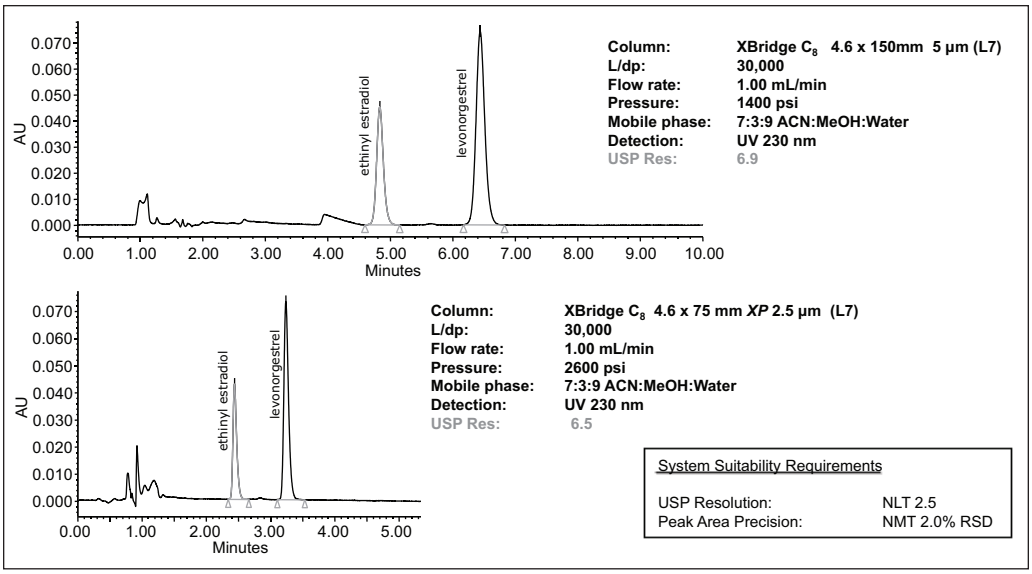

Figure 3: Transfer of an isocratic USP method on an Alliance HPLC System, changing only the column dimensions per USP <621> guidelines.

Gradient method adjustments

For many years, QC labs using USP compendial gradient methods enjoyed the same flexibility in allowed adjustments as isocratic methods. Under the updated <621> guidelines in USP37-NF32 S1, no column adjustments to gradient monograph methods are allowed, requiring revalidation for those who cannot meet the suitability criteria defined in the monograph.

Compendial gradient methods are typically developed and submitted by a donor for a specific manufacturer formulation. Since sources and quality of raw materials, drug substances, or excipients in manufacturer formulations of drug products frequently differ, compendial methods as written are not always the most optimal methods for the sample being tested. Given that any change to column configurations for existing gradient methods will now require full revalidation, this investment in time and resources would be best spent developing the most optimal method for the product being tested.

Using the most current technology available can extend the lifetime of the assay, minimizing the need for the method to be redeveloped and revalidated throughout the marketed lifetime of the product. With a properly redeveloped method, performed more efficiently with new technology,[3] pharmaceutical manufacturers can future-proof their methods with improved data quality, savings in time and solvent, and gain considerable return on investment.

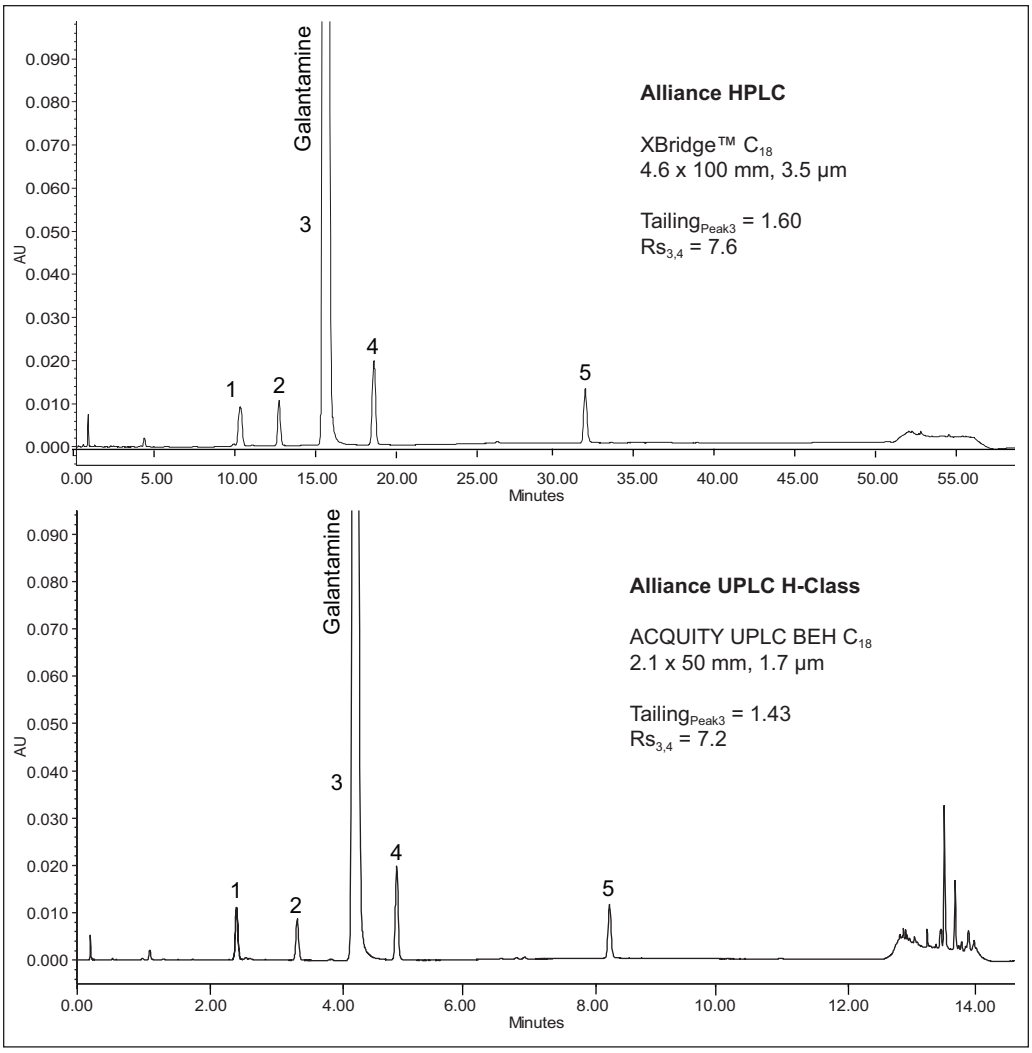

Figure 4: Transfer of a gradient separation from HPLC to UPLC.

Figure 4 shows the benefit of moving a gradient separation from an Alliance® HPLC System to an ACQUITY UPLC H-Class System, achieving a significant reduction in run time from 60 minutes to 15 minutes, while still maintaining separation performance.

The requirement to validate can be prohibitive to implementing change in regulated labs due to the documentation requirements and complexity of the validation process. However, this can be facilitated by utilizing the Waters Empower® 3[4] Software's Method Validation Manager (MVM). MVM software allows this typically manual process to be paperless, automated, and offers a guided workflow within a secure, audit-trailed, and compliant-ready environment.

CONCLUSIONS

Recent updates in USP-NF Chapter <621> guidelines illustrate the USP's commitment to modernization of methods. This represents one pathway for laboratories to adopt modern technology as well as a profound opportunity for regulated labs to incorporate far-reaching improvements to their organizations.

- Updated guidelines for isocratic methods allow greater flexibility in implementing the newest column technology while still adhering to existing monographs
- In some cases, the range of acceptable allowances allows for the adoption of UPLC technology without having to revalidate methods, resulting in significant time and material savings
- Changes to gradient methods may now require revalidation, but this provides an opportunity to redevelop a more optimal method for samples being tested; and to use modern technologies to facilitate/streamline the process of revalidation

Although valuable time and resources may be spent aligning existing methods and equipment with new guidelines, incorporating newer technology can result in benefits that multiply the return on investment, especially over time. As a result, such a future-looking laboratory also becomes empowered to develop more effective and efficient methods that will extend well beyond the lifetime and capabilities of their previous equipment.

References

1. FDA http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm128080.htm
2. Neue, Uwe D. *et al*. Transfer of HPLC procedures to suitable columns of reduced dimensions and particle sizes. *Pharmacopeial Forum* 35. 1622-1626 (2009).
3. Maziarz, M, McCarthy, SM, and Wrona, M. *Improving Effectiveness in Method Development by Using a Systematic Screening Protocol.* Application Note 720005026en. Waters Corporation; 2014.
4. Maziarz, M, McCarthy, SM, and Wrona, M. *Increasing Efficiency of Method Validation for Metoclopramide HCl and Related Substances with Empower 3 MVM Software.* Application Note 720005111en. Waters Corporation; 2014.

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