

Pharmaceutical Applications Compendium

# PURITY AND IMPURITY ANALYSIS

The Measure of Confidence



Agilent Technologies

# APPLICATION OF CHROMATOGRAPHY AND MASS SPECTROMETRY IN PHARMACEUTICAL PURITY AND IMPURITY ANALYSIS

Accurate assessment of product quality requires robust analytical methods. To remain competitive, drug development and quality control programs must find efficient and effective ways to develop new analytical methods and to transfer and optimize existing procedures. Increased regulatory attention on the control of impurities (e.g., much lower thresholds for genotoxic impurities) has fueled the need for analytical procedures that allow significantly lower detection limits. This in turn requires more sensitive instruments and places higher demands on selectivity, since many additional impurities may be present at lower concentration ranges.

UHPLC offers significant advantages in analytical performance, speed, sensitivity, and resolution. Today's labs must also collaborate with global partners using a variety of instruments. As a result, flexibility in method development and transfer has become a key component of success in the pharmaceutical industry. The application of various mass spectroscopy (MS) detectors to genotoxic impurity analysis has enabled breakthrough detection limits of as little as a few hundred ppm. MS-based methods generally provide additional robustness compared to techniques such as UV alone, due to their high specificity and sensitivity.

## What's Inside?

This applications compendium has a number of practical examples that demonstrate how Agilent can help you in developing cost-effective methods for purity and impurity analysis, reducing analysis time and solvent consumption while remaining compliant with pharmacopeia guidelines. Example applications are provided that demonstrate accurate analysis of trace level impurities through the use of Agilent's highly sensitive LC, LC/MS, GC, GC/MS and SFC solutions.

We have also included a number of additional resources that provide good information related to purity and impurity profiling. They can be found listed as "Other resources" in the pages that follow.

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## Systems solutions

### Cost-effective method development as per USP/EP

Analysis of Neoprofen Using Poroshell 120 EC-C18: Headache-Free Method Adjustment;  
Pub #: 5990-7456EN

Developing Faster Methods for Generic Drugs Within EP 2.2.46E Allowed Limits;  
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Effective Use of Pharmacopeia Guidelines to Reduce Cost of Chromatographic Analysis;  
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Transfer of a USP Method for Tolazamide from Normal Phase HPLC to SFC Using the Agilent  
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USP Analysis of Diphenhydramine and Pseudoephedrine Using an Agilent Poroshell 120  
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USP Analysis of Norethindrone and Mestranol Tablets with Agilent Poroshell 120 EC-CN and  
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Analysis of Risedronate According to USP Using the Agilent 1260 Infinity Bio-inert  
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USP Analysis of Warfarin Sodium Tablets Using Agilent Poroshell 120 EC-CN and SB-C8  
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Seamless Method Transfer from the Agilent 1200 Series to the Agilent 1220 and 1260 Infinity LC Systems – Comparison of System Suitability Results According to USP Method USP/NF 23 for the Analysis of Paracetamol (Acetaminophen) and Aspirin in Pain Relievers; Pub #: 5990-6206EN

Seamless Instrument-to-Instrument Method Transfer of an USP/EP Method from an Agilent 1220 Infinity LC to an Agilent 1290 Infinity Binary LC Using Intelligent System Emulation Technology (ISET); Pub #: 5991-1433EN

Transferring Methods to the Agilent 1290 Infinity LC Using Intelligent System Emulation Technology (ISET) – Analysis of Metoclopramide Hydrochloride and Its Impurities; Pub #: 5990-9692EN

Transferring Methods to the Agilent 1290 Infinity LC Using Intelligent System Emulation Technology (ISET) – Analysis of Paracetamol and Its Impurities; Pub #: 5990-9703EN

Fast Screening of Mobile and Stationary Phases with the Agilent 1290 Infinity LC and Seamless Method Transfer to an Agilent 1200 Series LC Using ISET; Pub #: 5991-0989EN

Method Development on the Agilent 1290 Infinity LC Using Intelligent System Emulation Technology (ISET) with Subsequent Transfer to an Agilent 1100 Series LC; Pub #: 5990-9715EN

## Impurity analysis – taking advantage of UHPLC speed and sensitivity, fast columns, and mass spectrometry for accurate analysis of trace impurities

Analysis of Amoxicillin and Five Impurities on the Agilent 1220 Infinity LC System; Pub #: 5990-6093EN

Chiral Impurity Analysis and Enantiomeric Excess Determination with the Agilent 1260 Infinity Analytical SFC System; Pub #: 5990-5969EN

Sensitive Determination of Impurities in Achiral Pharmaceuticals by Supercritical Fluid Chromatography Using the Agilent 1260 Infinity Analytical SFC System; Pub #: 5990-6413EN

Analysis of Potential Genotoxic Arylamine and Aminopyridine Impurities in Active Pharmaceutical Ingredients; Pub #: 5990-5732EN

Sensitivity Enhancement for Potential Genotoxic Impurity Determination Using the Agilent 1290 Infinity LC System and a 60 mm Agilent Max-Light Cartridge Cell; Pub #: 5990-7443EN

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## Impurity analysis – taking advantage of UHPLC speed and sensitivity, fast columns, and mass spectrometry for accurate analysis of trace impurities *continued*

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Pharmaceutical Impurity Identification and Profiling Using Agilent Q-TOF LC/MS Combined with Advanced MassHunter Data Processing Software; Pub #: 5991-1375EN

Analysis of Counterfeit Antidiabetic Drugs by UHPLC with the Agilent 1220 Infinity Mobile LC; Pub #: 5991-2177EN

## Impurity analysis – identification and quantification of trace level impurities in the presence of large amounts of drug substances

Single-Run Assay and Impurity Testing of Fixed-Dose Combination Drugs Using the Agilent 1200 Infinity Series High Dynamic Range Diode Array Detector Solution;  
Pub #: 5991-0115EN

Reliable and Automatic Integration of Trace Compounds Using the Agilent 1200 Infinity Series High Dynamic Range Diode Array Detector Solution; Pub #: 5991-1409EN

## Impurity analysis – identification of trace impurities coeluting with main compounds

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Residual Solvents in Spiranolactone by Headspace GC/FID and Agilent J&W DB-Select 624UI; Pub #: 5991-2206EN

Residual Solvent Analysis with a Specifically Designed and Tested Agilent J&W DB-Select 624UI for USP <467> Column; Pub #: 5991-0616EN

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## Other resources

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Validation of Analytical Methods; Pub# 5990-5140EN

Agilent 1220 Infinity LC Solutions for Easy-to-Use and Affordable UHPLC Application  
Compendium; Pub # 5991-1023EN

Genotoxic Impurities in Pharmaceutical Products: Regulations and Analysis;  
Pub #: 5991-1876EN

Infinity Series/Agilent LC Columns Pharmaceutical Compendium: Optimize UHPLC and  
Method Transfer Productivity; Pub #: 5991-0828EN



## Liquid Chromatography (LC)

### Agilent 1200 Infinity Series LC Systems

Agilent 1200 Infinity Series LC Systems deliver the speed, resolution, flexibility, and sensitivity necessary for comprehensive purity and impurity analysis. The wide power range of the 1200 Infinity Series accommodates any particle type, column dimension, or mobile/stationary phase, while innovative components offer the next level of performance for UHPLC, RRLC, and HPLC applications.

- Multi-method and method development solutions help by reducing repetitive tasks. The Agilent automated column and mobile phase screening system, and the Method Scouting Wizard software, allow you to select up to 8 columns and 26 different solvents using one-click operation for more than 1000 different test conditions for binary, ternary, or quaternary gradients.
- Intelligent System Emulation Technology (ISET) lets you emulate any HPLC or UHPLC instrument in your worldwide network for fast, reliable method transfer between LC systems – optimal results with no method modification required.
- The ultrasensitive detection of impurities can be optimized using the revolutionary Agilent Max-Light cartridge cell, with a 60 mm optical path length for even lower detection limits and higher sensitivity.
- The 1200 Infinity Series High Dynamic Range DAD (HDR/DAD) Solution offers a 30x wider linear UV-range to expand detection capabilities and quantify all sample components in a single run, making it ideal for the measurement of low-level genotoxic impurities present in active pharmaceutical ingredients.
- The 1290 Infinity 2D-LC Solution is the perfect tool for your most complex separations. Powerful new features like peak-triggered operation, shifted gradients, and innovative valve technology deliver significantly better separation compared to standard one-dimensional LC.

### Agilent 1260 Infinity Analytical SFC Solution

The 1260 Infinity Analytical Supercritical Fluid Chromatography (SFC) Solution provides orthogonal separation power at high speed and unprecedented power range for SFC separations, LC-like sensitivity and ease of use combined with low cost of ownership driven by an environmentally friendly separation technology with little toxic solvent consumption and waste generation.

Learn more at [www.agilent.com/chem/infinity](http://www.agilent.com/chem/infinity)



## LC Columns and Supplies

### Agilent LC Column Family

Agilent's broad family of LC columns delivers the best choice for your analytical separations, while facilitating your implementation of pharmacopoeia methods and ongoing method development.



Poroshell 120 provides Fast LC resolution and speed without high backpressure, so you can use it on older instruments, and transfer easily to the 1260 Infinity LC, to optimize UHPLC performance up to 600 bar. The Poroshell 120 family has nine phases, including HILIC, and Fast Guards for UHPLC are available to help extend column life.

ZORBAX Rapid Resolution High Definition (RRHD) columns, 1.8  $\mu\text{m}$ , are stable to 1200 bar so you can get the highest sensitivity and speed from your 1290 Infinity LC. You can achieve maximum scalability across laboratory development settings, and benefit from worldwide service and support. Fast Guards for UHPLC are also available for ZORBAX RRHD columns.

For help finding the best Agilent column for your separation, check out the LC Columns Navigator for web and mobile devices, at [www.agilent.com/chem/navigator](http://www.agilent.com/chem/navigator).

### Increase Performance and Reduce Costs with Agilent Lamps

Only Agilent lamps are designed to extremely tight quality control specifications, to optimize the performance of your instrument, increase light intensity and decrease noise. They are stable, rugged and long lasting to ensure a low cost of ownership. Always choose Agilent lamps to save time, avoid trouble, and enjoy optimal performance.



### Agilent Captiva Premium Syringe Filters

Sample filtration is often avoided during routine pharmaceutical drug analysis due to fear of drug adsorption on the membrane, as well as the possibility of extractables contaminating the sample. Agilent Captiva Premium syringe filters eliminate those concerns, so the critical filtration step can be added back in to your workflow. Our syringe filters are certified to be free of extractables and demonstrate excellent recoveries of a variety of drug assays. Our syringe filters have been demonstrated to be more effective at particulate removal than centrifugation alone.

Learn more visit us at [www.agilent.com/chem/captiva](http://www.agilent.com/chem/captiva)





## LC/MS Systems

### Agilent 6100 Series LC/MS Systems



Agilent 6100 Series LC/MS Systems deliver faster acquisition speeds that let you take full advantage of UHPLC separations. Valuable structural information is provided by variable energy, in-source fragmentation. Intuitive Agilent ChemStation software lets you set up and control both LC and MS from a single screen, and integration with MassHunter software adds analytical power. Even at scan speeds up to 10,000  $\mu$ /sec, you get excellent spectral quality and accurate isotope ratios for confident identification and confirmation. Agilent Jet Stream thermal gradient focusing technology is now available on 6130B and 6150B models for enhanced sensitivity.

### Agilent 6400 Series Triple Quadrupole Mass Spectrometers



Agilent 6400 Series Triple Quadrupole Mass Spectrometers all offer robust solutions for busy laboratories, with a fifty-fold increase in sensitivity from the 6420 to the top-of-the-line 6490 so you can match the system to your requirements. The 6400 Series helps streamline method development using dynamic multiple reaction monitoring (dMRM), simplifies method development and ensures consistent ion statistics with constant cycle times, resulting in reproducible peak area measurements. You can speed up analysis times with triggered MRM, and combine MRM quantitative analysis with the generation of a product ion spectrum for library searching and compound confirmation. Powerful MassHunter Workstation software dramatically enhances productivity, from method optimization and data acquisition to data processing and reporting.

### Agilent 6500 Series Accurate-Mass Q-TOF



With the Agilent 6500 Series Accurate-Mass Q-TOF, you can achieve femtogram-level sensitivity using Agilent iFunnel technology, which increases ion transfer rates to achieve the lowest detection levels of any high-resolution LC/MS instrument. The Agilent 6500 Q-TOF maintains resolution and mass accuracy using ion beam compression and shaping (IBCS) technology that provides the greatest sensitivity while maintaining 40 k mass resolution and sub ppm mass accuracy from  $m/z$  20–10,000. In addition, the in-spectrum dynamic range of up to 5 orders of magnitude reveals trace-level targets (such as genotoxic impurities) even in the presence of much more abundant compounds (such as API). The advanced MassHunter data analysis software features molecular feature extraction (MFE) and molecular formula generation (MFG), along with molecular structure correlator (MSC) software, help address your challenges in genotoxic impurity analysis.

Find easy access to LC/MS application notes and published literature for pharma at [www.agilent.com/chem/insidelcms](http://www.agilent.com/chem/insidelcms)

## Gas Chromatography (GC) and GC/MS

Static headspace gas chromatography and GC-MS are used for USP <467> for residual solvent analysis. Agilent offers a complete selection of gas chromatography accessories that allow you to configure a system that meets the exact needs of your lab.



The Agilent 7697A Headspace Autosampler can be configured for 12 or 111 vial capacity. Configured for 111 vials the 7697A three 36-vial racks can be exchanged while the instrument is operating, making the 7697A the ideal choice for high-throughput laboratories. The Agilent 7890B GC System features breakthrough Ultra Inert Flowpath and Capillary Flow Technology which enables reliable, leak-free in-oven connections, provides versatile means of analyzing complex matrices and enhances productivity and data integrity. The Agilent 5977A Series GC/MSD System offers all ionization modes (PCI, NCI and EI) in one automated sequence using the standard CI source with an Auto CI feature that makes CI as easy as EI.

### Agilent MassHunter Software for MS detection

Agilent MassHunter Software, for MS detection, and Agilent OpenLAB CDS, for FID detection, both provide the ability to analyze data more efficiently and allows laboratories to meet FDA 21 CFR Part 11 guidelines if required.

Learn more about Agilent GC/MS and MassHunter software at [www.agilent.com/chem/ms](http://www.agilent.com/chem/ms)



### Agilent J&W GC Columns

Agilent J&W DB-Select 624UI <467> Ultra Inert GC columns are designed specifically for United States

Pharmacopeia Method <467>. Equivalent to USP stationary phase G43, this phase is engineered to provide the best sensitivity and resolution of the critical pairs specified in USP Method <467> analysis of residual solvents in active pharmaceutical ingredients.

Learn more at [www.agilent.com/chem/Ulcolumns](http://www.agilent.com/chem/Ulcolumns)

# SYSTEMS SOLUTIONS

## Software and Informatics



Agilent's OpenLAB Software Suite addresses the complete life cycle of scientific data, including experimental design, data acquisition and analysis, and knowledge management. OpenLAB is based on an open system architecture that supports multivendor interoperability and integrates applications, instruments, and data to make your lab more efficient. The Agilent OpenLAB portfolio includes OpenLAB Chromatography Data System (CDS), OpenLAB Electronic Lab Notebook (ELN), and OpenLAB Enterprise Content Manager (ECM) or DataStore to help you capture, analyze, and share information. To complete your solution, Agilent OpenLAB offers services and support designed to improve your overall experience, and increase your return on investment.

Learn more at [www.agilent.com/chem/openlab](http://www.agilent.com/chem/openlab)

## CrossLab Enterprise Solution, Instrument Services and Supplies

Agilent has combined standard repair, maintenance, and instrument qualification with dedicated onsite resources, instrument performance data, and decades of asset management insights to provide a customized service package designed to maximize laboratory productivity and ROI for laboratory assets.

CrossLab instrument services were developed in-house, based on Agilent's industry leading design, manufacture, and service of laboratory instruments. Service protocols and delivery adhere to the same strict performance standards applied to Agilent instruments. Our proprietary Remote Advisor instrument monitoring and Laboratory Business Intelligence data management software provide deep insights into asset management and technology deployment. The end result is the highest scientific instrument productivity for every dollar spent on services.

For the major brands of instruments in your lab, order high-quality, compatible GC, HPLC, and electrochemistry supplies from a name you trust. CrossLab supplies – such as Ultra Inert liners for your GCs and LC lamps for your HPLCs – will synchronize your lab's workflow, supply ordering, and productivity. And, Agilent CrossLab Services help you achieve the highest levels of productivity regardless of instrument manufacturer.

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