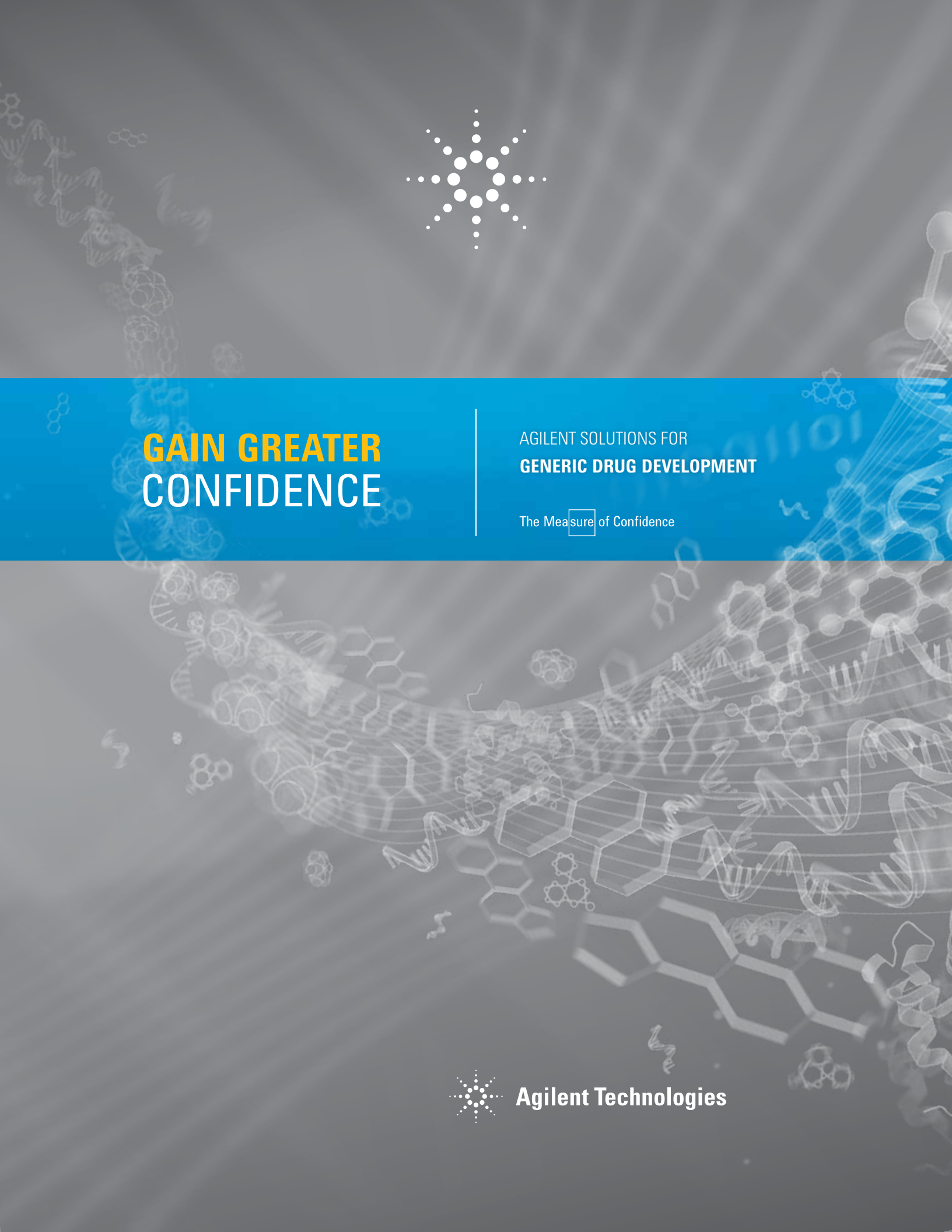


GAIN GREATER CONFIDENCE

AGILENT SOLUTIONS FOR

GENERIC DRUG DEVELOPMENT

The Measure of Confidence

Agilent Technologies

ACCELERATE GENERIC PHARMACEUTICAL DRUG DEVELOPMENT WITH PRECISE, RELIABLE SOLUTIONS

Competition and potential opportunities in the generics drug market have never been greater. Many of the most successful pharmaceutical compounds are reaching the patent cliff and generic pharmaceutical companies are rushing to seize this opportunity by being first to market with generic alternatives. The potential for growth in generic drug development has also expanded, moving beyond traditional US, European, and Japanese markets to new opportunities in emerging markets, such as Brazil, Russia, India, and China (BRIC). Those companies that can achieve faster development timelines and more efficient navigation of complex global regulatory approvals have the best chance of success.

Realizing these opportunities while staying ahead of the competition requires rapid increases in productivity, reduced costs, and streamlined efforts to meet regulatory requirements. Therefore, it is now even more critical to work with a trusted analytical partner with the relevant expertise to facilitate your efforts to increase development speed while maintaining the highest levels of quality and compliance.

Agilent Technologies delivers unique, comprehensive solutions based on industry-leading technology, enabling optimal resource utilization so you can improve productivity and be first to market.

The Agilent toolbox for accelerating generic pharmaceutical development

From confidently developing an efficient process for active pharmaceutical ingredients and finished dosage forms to manufacturing them with reliable, regulatory-compliant quality control processes, Agilent has the solutions you need to accelerate your efforts to be first to market:

- Infinitely better UHPLC for efficient, cost-effective method development and a commitment to quality by design (QbD) principles
- Chromatography, spectrometry, and spectroscopy for accurate analysis of all three major impurity types
- Solid-state NMR solutions for definitive polymorph identification
- Online and offline dissolution testing for superior dosage form performance characterizations
- Robust LC/MS solutions for dependable bioequivalence testing
- Spectroscopy and chromatography for reliable raw material quality control testing
- Sixteen years as a top-ranked compliance services provider

EFFICIENT ANALYTICAL METHOD DEVELOPMENT AND TRANSFER

The ability to efficiently and effectively develop new analytical methods, and to transfer and optimize existing procedures, is essential for any successful generic drug development program. Liquid chromatography (LC) methods are at the core of many stages of pharmaceutical development and are often the rate-limiting step. Their development is a laborious trial-and-error process which must be addressed before reaching an efficient solution for assessing product quality. Furthermore, once LC methods are developed they must also be transferred to other departments complicating efforts to maintain performance.

Agilent offers infinitely better liquid chromatography solutions that help you to realize cost savings and higher throughput in method development by reducing analysis time and solvent consumption.

1200 Infinity Series LC Systems

- Faster results with greater resolution and higher sensitivity
- Options suitable for any budget
- A high dynamic range diode array detection solution that provides a 30-fold wider linear dynamic UV-range to enable detection and quantification of main and trace compounds in a single run
- Intelligent System Emulation Technology (ISET) for simplified method transfer
- Agilent Instrument Control Framework (ICF)
  - Comprehensive and straightforward control of your Agilent LC instruments and modules regardless of the chromatography data system

A family of fast LC columns

- Increase LC and LC/MS assay productivity with the latest column options from UHPLC to HPLC: Poroshell 120, ZORBAX Rapid Resolution High Definition (RRHD), and 1.8 µm columns

OpenLAB CDS Software

- Scalable from individual workstations to fully distributed enterprise-wide systems
- Add OpenLAB ECM or Data Store
  - For secure central data storage
  - For support of all GxP and 21 CFR Part 11 regulations

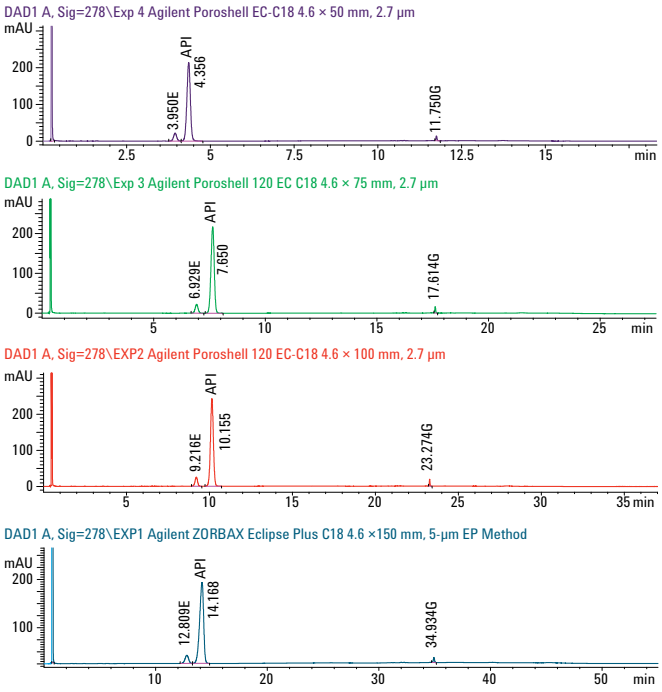


Figure 1. Separation of a salmeterol xinafoate system suitability mix using EP-compliant, cost-saving methods.[1]

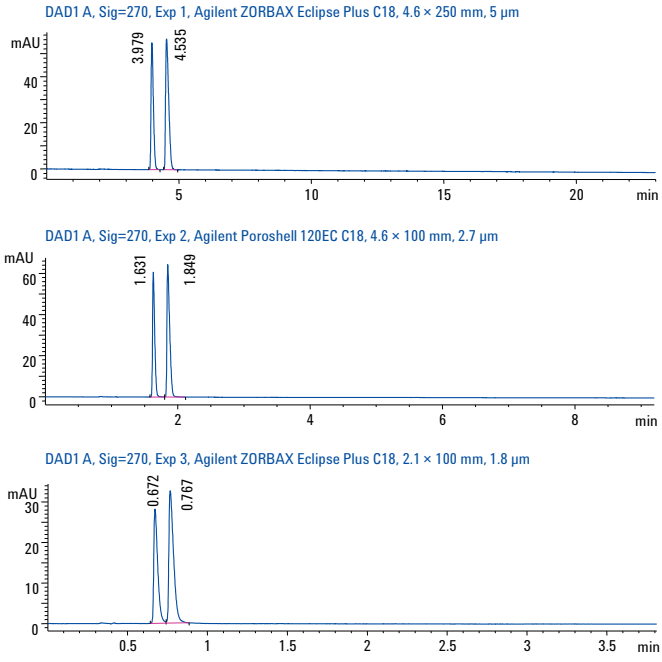


Figure 2. Separation of a tramadol system suitability mix using USP requirements and newly developed cost-saving methods.[3]

Reduce the cost per analysis and increase throughput by varying column dimensions

In this example, a European Pharmacopoeia (EP) method of chromatographic purity is demonstrated for salmeterol xinafoate. An Agilent 1290 Infinity LC with various pump and auto sampler modules was selected using ISET technology according to the column dimension used. The results show that significant time and solvent savings can be achieved as compared to the original pharmacopoeia method by simply modifying column length and particle size (Figure 1). Since the modifications are within the EP guidelines of allowed column dimensions, no method revalidation was required.

Increase laboratory productivity for method development

A six-fold improvement in laboratory productivity was achieved for tramadol method development (Figure 2). When column length and particle size were varied within the current USP<621> limits as per USP 35-NF, a significant reduction in analysis time (>50 %) was achieved compared to the USP method. Switching from an HPLC method using a 25 cm long 5 µm column to a UHPLC method with a 10 cm long, 1.8 µm column (taking advantage of the USP's pending decision to relax current restrictions for isocratic separations) saved 90 % of solvent consumption and 80 % of the previous analysis time.

Reference Publications

1. Higher throughput and cost reduction for salmeterol xinafoate analysis using the Agilent 1290 Infinity LC System with ISET. Agilent publication **5991-0394EN**.
2. Higher throughput and cost reduction for purity analysis of olanzapine tablets using the Agilent 1290 Infinity LC System with ISET. Agilent publication **5991-0278EN**.
3. Reducing analysis time and solvent consumption for isocratic USP assay methods with current and proposed USP guidelines using the Agilent 1290 Infinity LC System. Agilent publication **5991-0733EN**.
4. Reducing total analysis cost for generic drugs within USP <621> allowed limits. Agilent publication **5991-0396EN**.

QbD studies assure the stability and quality of analytical measurements, as well as the robustness of measurement methods. Agilent supports the QbD approach to analytical method development by providing instrumentation and software tools that automate the process and facilitate the performance of the multivariate experiments required for the implementation of QbD principles. A wide range of column selectivities are available that can be used with various conditions to support the exploration of design options.

Agilent automated method development solutions facilitate the implementation of QbD principles in analytical development.

1200 Infinity Series method development solution

- Up to 8 columns and 26 solvents
- Over 1000 unique separation conditions
- Four to six different temperature zones
- ID columns from 2.1–4.6 mm and up to 300 mm length
- Different configurations/detectors

Simple to sophisticated software choices

- Method scouting wizard
  - For automated testing of all experimental variables
  - Screens samples against a multidimensional matrix of columns, solvents, gradients, and temperatures
- Advanced functionality with solutions from Agilent partners: Chromsword, ACD/Labs, and Fusion AE
  - Completely aligned with QbD principles
  - Fully automatic design of experiments for univariant or multivariant robustness testing and characterization of a method design space
  - Rapid results browsing and automatic report generation

A robust LC columns portfolio

- A wide range of selectivities can be used to optimize resolution, including phases used for pH and temperature extremes
- Varying dimensions and pressure capabilities help optimize your productivity
- Multiple lot availability enables thorough evaluation

Analytical methods are frequently transferred between laboratories, from development groups to quality control, or to an outsourcing partner. In this case, QbD principles necessitate eliminating risk in method transfer that can be caused by method variation and instrumentation from different vendors.

Agilent ISET enables seamless method transfer without method modification.[5]

1290 Infinity LC and ISET

- Simple and flexible: executing any legacy HPLC or the latest UHPLC methods while delivering the same chromatographic results with a single mouse click
- With exact knowledge about the system behavior of a selected LC instrument, ISET creates an emulation function, based on knowledge of the system behavior of a selected LC instrument, so the 1290 Infinity LC delivers the same gradient conditions without shifts in retention times or changes in resolution
- Optimal results with no method modification required

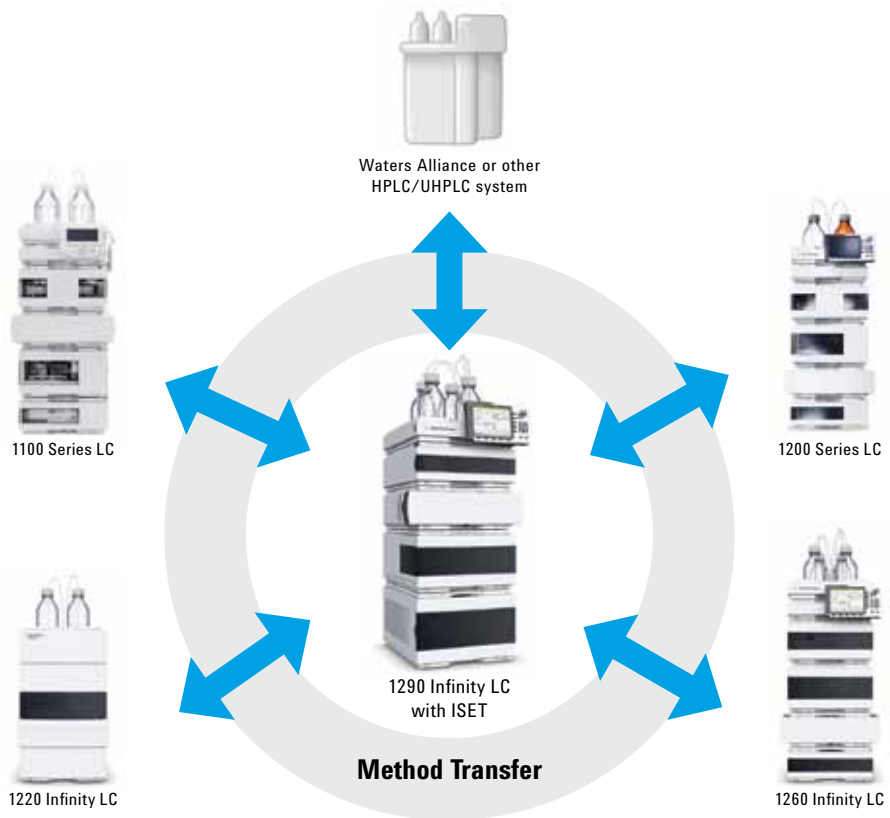


Figure 3. Agilent's ISET system can be used to efficiently transfer methods from a range of systems to the final QC environment.

Reference Publications

5. Infinitely better method transfer: Agilent 1290 Infinity LC with Intelligent System Emulation Technology. Agilent publication 5990-8670EN.

ACCURATE IMPURITY ANALYSIS

The nature and quantity of impurities found in drug substances determines the ultimate safety of the final pharmaceutical product. Regulatory pressures have brought increased attention to the analysis of impurities in chemical entities, and as a result the identification, quantitation, qualification, and control of impurities are now a critical part of the drug development process. Regulations typically cover three impurity types: organic impurities, elemental impurities, and residual solvents. Genotoxic impurities, which may potentially increase cancer risks in patients, are controlled at levels much lower than other impurities, complicating matters further because their analysis in trace quantities can be very complex.

Agilent leads the industry in impurity analysis, with comprehensive solutions for the three major impurity types—organic, elemental, and residual solvents.

Category	Application	Instrumentation
Organic impurities 	Impurity detection and rapid method scouting	1200 Infinity Series LC + Diode-array Detector SL
	Analysis of highly polar compounds	7100 CE instrument
	Detection of chiral impurities	1260 Infinity Analytical SFC System
	Isolation of impurities	1260 Infinity Prep-scale Purification System
	Identification of impurity structure	Cary 630 FTIR, DD2 NMR, 1200 Infinity Series LC, 6100 Series Single Quad MS, 6200 Series TOF MS, and 6500 Series Q-TOF MS
	Quantitation of genotoxic impurities	1200 Infinity Series LC + 6400 Series Triple Quad LC/MS Systems
Elemental impurities 	Analysis of all 16 regulated elements as per USP <233> method, including large sample dilutions	7700 Series ICP-MS
	Analysis of elemental impurities at the basic requirements of USP not necessitating the lowest detection limits	700 Series ICP-OES
	Speciation of regulated elements such as As and Hg	1200 Infinity Series LC + 7700 Series ICP-MS
Residual solvents 	Analysis per USP <467> procedures	7890A GC + 7967A Headspace sampler
	Analysis involving unknown peaks/solvents	7890A GC + 5975C GC/MS system + 7697A Headspace sampler

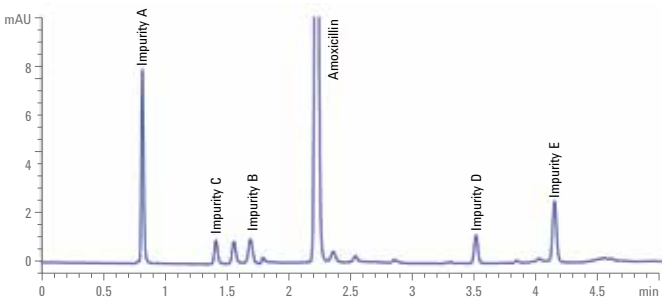


Figure 4. Analysis of amoxicillin and five impurities using the Agilent 1220 Infinity LC/UV System and a ZORBAX SB-Aq column.[6]

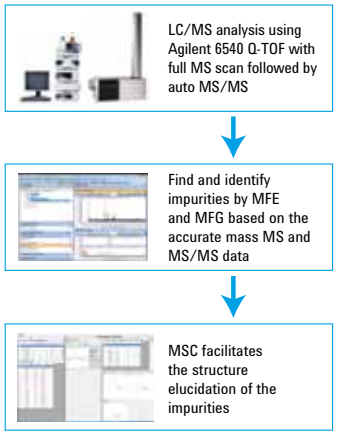


Figure 5. Software-assisted workflow for impurity identification and profiling of pharmaceuticals on the Agilent 1200 Infinity Series LC combined with an accurate mass Q-TOF, and MassHunter Qualitative Analysis and MSC software.[7]

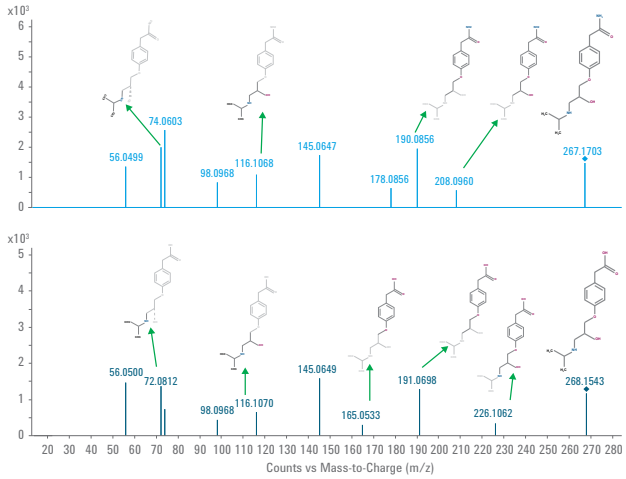


Figure 6. Structure elucidation of atenolol and impurity G demonstrates the wide usability of MSC software to assign structures for each fragment of atenolol (precursor m/z: 267.1703) and impurity G (precursor m/z: 268.1543).[7]

Routine quality control analysis using LC/UV

Agilent 1200 Infinity Series LC/UV systems are an ideal solution for impurity analysis in pharmaceutical quality control laboratories because they deliver the precision, linearity, sensitivity, and speed required to meet regulatory standards for impurity analysis. Figure 4 demonstrates the analysis of amoxicillin and its impurities using the Agilent 1220 Infinity LC System and a gradient method in combination with UV detection, an Agilent ZORBAX SB-Aq column, and OpenLAB CDS ChemStation Edition. This analysis was completed within 7 minutes and detected impurities down to a level of 0.01 %.

Trace level genotoxic impurity analysis using LC/MS/MS

The identification and profiling of atenolol and impurities benefited from the Agilent software-assisted workflow (Figure 5) for impurity identification and profiling of active pharmaceutical ingredients (API). Analysis was performed using the high-resolution accurate-mass Q-TOF LC/MS system (Figure 6). The results demonstrate the wide usability of molecular structure correlator (MSC) software for assigning structures for each fragment of atenolol (precursor m/z: 267.1703) and pharmacopeia-specified impurity G (precursor m/z: 268.1543).

Reference Publications

6. Analysis of amoxicillin and five impurities on the Agilent 1220 Infinity LC System. Agilent publication **5991-6093EN**.
7. Pharmaceutical Impurity Analysis Solutions. Agilent publication **5991-0090EN**.

DEFINITIVE POLYMORPH ANALYSIS

Crystallization is the most common method used for the final purification and isolation of the active pharmaceutical ingredient (API) or when synthesizing a drug at commercial scale. Molecules can adopt more than one type of crystal structures (polymorphs) upon precipitation, with varying physical properties associated with different polymorphs. These differences can cause serious issues in the pharmaceutical development due to changes in chemical stability, water absorbance, and dissolution rates, which must be measured, understood, and controlled for in drugs.

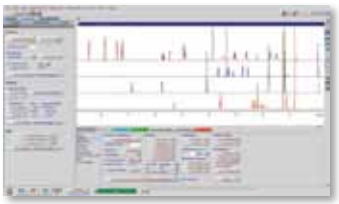
Definitively identify the polymorphic states of APIs with Agilent's robust solid-state NMR solutions.

DD2 NMR Spectrometer

- A robust and flexible choice that combines high-power RF generation with unsurpassed sensitivity
- Easy-to-use, fast, and reliable for routine analysis
- Advanced superconducting materials and cutting edge shielding technology minimize site space requirements and allow installation in wide range of environments

NMR Solids Probes

- A wide selection of probes for solid state NMR
- Built on transmission tuning tube (T3) technology with power handling that transfers magnetic pulses with minimal signal loss



VnmrJ software

- Accommodates experienced users developing complex pulse sequences
- Supports novice users with a comprehensive collection of ready-to-go pulse sequences
- Available with a 21 CFR Part 11 compliance software module

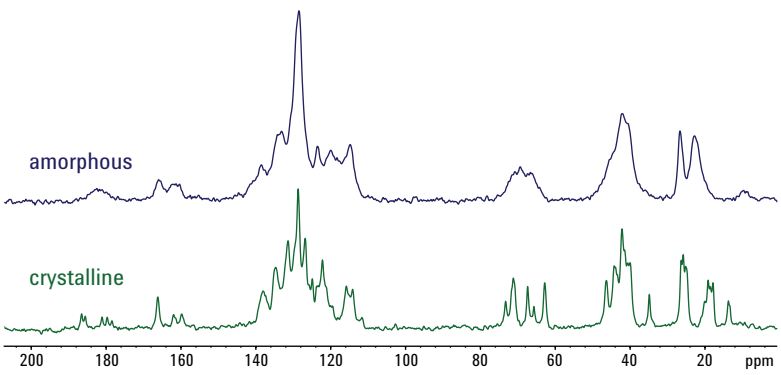


Figure 7. Solid state NMR spectra of amorphous and crystalline forms.

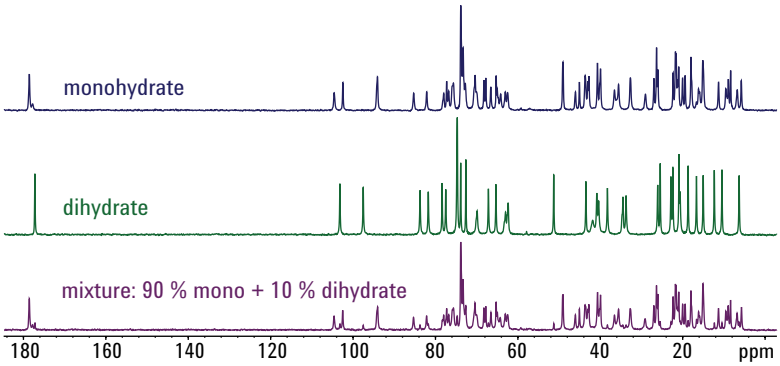


Figure 8. Polymorph analysis of an API using solid state NMR.

Distinguishing the presence of polymorphic forms

NMR spectra are exquisitely sensitive to changes in the local electronic environment, readily detecting changes in the NMR resonance frequency as small as 1 part per billion. This sensitivity to local structure makes solid-state NMR the definitive tool for testing and measuring the polymorphic state of pharmaceutical compounds. Each polymorph yields a distinctive spectrum that can be used as a fingerprint for that specific solvate or crystal form. Figure 7 compares the spectra of amorphous compounds, with characteristic broad lines, to that of crystalline forms.

When combined with the robust quantitation of an NMR experiment, this technique can be used to directly investigate drug substance or drug product materials, up to and including the final pills, for polymorphic integrity. As shown in Figure 8, the solid-state NMR spectra collected for the monohydrate and dihydrate pseudopolymorphs of the analyte are distinctly different. It is easy to distinguish the presence of the both forms in a 90/10 mixture of the two and, as all NMR signals yield a unit response factor, quantification of such mixtures is robust and reliable.

SUPERIOR DISSOLUTION TESTING

The dissolution test has evolved to become the definitive tool for characterizing the performance of solid oral dosage forms. *In vitro* dissolution data supports the evaluation and interpretation of bioavailability effects using gastrointestinal conditions and is of great importance when assessing changes in production site, manufacturing processes, and formulation changes. Dissolution is critical for ensuring the quality and consistency of batches, initially and over time. Dissolution testing also plays an important role in evaluating and controlling the quality attributes of drug products in Quality by Design (QbD) based pharmaceutical development.

Agilent's market leading dissolution apparatus and sampling systems integrate with on or offline analytical systems to test the full range of dosage forms.

708-DS and 709-DS Dissolution Apparatus

- Superior design supports innovative options such as media temperature monitoring, dosage delivery, and automated sampling for unattended testing
- Includes 21CFR Part 11 compliant dissolution workstation software

Integrated UV Dissolution Systems

- Diode-array UV analysis with the 8453 UV-Vis Spectrophotometer or scanning UV dissolution with the Cary 60 UV-Vis Spectrophotometer
  - Capabilities to support multicell, valve-based, multi-apparatus and fiber optic configurations
  - 21 CFR Part 11 compliant with ChemStation and OpenLAB ECM or Cary WinUV Dissolution software

Simplified LC analysis

- Maximum utilization of your dissolution apparatus and LC instrumentation
- LC Dissolution software automates LC instrument setup, incorporates dissolution methodology, performs sample analysis, and generates final reports

Applications and testing capabilities of Agilent Dissolution Apparatus.[8]

Dissolution Apparatus	Common Product Type
Stirred Vessel Methods—The basket and paddle dissolution apparatus are the most commonly used throughout the world. They traditionally require the placement of individual dosage forms into 1L glass vessels containing a fixed volume of fluid referred to as dissolution medium.	
Agilent 708-DS and 709-DS Dissolution Apparatus for Rotating Basket (USP Apparatus 1)	• Capsules • Tablets • Floating dosage forms • Modified release products • Beads • Suppositories
Agilent 708-DS and 709-DS Dissolution Apparatus for Rotating Paddle (USP Apparatus 2)	• Tablets • Capsules • Hydrogels • Powders • Suspensions • Microparticles
Agilent 708-DS and 709-DS Dissolution Apparatus for Paddle over Disk (USP Apparatus 5)	• Transdermal patches
Agilent 708-DS and 709-DS Dissolution Apparatus for Rotating Cylinder (USP Apparatus 6)	• Transdermal patches
Reciprocating Methods—The dosage form is placed within a chamber through which media flows in alternating directions, or on/within numerous holders specifically designed for novel extended release dosage forms.	
Agilent BIO-DIS Reciprocating Cylinder Apparatus (USP Apparatus 3)	• Capsules • Beads • Enteric coated products • Extended, modified or sustained release formulations
Agilent Reciprocating Holder Apparatus and 400-DS Dissolution Apparatus (USP Apparatus 7)	• Transdermal systems • Osmotic pumps • Implants • Drug-eluting stents • High-potency, low-dose systems
Alternative Applications—Additional configurations were developed to provide drug release information for the API and topical formulations (for use with the 708-DS).	
Agilent Intrinsic Apparatus	• Pure drug substances
Agilent Enhancer Cell for Diffusion Cells Testing	• Ointments • Creams • Gels • Transdermal
Agilent Peak Vessel	• Beads • Products exhibiting coning problems

Qualification tools

All dissolution apparatus used in a cGMP setting should be re-qualified at regular intervals. Agilent provides a unique qualification solution for any open-head design dissolution apparatus. The 280-DS Mechanical Qualification System measures and records the critical physical parameters for each vessel location, as well as checking that the instrument is level and vibration-free. Whether your laboratory performs the Performance Verification Test (PVT) using prednisone tablets or has already made the switch to mechanical qualification, the 280-DS will simplify your qualification procedures.

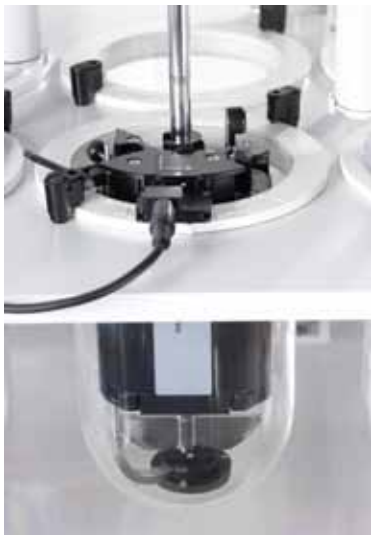


Figure 9. Paddle and vessel measurements taken with the Vessel Module of the 280-DS Mechanical Qualification System.[9]

Reference Publications

8. Dissolution Systems Source Book 2011-2012 Edition. Agilent publication **5990-8146EN**.
9. 280-DS Mechanical Qualification System Brochure, Agilent publication **5991-0110EN**.

DEPENDABLE BIOEQUIVALENCE STUDIES

Establishing bioequivalence with the commercially available branded drug product is a critical part of the generic drug development process which involves establishing that the active ingredient in a generic medicine is absorbed into the body at the same rate and amount as the branded product. In bioequivalence studies, highly sensitive and selective bioanalytical methods are developed to quantify drugs in biological matrices such as blood, plasma, and serum. In addition to ensuring ruggedness in method development and validation, a software environment that supports regulatory compliance is essential.

Agilent delivers solutions for dependable bioequivalence studies with industry leading LC/MS/MS sensitivity and software that supports regulatory compliance.

1200 Infinity Series LC Systems

- Infinitely better precision, accuracy, and speed for the routine analysis of a large number of samples in a high throughput workflow
- 1290 Infinity LC Injector HTC/HTS - capacity for up to 24-well plates with cooling

6400 Series Triple Quadrupole LC/MS Systems

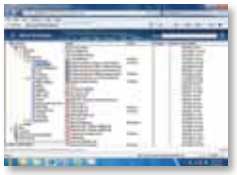
- Greater sensitivity, productivity, and value with iFunnel technology which dramatically increases the number of ions that enter the mass spectrometer for zeptomole sensitivity
- MassHunter MS Optimizer software that automatically optimizes ion transitions, and fragmentor and collision energies

Bond Elut SPE and Captiva Filtration Sample Prep

- Bond Elut Silica and Polymeric SPE for sample clean up and concentration
- Captiva ND^{Lipids} for lipid and protein depletion

MassHunter Software

- MassHunter Quantitative Analysis with compound- and sample-centric features like a parameter-less integrator that yields quantitative results with minimal manual intervention
- MassHunter Study Manager automates LC/MS bioanalytical workflows from sample submission and analysis to fully customizable data reports



MassHunter with OpenLAB ECM

- Compliance features include secure, audited access to all data, version control, audit trail, and electronic signatures
- Centralized storage of laboratory and instrumentation data
- Automated collection of data, methods, batches, and reports from MassHunter

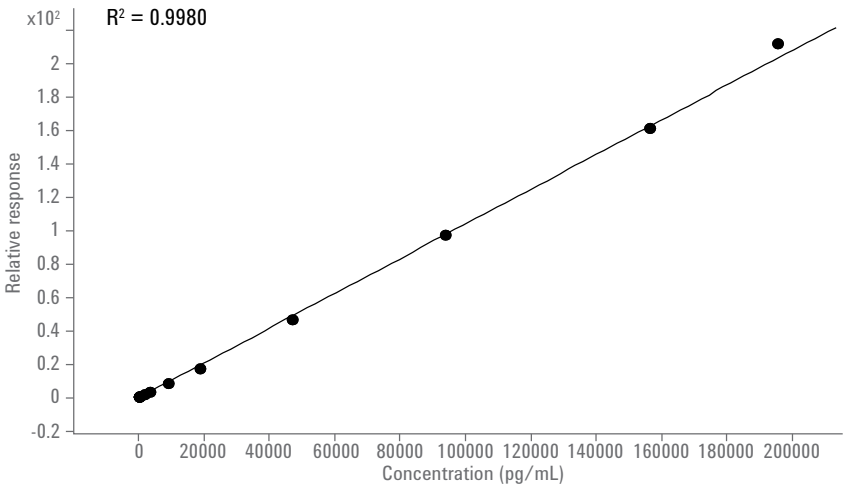


Figure 10. The calibration standard curve of atorvastatin measured using an Agilent 6460 LC/MS/MS System demonstrated linearity over a wide concentration range.[10]

Successful bioanalytical method transfer

A critical step in bioequivalence studies is the successful transfer of an LC/MS/MS assay between laboratories. Rapid and efficient transfers, such as those using Agilent Optimizer software, lead to rapid and efficient automated MRM analysis and greater the cost savings for new generic drug development. The transfer of a non-Agilent LC/MS/MS method to an Agilent 1290 Infinity LC System coupled to an Agilent 6460 Triple Quadrupole LC/MS System for the analysis of atorvastatin and its hydroxyl metabolites, in human plasma, is shown in Figure 10. The method was transferred with linearity, precision, and accuracy for all QC samples, in all batches, that met the bioanalytical acceptance criteria (Table 1), and with minimal down time.

A bupropion LC/MS/MS method was transferred from a non-Agilent LC/MS system to an Agilent 6460 Triple Quadrupole LC/MS System by optimizing only the source parameters while maintaining the same MRM transitions. The precision and accuracy results met the bioanalytical acceptable criteria with an excellent linearity, dynamic range, and LLOQ for both bupropion and the internal standard, risperidone (see Figure 11).

Table 1. Precision and accuracy of atorvastatin calibrations standards and QC samples in human plasma obtained on the Agilent LC/MS system.[10]

Levels	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	HQC	MQC	LQC
% CV (n = 3)	6.91	11.54	8.65	8.07	6.30	9.42	1.44	0.49	10.19	3.99	8.91	7.80	6.70
% Mean Accuracy (a = 3)	102.67	99.98	106.80	86.76	88.79	89.16	99.71	108.59	100.53	99.37	108.42	103.58	90.98

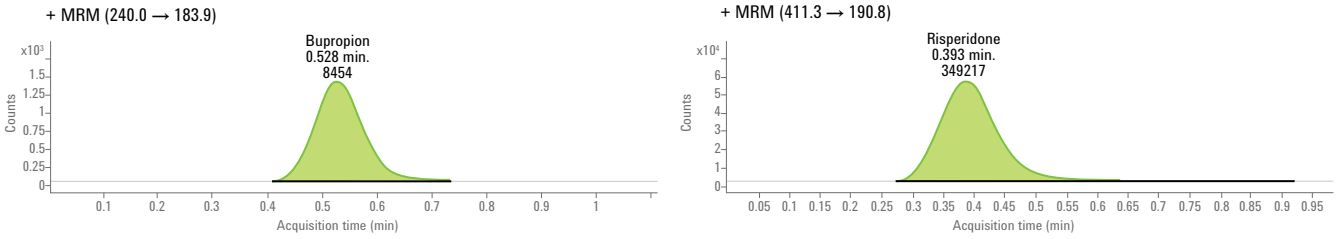


Figure 11. Chromatogram of bupropion and risperidone (IS) at LLOQ (1.502 ng/mL).[11]

Reference Publications

10. Development of an LC/MS/MS Assay for Atorvastatin in Human Plasma Using a 6460 Triple Quadrupole LC/MS System. Agilent publication **5990-9128EN**.
11. Development of an LC/MS/MS Method for Bupropion in Human Plasma Using a 6460 Triple Quadrupole LC/MS System. Agilent publication **5990-9233EN**.

RELIABLE RAW MATERIALS ANALYSIS

Confirming the identity and controlling the quality of raw materials against specifications is a crucial part of the manufacturing workflow. Rapid analysis using a minimum number of accessories is essential for facilitating the quick release of raw materials passing the set criteria for manufacturing. The systems used for testing raw materials must comply with GMP regulations, and with the following practices: equipment needs to be qualified, software and systems need to be validated, methods need to be validated or verified, and the security and integrity of data should be demonstrated and tested to meet the specifications of US, European, Japanese, Chinese, Indian, and International Pharmacopoeias. If alternative methods are used, then equivalency should be demonstrated and fully validated.

Agilent delivers high performance spectroscopy and chromatography solutions for the rapid, reliable quality control testing of raw materials in multi-user environments.

1200 Infinity Series LC Systems

- 1260 Infinity Isocratic LC System
  - Rugged design for demanding QC applications as well as routine use
  - Facilitates increased uptime, with consistent results for low operating and maintenance costs
  - Software with intuitive diagnostic and monitoring capabilities, and alert functions to minimize errors
- 1220 Infinity LC System
  - Affordable access to UHPLC quality and performance, with exceptional accuracy and precision, for all routine applications

OpenLAB Software Suite

- Integrated solution with a new easy-to-administer architecture that supports intuitive custom reporting and laboratory-wide data management
- Complies with regulatory guidelines such as GLP, GMP, and 21 CFR Part 11

Cary 630 FTIR Spectrometer

- Innovative technology in a sturdy, compact unit
- Revolutionary sampling technology
  - Suitable for measuring liquids, gas phase, and powdered or solid samples
  - Diamond attenuated total reflectance interface yields high-quality spectra without sample preparation
- Microlab software
  - Intuitive, and 21 CFR compliant
  - Method-driven picture-based program that facilitates rapid learning and precise, accurate results

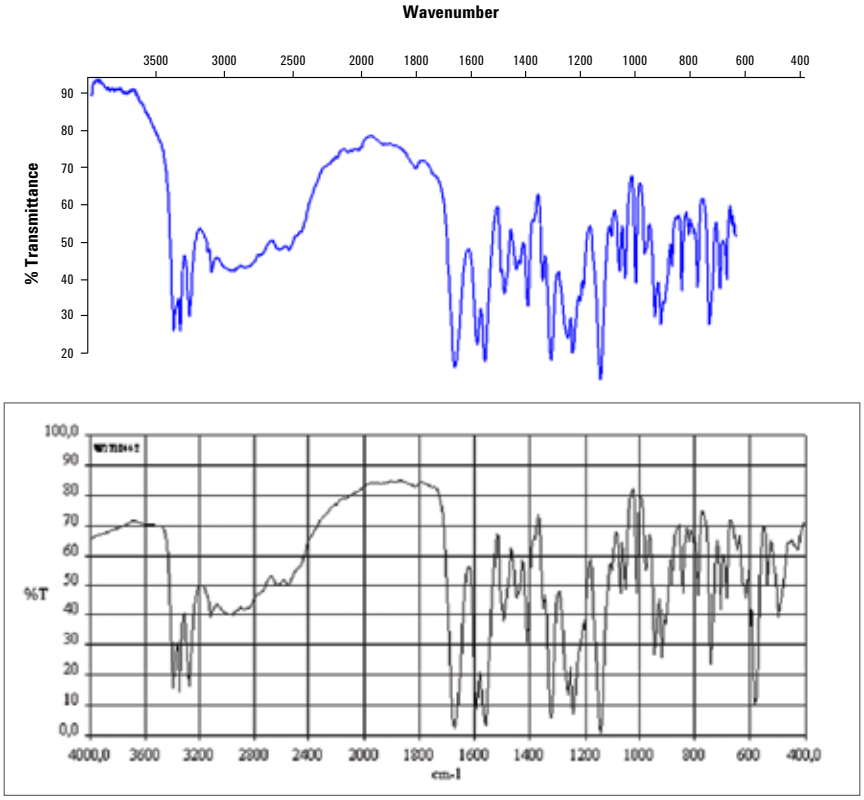


Figure 12. The FTIR spectra of furosemide, comparing the online spectrum from International Pharmacopoeia (Black, KBr pellet) to the one measured using the Cary 630 FTIR (Blue, DRIFT).[12]

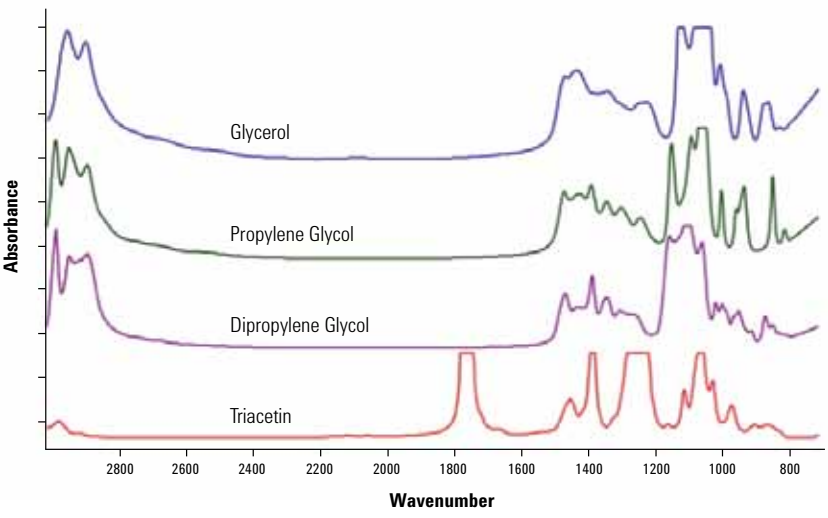


Figure 13. Spectra of 4 common drug additives recorded using the DialPath 30 µm pathlength. Spectra were recorded in less than 30 seconds and results compared to reference spectra, yielding near perfect match quality.[13]

Pharmaceutical identification by FTIR

The Agilent Cary 630 FTIR is an ideal tool for use in pharmaceutical quality control, and easily meets the performance specifications of the US, European, Japanese, Chinese, Indian and International Pharmacopoeias. A comparison of the diffuse reflectance spectrum of furosemide and the reference spectrum of furosemide from the International Pharmacopoeia website are shown in Figure 12. Excellent correlation of the frequencies present in the reference spectrum with those of the measured sample was observed.

Verification of the quality of incoming liquid raw materials

FT-IR spectra of common drug additives are shown in Figure 13. This technique can be used to verify the identity and overall purity of incoming liquid raw materials. These measurements were taken using Agilent's DialPath technology, a breakthrough in the measurement of liquids by FT-IR transmission.

Using the DialPath makes rapid quantitative and qualitative measurements easy because it can handle viscous liquids and volatile solvents equally well, and without the use of a transmission cell.

Reference Publications

12. Agilent Cary 630 FTIR Pharmacopoeia compliance. Agilent application note **5990-9379EN**.
13. Quality verification of incoming liquid raw materials using the Agilent 5500 DialPath FTIR spectrometer. Agilent application note **5990-7880EN**.

HIGH-QUALITY CLEANING VALIDATION

Avoiding the batch-to-batch contamination of manufacturing equipment is essential for ensuring production quality. Cleaning validation provides documented evidence that the methods employed within a facility consistently eliminate or limit the carryover of contaminants such as byproducts, previous products, solvents, cleaning agents, and micro-organisms to levels below predetermined requirements. The verification of cleaning method effectiveness is also considered a major bottleneck in batch manufacturing. Proper validation and reduction in equipment downtime is only possible when the analytical equipment used is capable of reliably and accurately detecting contaminants at lower concentration limits.

Agilent's reliable and sensitive cleaning validation solutions reduce equipment downtime while accurately monitoring contaminant removal.

4200 Flexscan FTIR

- Rugged, portable, and versatile for tracking the cleaning process
- Lightweight optical module (3 lb (1.36 kg)) with a smartphone user style interface enables measurement of a range of manufacturing equipment
- Specialized sampling interfaces for the direct analysis of metal and non-metal surfaces, complex shapes, and less accessible locations
- Flexscan software provides multiple quantitative results from a single method with definable thresholds and easy-to-follow red, yellow, and green warnings
- 21CFR Part 11 compliant

1200 Infinity Series LC Systems

- Speed, sensitivity, resolution, and low carry over
- Ultra UV-sensitivity based on the revolutionary Max-Light cartridge cell in the optical Agilent 1290 Infinity Diode Array Detector (DAD) design
- Next generation flow-through 1290 Infinity Autosampler design and automatic back-needle seat flushing that sets a new benchmark for the lowest carry over (typically < 0.0010 % and < 10 ppm)
- OpenLAB CDS, with OpenLAB ECM or Data Store, supports all GMP and 21 CFR Part 11 regulations

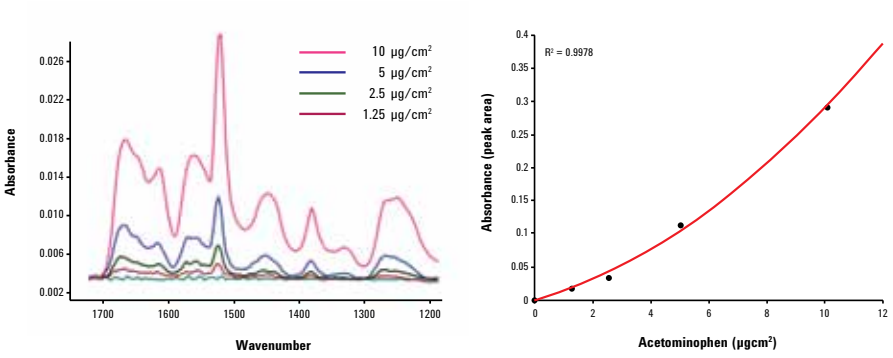


Figure 14. The cleaning validation spectra and calibration plot of acetominophen using the 4200 Flexscan FTIR.

Realtime, direct surface analysis

Application of FTIR spectroscopy in pharmaceutical cleaning validation and verification by direct surface analysis with Flexscan FTIR is demonstrated in Figure 14. In addition to ease of use, the hand held FTIR solution provides effective performance by achieving LOQs in cleaning validation.

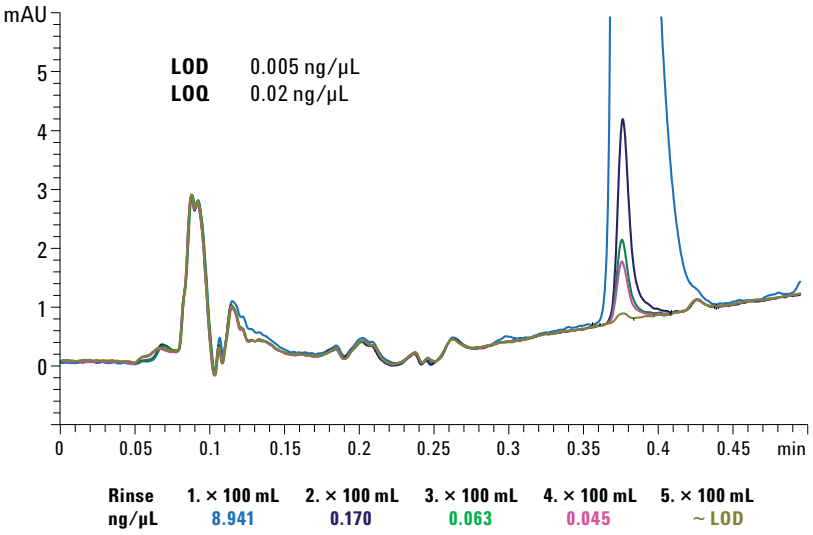


Figure 15. Residual active pharmaceutical product in equipment rinse solution after five applications of 100 mL MeOH measured with the Agilent 1290 Infinity DAD with 60 mm cell.[15]

Rapid, sensitive monitoring of trace level contaminants by UHPLC

The use of 1290 Infinity LC in cleaning validation studies for high sensitivity monitoring of active pharmaceutical product residues in cleaning solutions is demonstrated by the example shown in Figure 15. When it is necessary to determine trace levels of contaminants, the high sensitivity 60 mm flow cell gives better certainty of results and helps to monitor cleaning procedures with higher reliability and safety. In addition to the increased sensitivity for detection of residuals, the analysis time per sample was only one minute. The entire analysis took less than 30 minutes, including all replicates, quality controls, and system suitability samples. This allows faster decisions about production equipment use. The net result is reduced downtime of equipment leading to higher productivity and reduced costs.

Reference Publications

14. Highly Sensitive UV Analysis with the Agilent 1290 Infinity LC System for Fast and Reliable Cleaning Validation. **Part 1:** Measurement of calibration curves, determination of LOD and LOQ and method validation using a DAD equipped with standard or high sensitivity flow cell. Agilent publication **5990-6929EN**.
15. Highly Sensitive UV Analysis with the Agilent 1290 Infinity LC Systemfor Fast and Reliable Cleaning Validation. **Part 2:** Monitoring of a cleaning validation procedure using a DAD equipped with standard or high sensitivity flow cell. Agilent publication **5990-6930EN**.
16. Highly Sensitive UV Analysis with the Agilent 1290 Infinity LC System for Fast and Reliable Cleaning Validation. **Part 3:** Determination of residual active pharmaceutical impurities from a previous production batch using a DAD with standard or high sensitivity flow cell. Agilent publication **5990-6931EN**.

DEPENDABLE COMPLIANCE SUPPORT

Every cGMPs and GLPs regulated laboratory must manage the costs of compliance, which include the time and expense of implementing adequate analytical instrument qualification (AIQ) procedures, while keeping pace with regulatory trends. When you consider the cost of a comprehensive AIQ program, it is not sufficient to simply compare hard costs. You must also identify and consider all the soft costs associated with the alternatives, including the intangible benefits of increased efficiency, reduced risk, and future positioning.

Striving for continuous improvement in laboratory management while addressing the daily demands of meeting production schedules, keeping instruments maintained and calibrated, and assuring regulatory compliance leaves little time for improving processes. Using an expert partner can help meet your regulatory demands while improving productivity.

Agilent has been ranked #1 in compliance for 16 years and is the virtually audit-proof analytical instrument qualification source for system users and manufacturers. Streamline your company's compliance strategy to maximize laboratory productivity using an integrated service solution regardless of the source or type of analytical equipment.

Agilent enterprise compliance services

- Employs a fully automated, paperless program that's compatible with instruments from Agilent and comparable equipment manufacturers
- Achieves a multi-vendor support solution with a single contract that covers instrument maintenance, repair, and compliance
- Improves compliance using Agilent Enterprise Edition to ensure that your LC, GC, and MS systems meet 21 CFR Part 11, EU Annex 11, EU GMP (PIC/S), and 21 CFR Part 211 regulations
- Uses Agilent Compliance Engine (ACE) software for full system-level qualification services you can trust
- An active, compliance partner with over 100,000 successful deliveries worldwide

CASE STUDY

Agilent provides service for ~100 chromatography instruments in one of the largest generic pharmaceutical companies in the world.[17]

The challenge

The laboratories contained instruments from multiple manufacturers that were serviced and maintained by separate representatives, requiring several independent contracts that created an administrative burden and operational complexity. As a result, valuable scientific resources were diverted from research and production to instrument service management.

In addition, operational qualification (OQ) was performed using instrument-specific, paper-based protocols from each manufacturer, complicating the management of reports and preparation for compliance audits.

The result

All instrument service needs were combined into one Agilent CrossLab Services agreement for harmonized, electronic compliance protocols using the Agilent Enterprise Edition compliance solution, along with dedicated onsite labor and parts.

- Instrument downtime was reduced by 50 %
- Costs were reduced by more than 20 %
- Regulatory compliance and audit procedures were harmonized and streamlined
- Product development and manufacturing timelines were accelerated
- Overall asset productivity was increased by optimizing asset utilization and technology lifecycle decisions

The CrossLab Enterprise Solution and Instrument Services

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 inhouse, 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.

Reference Publications

17. Maximize Laboratory Productivity: Compliance Using an Integrated Service Solution. Agilent publication **5990-8855EN.**
18. Hidden Costs and Undiscovered Opportunities in Analytical Instrument Qualification. Agilent publication **5989-7054EN.**
19. Analytical Instrument Qualification and System Validation. Agilent publication **5990-3288EN.**

APPENDIX: COLUMNS, SUPPLIES, AND SOFTWARE

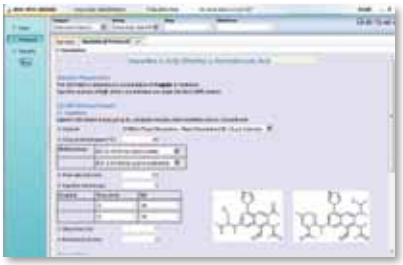
Columns and supplies

Agilent offers a comprehensive portfolio of GC and LC columns, sample prep reagents, and supplies for chromatography, spectrometry, and spectroscopy. All Agilent columns, reagents, and supplies meet ISO 9001 standards to ensure maximum instrument performance and reproducible results.

Agilent leads the LC industry with column choices that meet a wide range of analytical needs and support the pharmaceutical lifecycle with maximum scalability across laboratory development settings, and around-the-world service and support. For example, Poroshell 120 columns can save significant analysis time, and RRHD columns offer maximum flexibility in solvent selection and flow rates. Agilent also has the broadest portfolio of GC columns available, including our innovative, Ultra Inert GC columns. The Bond Elut SPE and Captiva Filtration Sample Prep reagents offer the widest range of format and solutions available in the market today. Agilent's comprehensive portfolio of supplies includes vials, syringes, gas management, flow meters, leak detectors, fittings, tools, and standards, all engineered or selected by our instrument design teams, manufactured to our demanding specifications, and tested under a variety of conditions.

Software and informatics

Experimental Design

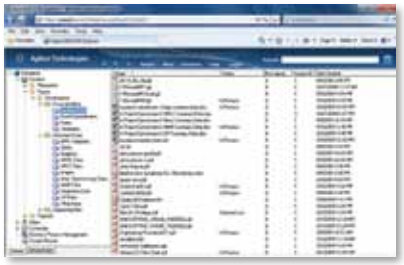


OpenLAB Electronic Lab Notebook (ELN)

Data Acquisition and Analysis

OpenLAB Chromatography Data System (CDS)

Scientific Data Management



OpenLAB Enterprise Content Manager (ECM)

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.

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