

# Useful Strategies for Modernizing USP Methods

Application Compendium



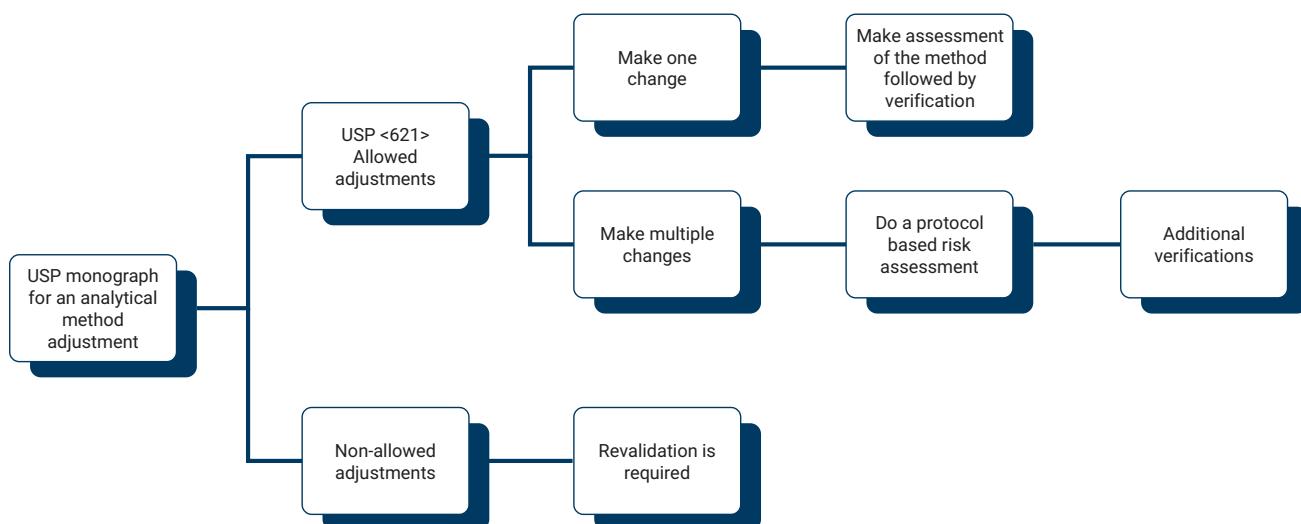
# Modernization of USP Methods

## Application Compendium

### Foreword

The pharmaceutical industry is undergoing a transformative shift, driven not only by the demand for more efficient and sustainable analytical methodologies but also by evolving regulatory expectations. Central to this evolution is the U.S. Pharmacopeia (USP), which, in collaboration with the United States Food and Drug Administration, European Pharmacopoeia, and British Pharmacopoeia, is leading a global initiative to modernize monographs and general chapters to reflect current scientific standards. This modernization effort aims to replace outdated, nonspecific tests with advanced techniques such as high-performance liquid chromatography (HPLC) and ion chromatography (IC), enhancing the accuracy, safety, and reliability of pharmaceutical testing. As these standards become enforceable and increasingly adopted worldwide, laboratories must align with these changes to maintain compliance and ensure product quality. In this complex regulatory landscape, organizations are seeking reliable partners who can provide both technical expertise and strategic guidance to help navigate modernization requirements and uphold the integrity of their analytical practices.

#### Assessment of Analytical Methods



This application compendium showcases Agilent's commitment to supporting the modernization of small-molecule analytical methods. Each application note demonstrates practical, real-world strategies for improving method performance, sustainability, and regulatory compliance, utilizing our innovative portfolio of instruments, columns, and software.

Agilent is your partner in progress. Bring your scientific vision to life with our expert support and cutting-edge solutions. Together, we can work to streamline and elevate your method modernization, achieving the precision, robustness, and reliability your laboratory demands.

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## Introduction

As the pharmaceutical industry continues to evolve, so too must the analytical techniques that support the development, quality, and safety of small-molecule therapeutics. This application note compendium presents eight application notes that exemplify Agilent's innovative approaches to updating and enhancing analytical methods, serving as a practical guide for laboratories seeking to align with USP modernization efforts while embracing sustainability, efficiency, cost-savings, and analytical excellence.

Explore our range of modernization strategies, including: optimizing LC methods to superficially porous particle (SPP)-based columns for improved throughput and cost savings; updating the use of legacy instrumentation to more future-ready technology; adopting greener practices like reduced solvent consumption and the use of helium as a carrier gas in GC; and many more. For more information on USPs modernization initiatives and resources, visit Agilent's [Revisions per USP 621](#).

# LC method modernization

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LC remains a cornerstone of pharmaceutical analysis, yet many small-molecule testing methods still rely on outdated column technologies, legacy instrumentation, and environmentally or LC-damaging mobile phases. Not only does this impact accuracy and reproducibility of testing results but also leads to workflow inefficiencies, higher costs, and lack of sustainability.

Modern LC technologies—such as SPP columns and UHPLC systems—enable scientists to significantly reduce analysis time, solvent consumption, and operational costs while achieving robust analytical performance, data quality, and regulatory compliance.

**The following application notes illustrate practical solutions for implementing LC method modernization. The examples presented here include:**



Application Note  
Biopharma/Pharma

Agilent  
Innovate | Believe | Deliver

Modernizing LC Methods for USP Phenylephrine HCl and Pramoxine HCl in OTC Products

**Abstract**  
Phenylephrine HCl and pramoxine HCl are active pharmaceutical ingredients (APIs) commonly used in over-the-counter (OTC) products. In this application note, the authors describe the implementation of a modern LC method for the analysis of these two APIs. The method was developed using a combination of two different extraction techniques, HPLC methods with modified column technology, and a novel LC method with a modern column technology. The new LC method is a more efficient and accurate method with a friendly mobile phase and smaller particle size column. The new LC method also provides better precision and reproducibility of results. Quality control (QC) testing, an LC method to determine the compatibility of the new LC method with the old LC method, and a comparison of the new LC method with the old LC method are also presented. The results show that the new LC method is more accurate and precise than the old LC method. The analysis was conducted on an Agilent 1260 Infinity II LC system with a Waters BEH C18 column and a Waters BEH C18 column with a Waters BEH C18 column detector at 224 nm.

Combining the analysis of two APIs into a single, efficient testing method with LC-friendly mobile phases and smaller modernized particle column technology

[Read application note](#)



Application Note  
Biopharma/Pharma

Agilent  
Innovate | Believe | Deliver

USP Method Transfer from an Agilent 1100 Series Quaternary LC to an Agilent 1260 Infinity II LC

**Abstract**  
Method transfer from legacy equipment to new generation LC is an important part of the modernization of pharmaceutical analysis. In this application note, the authors describe the transfer of a USP monograph method from an Agilent 1100 Series Quaternary LC System to an Agilent 1260 Infinity II LC System. The method was developed using a combination of two different extraction techniques, HPLC methods with modified column technology, and a novel LC method with a modern column technology. The new LC method is a more efficient and accurate method with a friendly mobile phase and smaller particle size column. The new LC method also provides better precision and reproducibility of results. Quality control (QC) testing, an LC method to determine the compatibility of the new LC method with the old LC method, and a comparison of the new LC method with the old LC method are also presented. The results show that the new LC method is more accurate and precise than the old LC method. The analysis was conducted on an Agilent 1260 Infinity II LC system with a Waters BEH C18 column and a Waters BEH C18 column with a Waters BEH C18 column detector at 224 nm.

Seamlessly transferring a USP monograph method from a legacy LC to a new, future-ready UHPLC system

[Read application note](#)

# Sustainability and cost-saving enhancements

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The first step in enhancing sustainability and cost-savings is through reduction of time, resources, and waste. By adopting streamlined workflows with shorter run times, laboratories can use significantly less mobile phase per analysis. This not only cuts down the volume of costly and often environmentally hazardous organic solvents but also reduces energy consumption and instrument wear. In turn, this leads to lower operational costs, less hazardous waste, and more efficient use of staff time—delivering both environmental and economic benefits without compromising performance.

## The following application notes illustrate practical solutions for:



Application Note  
Pharma/Biopharma

Agilent

Gradient Method Transfer of the Iohexol USP Monograph HPLC Method for Related Compounds to Smaller Particle Size ZORBAX Columns

**Abstract**  
The original Iohexol USP monograph method of analysis for iodinated contrast media transferred to smaller particle size 3.5 and 5 µm Agilent ZORBAX columns. The method was modified to reduce analysis time and solvent use. The original method uses gradient separation with a 4.0–20% acetonitrile gradient over 20 min. The analysis time was reduced to 10 min by decreasing the gradient to 4.0–10% acetonitrile over 10 min. The detection limit was also reduced from 40 to 8 µg iodine when the method was transferred to the Agilent ZORBAX 3.5 and 5 µm columns. The analysis time was reduced by 50% and 40% respectively, while method resolution, all detection limits, and solvent consumption remained the same.

Improving gradient separations by transferring to smaller columns to reduce solvent use and analysis time

[Read application note](#)



Application Note  
Pharma and Biopharma

Agilent

Residual Solvents Analysis for the Pharmaceutical Industry Using the Agilent 8697 Headspace Sampler and 8850 GC-FID System

**Abstract**  
The residual solvent analysis process for active pharmaceutical ingredients (APIs) may contribute to residual solvents remaining in the final product. Due to regulatory requirements, pharmaceutical manufacturers are required to analyze residual solvents in the waste air. Agilent 8697 gas chromatograph (GC) system coupled with 8850 GC-FID detector was used to analyze residual solvents in pharmaceutical waste air. The method was developed to analyze residual solvents in pharmaceutical waste air with acceptable resolution, quantification accuracy, and quantitation precision using both helium and hydrogen carrier gas.

Simplifying GC method transfer of residual solvent analysis from using helium to the more sustainable and cost-effective hydrogen carrier gas

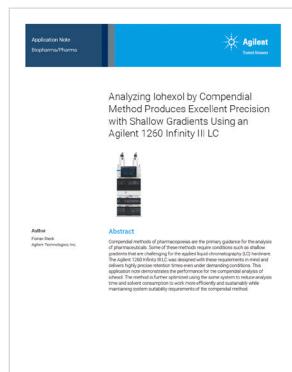
[Read application note](#)

# Revisions to USP General Chapter <621>

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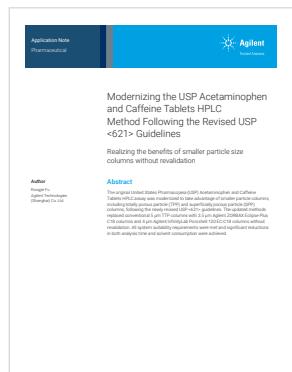
Historically, strict method parameters limited the ability of laboratories to optimize efficiency, sustainability, or newer instrumentation. The revision of USP <621> Chromatography now allows for greater flexibility in method adjustments, including changes to column dimensions, particle sizes, flow rates, and gradient conditions, as long as system suitability is maintained. With this new revision, laboratories are empowered to modernize their legacy methods without the need for full revalidation, helping them adopt more efficient and environmentally conscious techniques without compromising on performance or compliance.

**The following application notes illustrate how these new revisions can be applied in practice, including:**



Refining a compendial method for an API with modern LC equipment, reduced analysis time, and less solvent consumption

[Read application note](#)



Applying USP <621> revisions to modernize the acetaminophen and caffeine tablets HPLC assay with smaller particle size columns for improved performance without revalidation

[Read application note](#)

# Excipient and API impurities analysis

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Excipients and impurities play a critical role in influencing the safety, stability, and performance of pharmaceutical products. Therefore, their accurate analysis is essential throughout drug development and quality control processes. As formulations become increasingly complex and regulatory standards continue to evolve, traditional analytical strategies—particularly those involving LC—often lack the ruggedness, speed, and sensitivity required to meet modern expectations.

Modernization of LC methodologies enables analysts to detect and quantify excipients and impurities with significantly improved precision. In addition to enhanced analytical performance, these updated methods offer benefits such as reduced analysis time, improved sustainability, and cost savings, making them highly valuable in today's regulatory and operational landscape.

## The following application notes present practical solutions for:



Application Note  
Pharmaceutical

Agilent

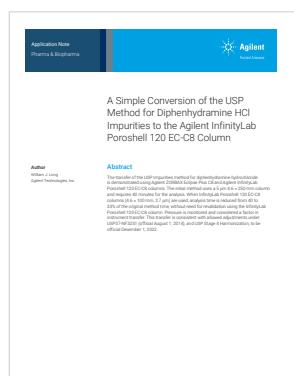
Modernizing the USP Ceftizoxime Sodium HPLC Method Following the Revised USP-621 > Guidelines

Realizing the benefits of smaller particle size columns without revalidation

**Abstract**  
The original United States Pharmacopeia (USP) Ceftizoxime Sodium HPLC method was developed using a 10  $\mu$ m particle size column. This application note describes a modernized method using a 3.5  $\mu$ m particle size column. The original USP method uses a 100 mm column and a 3.9  $\mu$ m particle size column. The modernized method uses a 150 mm column and a 3.5  $\mu$ m particle size column. The modernized method shows significant improvements in analysis time and detection limits without re-validation.

Modernizing a USP assay for an API by replacing outdated 10  $\mu$ m columns with smaller particle columns without revalidation, enabling significant improvements in efficiency.

[Read application note](#)



Application Note  
Pharmaceutical

Agilent

A Simple Conversion of the USP Method for Diphenhydramine HCl Impurities to the Agilent InfinityLab Poroshell 120 EC-C8 Column

**Abstract**  
The resolution of the USP impurities method for diphenhydramine hydrochloride is described. Diphenhydramine hydrochloride is a well-known antihistamine. The USP method uses a 100 mm column and a 5  $\mu$ m particle size column. The Agilent method uses a 150 mm column and a 3.5  $\mu$ m particle size column. The Agilent method shows improved resolution and faster analysis time.

Easily converting a USP impurity analysis to SPP columns with faster analysis and higher resolution

[Read application note](#)

# Modernize your methods with confidence

The USP's initiative to modernize monographs and the revised USP Chapter <621> provides greater flexibility for method adjustments, empowering scientists to adopt these innovations while remaining within compendial guidelines. By modernizing your current USP methods, you can not only prepare your laboratory for evolving regulatory requirements but also enhance operational efficiency—saving you time, money, and resources.

Providing easy access to real-world strategies for method modernization, Agilent offers a roadmap for transforming outdated methods into high-performance, sustainable, and future-ready workflows. As your reliable partner, we can provide the expertise, technologies, and solutions to update your small-molecule analytical methods with confidence.



For more information, visit:

[www.agilent.com/en/solutions/biopharma-pharma/pharmaceutical-small-molecules](http://www.agilent.com/en/solutions/biopharma-pharma/pharmaceutical-small-molecules)

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