MASS SPECTROMETRY

LC-MS/MS Solutions for the Pharmaceutical and CRO Industries

TSQ Series™-based Solutions for Drug Discovery and Development

Part of Thermo Fisher Scientific

Thermo SCIENTIFIC

ACCELERATING THE PACE OF DISCOVERY

TSQ Series-based integrated solutions provide different levels of system and data integration to streamline workflows specific to the drug discovery and development process.

The Challenge

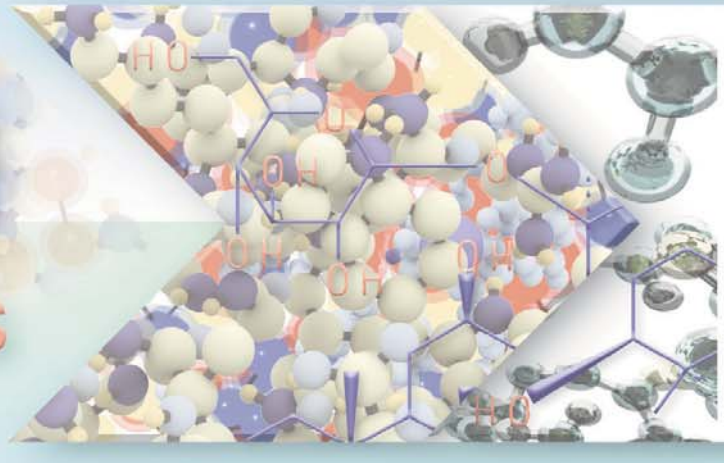
Quantitative analyses are used throughout the drug discovery and development process. Whether it is in high throughput lead optimization or in regulated bioanalytical assay development, a TSQ Series solution can help meet the rigorous demands of the various phases of drug development.

The drug discovery and development process involves the bioanalysis of xenobiotics, metabolites, endogenous analytes, and biomarkers. Bioanalytical assay support or quantitation is required throughout the drug development life-cycle, a process divided into two diverse paradigms.

First, thousands of structurally diverse compounds are screened to find a candidate. Several physico-chemical properties are tested *in vitro* before the lead candidate is tested in animal models (preclinical testing). If the candidate meets the criteria of preclinical testing, an investigational new drug (IND) application is filed with the U.S. Food and Drug Administration (FDA). A TSQ Series mass spectrometer, powered by QuickQuan™ software and Galileo LIMS, provides a full solution during this phase.

Upon approval, the development moves to the process of evaluating the drug in humans (clinical trials). The FDA then evaluates the results from the clinical trials and if all requirements are satisfied, approves the new drug application (NDA). The drug can then be prescribed. A TSQ Series mass spectrometer with FAIMS, LCQUAN and Watson LIMS provides a comprehensive solution to meet the strict compliance requirements with confidence.

5000 Compounds



DRUG DISCOVERY SOLUTIONS: QUICKQUAN

QuickQuan software, developed in partnership with the pharmaceutical industry, supports high-throughput screening applications with automation and sensitivity.

QuickQuan offers a rational approach to workflow automation that significantly improves the throughput of drug discovery assays such as metabolic stability, permeability (CACO-2, PAMPA), protein binding, and preliminary pharmacokinetics. It was developed from the scientist's perspective in order to improve the efficiency of the lead candidate selection process.

Consider this statistic: in 2005, the FDA approved only 20 new molecular entities (NME), the same number it approved in 1974. Clearly, there is a need to screen potential drug compounds more accurately and to provide flexibility in assay design, while accelerating early compound assessment and offering a cost-effective, integrated LC-MS/MS solution.

QuickQuan enables automated LC-MS/MS quantitative analysis of chemically diverse compounds and was developed together with input from scientists at multinational pharmaceutical companies such as AstraZeneca, Novartis, and BMS. The software manages the data acquisition and processing for all compounds in the analytical run and generates quantitative results automatically.

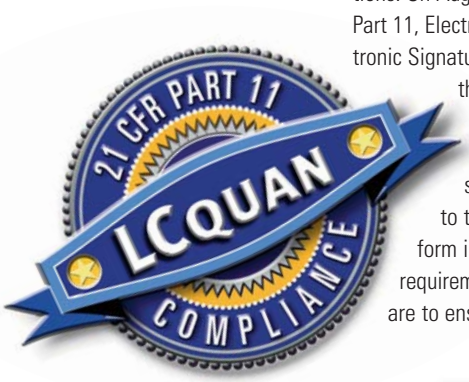
Data generated by QuickQuan is stored in a central Microsoft® Access or Oracle® database. The database provides fast and efficient retrieval of information about a specific compound and allows the compound to be used in multiple assays.

QuickQuan Benefits

- **Increased Throughput**
  ~ 70 second tuning time per compound
- **High Sensitivity**
  Always selects the most sensitive transition using reverse energy ramp (RER)
- **Plug-and-play Software**
  Minimal user intervention is required to generate information
- **Database Advantages**
  Fast and efficient retrieval of analytical information

BIOANALYSIS SOLUTIONS: LCQUAN AND WATSON LIMS

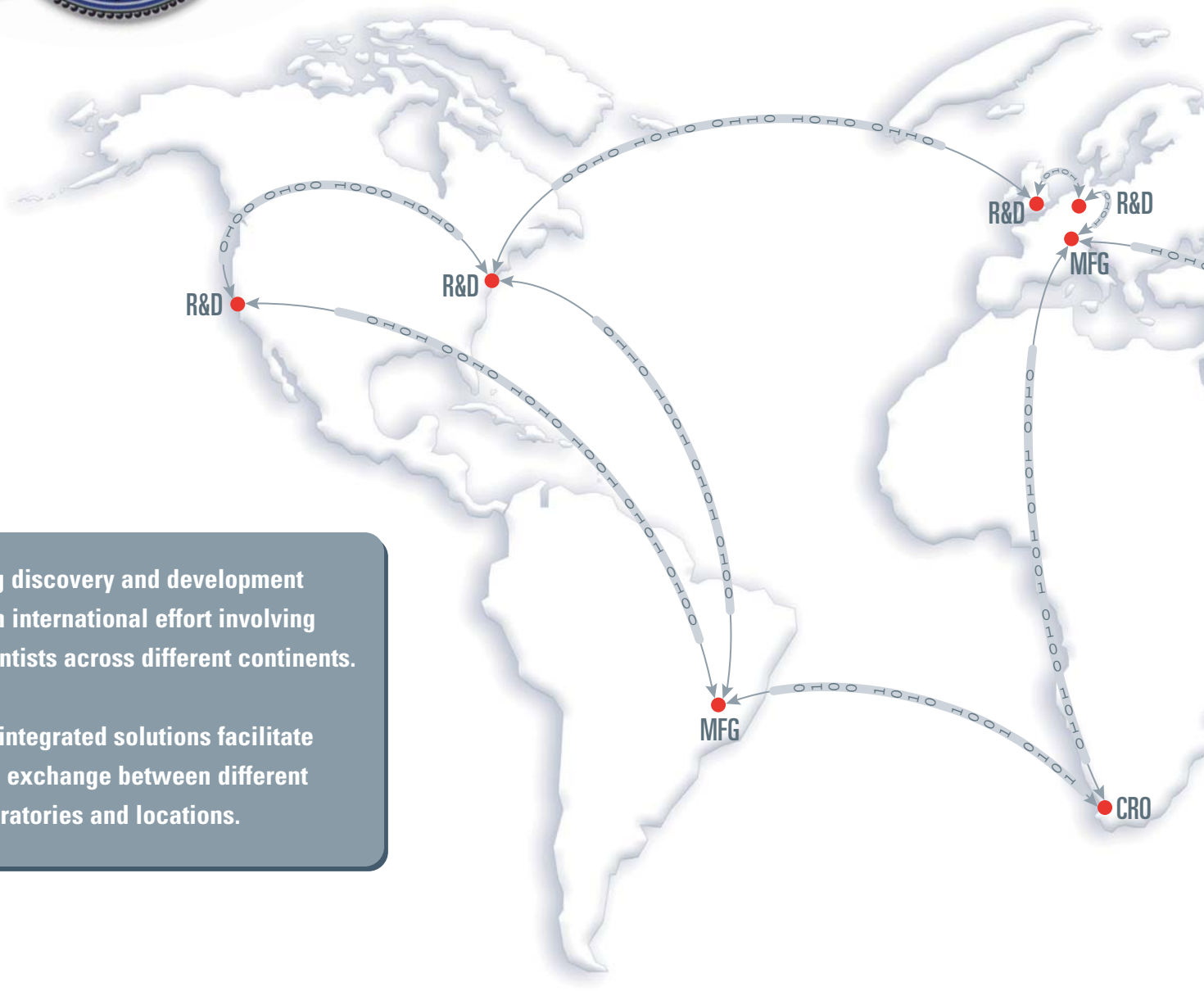
All of the tools necessary to design, implement, and analyze pharmacokinetic data on a global basis.



21 CFR Part 11 and LCQUAN

Companies in regulated industries, such as pharmaceutical companies, must comply with numerous regulations. On August 20, 1997, 21 CFR Part 11, Electronic Records and Electronic Signatures, was instituted by the FDA. The purpose is to allow pharmaceutical companies to submit their documents to the FDA in electronic form in place of paper. The requirements of the regulations are to ensure the security and integrity of the electronic records and to ensure the electronic signature is treated with the same level of importance as the handwritten signature.

Building on the dedicated post-processing standalone application, LCQUAN has been expanded into a complete, secure data system largely specified and designed by customer input. LCQUAN gives the user the necessary resources for importing sequence information from external systems, method development, data review, data processing, data reporting, and exporting results to external systems, all within a 21 CFR Part 11 compliant environment. LCQUAN also provides multi-level security access, giving system administrators the freedom to modify user privileges from full system access to data review only. In addition, the software enables the user to safely process data stored on network-based computing systems.



Drug discovery and development is an international effort involving scientists across different continents.

Our integrated solutions facilitate data exchange between different laboratories and locations.

A SINGLE-VENDOR SOLUTION

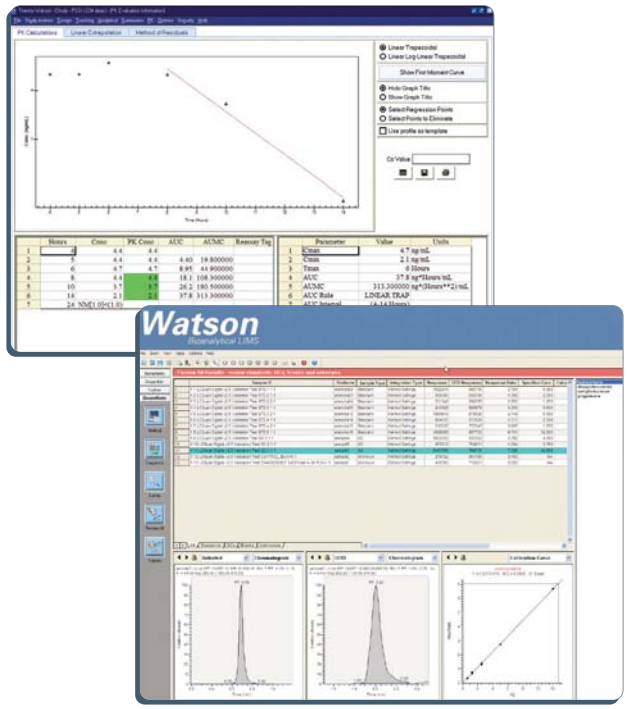
When it comes to complying with the exacting standards of 21 CFR Part 11, LCQUAN and Watson LIMS provide a seamlessly integrated solution that facilitates confident data submission for regulatory purposes.

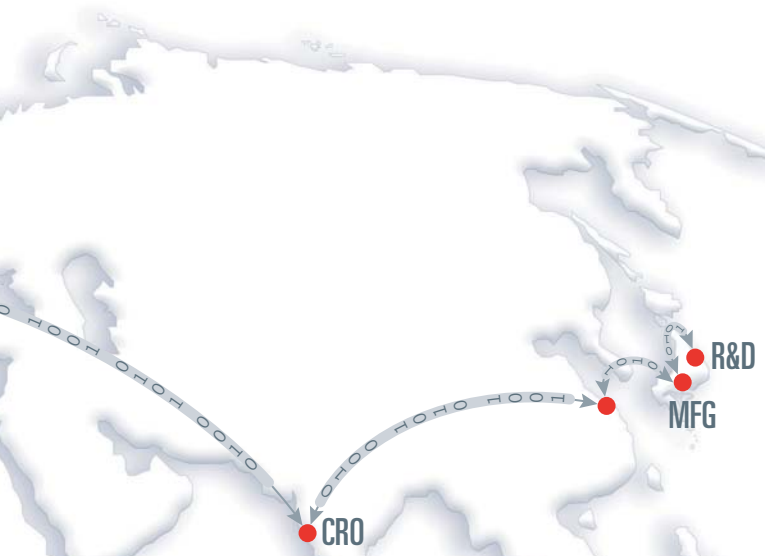
Synchronization of the bioanalytical workflow with the Watson LIMS system provides data management security. Watson LIMS is widely utilized among the majority of global pharmaceutical companies, and LCQUAN software is our quantitative data acquisition tool for GLP studies.

With LCQUAN and Watson LIMS working seamlessly together, you can:

- Meet the most stringent 21 CFR Part 11 and other compliance mandates
- Track study progress
- Simplify the auditing process
- Review and print chromatograms within Watson LIMS

And this is just the beginning. With complete control over future developments of the world's most advanced quantitative LC-MS/MS system, Thermo Fisher Scientific is committed to providing you with everything you need to be confident in the quality, security, and efficiency of your GLP studies.





Discovery Challenges

- Large sample load
- Data storage and processing
- Chemically diverse compounds
- Requires speed, automation, and scalability
- Reliable instruments for 24/7 operation

5000
Compound

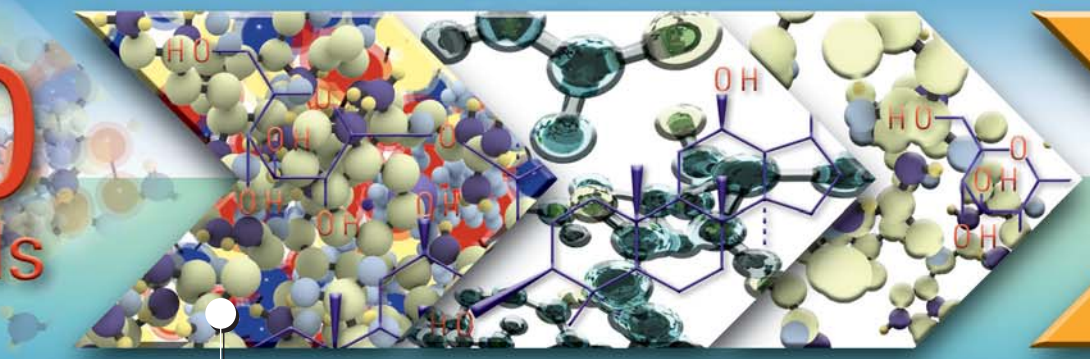
TSQ Series Solutions for th

Galileo LIMS

QuickQuan

L

Discovery



Preclinical Testi

3-5 Years

3 Years

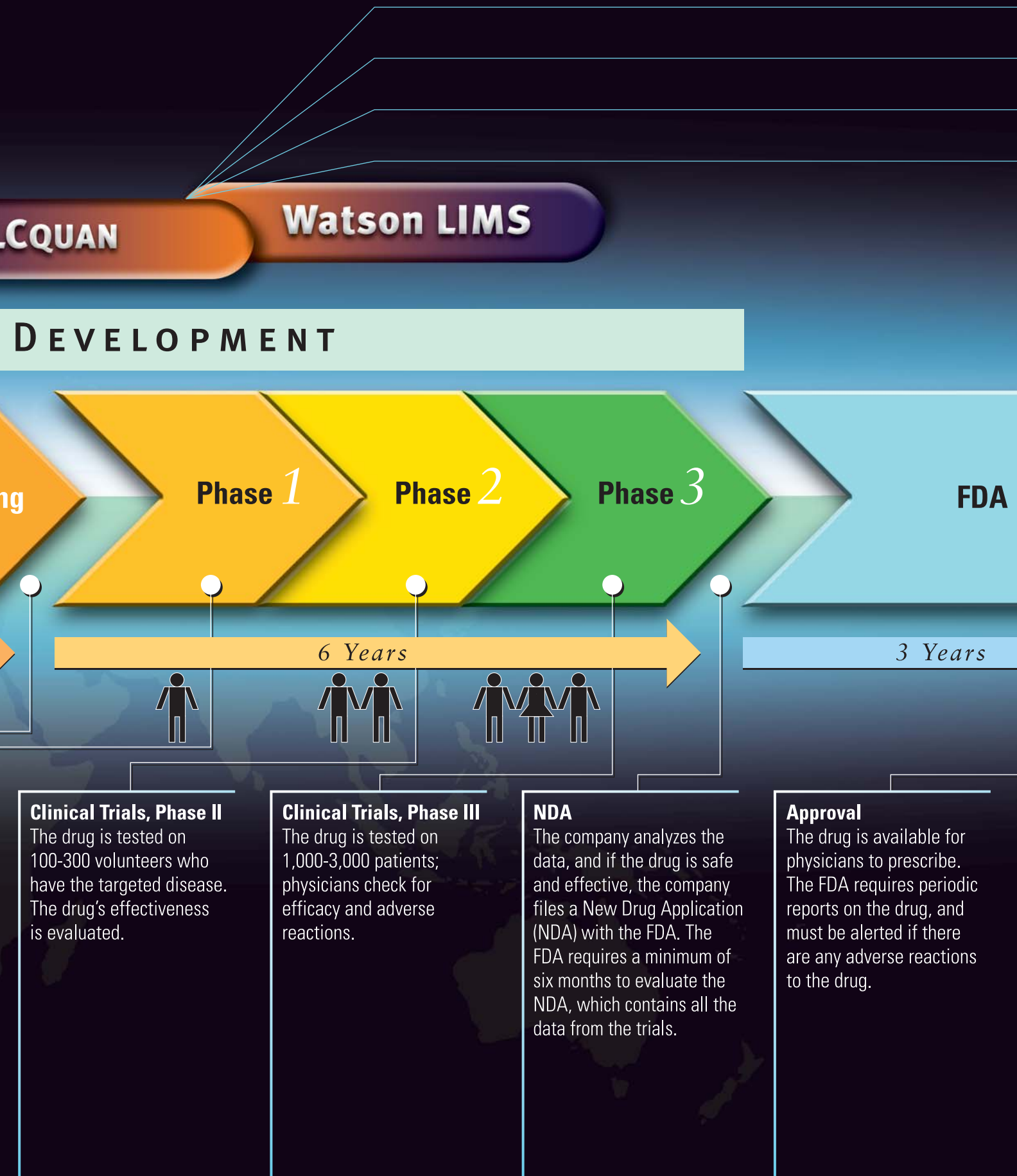
Discovery
The process starts with the screening of chemically diverse compounds from synthetic or natural sources for activity (antagonist, agonist, inhibition) against "targets" such as G-Protein Coupled Receptors (GPCRs) or protein kinases. The typical success rate at this stage is usually around 0.1%, or 5 out of every 5,000 screened.

Preclinical Testing
In this phase, the pharmaceutical company conducts laboratory and animal studies to test the biological activity of a compound against a disease. The compound is evaluated for safety.

IND
The Investigational New Drug (IND) application is filed with the FDA after preclinical testing. The IND shows previous experimental results and outlines how the next studies, in which the drug is tested in people, will be conducted. The IND includes the chemical structure of the compound, how it works in the body, its toxic effects, and how it is manufactured.

Clinical Trials, Phase I
Tests on 20 to 80 healthy volunteers check the drug's safety profile, establish the safety dosage and duration of its action. Studies focus on how the drug is absorbed, distributed, metabolized, and excreted (ADME).

ne Pharmaceutical Industry



Clinical Trials, Phase II
The drug is tested on 100-300 volunteers who have the targeted disease. The drug's effectiveness is evaluated.

Clinical Trials, Phase III
The drug is tested on 1,000-3,000 patients; physicians check for efficacy and adverse reactions.

NDA
The company analyzes the data, and if the drug is safe and effective, the company files a New Drug Application (NDA) with the FDA. The FDA requires a minimum of six months to evaluate the NDA, which contains all the data from the trials.

Approval
The drug is available for physicians to prescribe. The FDA requires periodic reports on the drug, and must be alerted if there are any adverse reactions to the drug.

Development Challenges

- 21 CFR Part 11 compliance
- Secure data processing and archiving
- Validated methods must be robust
- Re-assay decisions and reporting
- Ion suppression and need for high sensitivity

15-17 Years

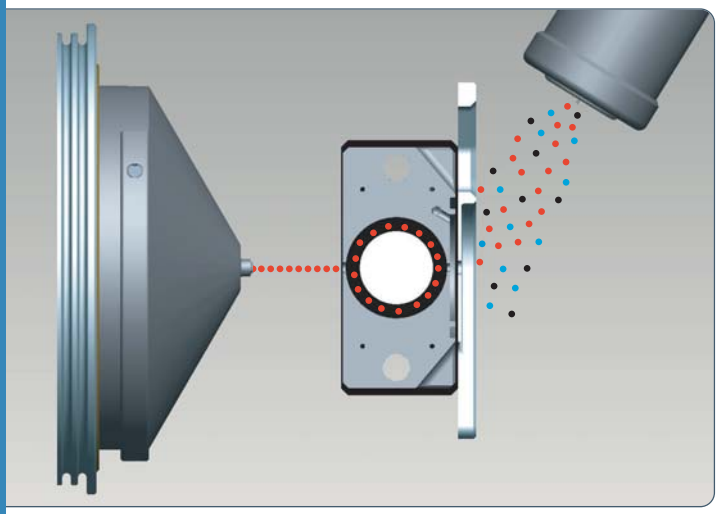
NOISE REDUCTION TECHNOLOGY FOR LC-MS/MS QUANTITATION

Significantly enhance assay robustness and sensitivity by eliminating drug-related, endogenous, and non-endogenous chemical interferences using FAIMS.

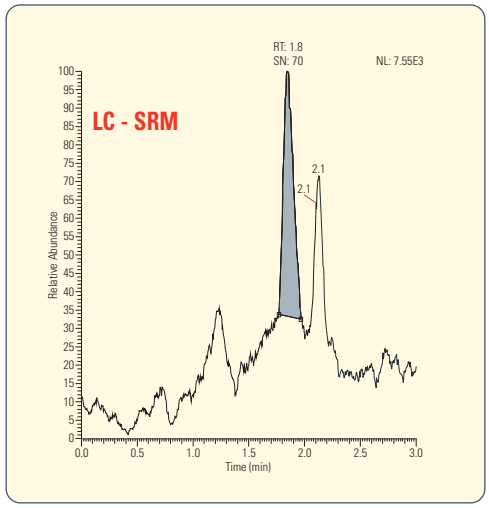
A robust bioanalytical assay consistently delivers precise quantitative results regardless of the challenges posed by the matrix or other sources of chemical noise.

A TSQ Series mass spectrometer with high-Field Asymmetric Waveform Ion Mobility Spectrometry (FAIMS) and H-SRM provides significant immunity against chemical interferences and facilitates development of robust bioanalytical assays that withstand the test of time. Faster method development at the highest possible sensitivity is routinely achievable with these two highly desirable features.

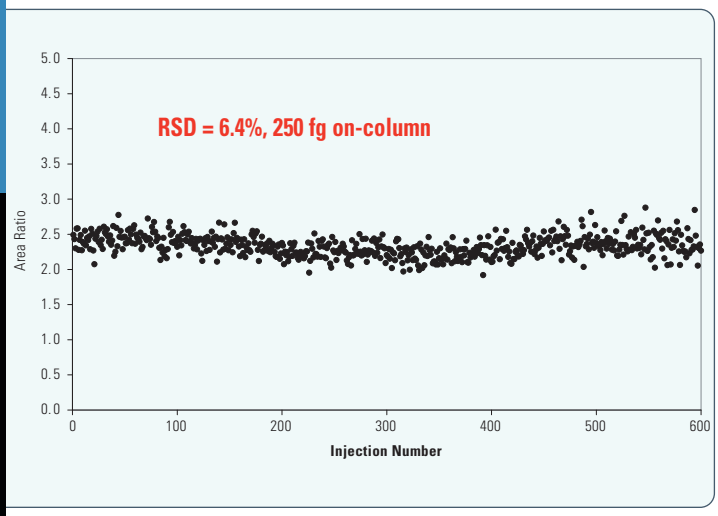
The increases in selectivity offered by FAIMS and H-SRM result in cleaner chromatograms that are more easily and more reproducibly integrated. Therefore, a bioanalytical method developed using FAIMS and H-SRM will be robust enough to withstanding the challenges posed by different matrices and their sample preparation procedures, without significant method redevelopment. This translates to consistent, highly sensitive quantitative results, injection after injection.



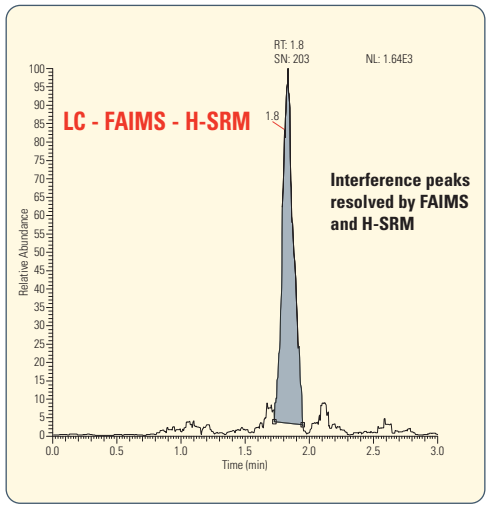
FAIMS reduces chemical noise and matrix interferences, resulting in improved assay robustness and increased assay sensitivity.



Representative LC - SRM chromatogram for clenbuterol in human urine. Unit mass resolution without FAIMS.



Robustness of FAIMS interface on TSQ Quantum Ultra



Representative LC - FAIMS - H-SRM chromatogram for clenbuterol in human urine. High (0.1 FWHM) mass resolution, combined with FAIMS selectivity.

SIGNIFICANTLY REDUCE MATRIX EFFECTS

"In the case of LC-MS-MS-based procedures, appropriate steps should be taken to ensure the lack of matrix effects throughout the application of the method, especially if the nature of the matrix changes from the matrix used during method validation."

–Page 8, Guidance for Industry, Bioanalytical Method Validation, FDA, CDER, May 2001.
http://www.fda.gov/cder/guidance/index.htm

The ability to directly inject samples from urine, plasma or serum into a triple stage quadrupole and perform highly sensitive bioanalysis is the direct result of TurboFlow™ technology.

When samples are analyzed using TurboFlow technology, ion suppression-causing sample components such as proteins and hydrophilic macromolecules are removed. TurboFlow technology uses the combined effects of column chemistry and size exclusion technology to clean every injected sample before it is ionized, resulting in highly sensitive LC-MS/MS analysis.

The Thermo Scientific Transcend™ system combines the power of on-line sample clean-up using our patented TurboFlow technology, with the speed of ultra high pressure liquid chromatography (uHPLC). A Transcend-enabled TSQ Series mass spectrometer harnessing the power of FAIMS and H-SRM technology is the most sensitive integrated single-vendor solution for Phase I-III bioanalysis.

The number of sample preparation steps is significantly reduced with TurboFlow technology.

More Steps = More Time

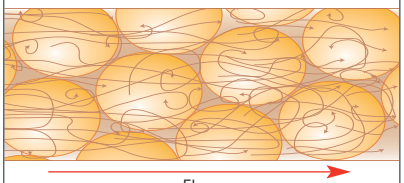
Liquid-Liquid Extraction (LLE)	Solid Phase Extraction (SPE)	Protein Precipitation (PPT)	TurboFlow – 4 Steps
1. Aliquot of sample	1. Aliquot of sample	1. Aliquot of sample	1. Aliquot of sample
2. Spike with IS	2. Spike with IS	2. Spike with IS	2. Spike with IS
3. Add buffer	3. Add 0.1N HCL	3. Add acetonitrile	3. Centrifuge
4. Add MTBE	4. Condition sorbent	4. Centrifuge	4. Inject onto column
5. Shake 10 min	5. Add sample to sorbent	5. Remove supernatant	
6. Centrifuge	6. Wash	6. Reconstitute	
7. Remove organic	7. Evaporate	7. Transfer to plate	
8. Evaporate to dryness	8. Reconstitute	8. Inject onto column	
9. Reconstitute	9. Transfer		
10. Transfer to plate	10. Inject onto column		
11. Inject onto column			

FASTER RESULTS!

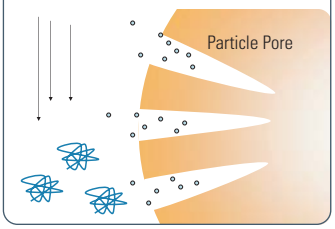
Using TurboFlow methods on the TLX System allows you to remove most of the time-consuming steps in the sample preparation process, which speeds sample throughput while minimizing errors and variability.

WHY TURBOFLOW TECHNOLOGY IS SUPERIOR

High linear velocities and large particles create turbulence within the column



TurboFlow technology leverages the difference in diffusion rates of small and large molecules



Particle chemistry binds small molecules while large molecules flow to waste

Laboratory Solutions Backed by Worldwide Service and Support

Tap our expertise throughout the life of your instrument. Thermo Scientific Services extends its support throughout our worldwide network of highly trained and certified engineers who are experts in laboratory technologies and applications. Put our team of experts to work for you in a range of disciplines – from system installation, training and technical support, to complete asset management and regulatory compliance consulting. Improve your productivity and lower the cost of instrument ownership through our product support services. Maximize uptime while eliminating the uncontrollable cost of unplanned maintenance and repairs. When it's time to enhance your system, we also offer certified parts and a range of accessories and consumables suited to your application.

To learn more about our products and comprehensive service offerings, visit us at www.thermo.com.

In addition to these offices, Thermo Fisher Scientific maintains a network of representative organizations throughout the world.

Africa-Other
+27 11 570 1840 • analyze.sa@thermo.com

Australia
+61 2 8844 9500 • analyze.au@thermo.com

Austria
+43 1 333 50 34 0 • analyze.at@thermo.com

Belgium
+32 2 482 30 30 • analyze.be@thermo.com

Canada
+1 800 530 8447 • analyze.ca@thermo.com

China
+86 10 8419 3588 • analyze.cn@thermo.com

Denmark
+45 70 23 62 60 • analyze.dk@thermo.com

Europe-Other
+43 1 333 50 34 0 • analyze.emea@thermo.com

Finland / Norway / Sweden
+46 8 556 468 00 • analyze.se@thermo.com

France
+33 1 60 92 48 00 • analyze.fr@thermo.com

Germany
+49 6103 408 1014 • analyze.de@thermo.com

India
+91 22 6742 9434 • analyze.in@thermo.com

Italy
+39 02 950 591 • analyze.it@thermo.com

Japan
+81 45 453 9100 • analyze.jp@thermo.com

Latin America
+1 608 276 5659 • analyze.la@thermo.com

Middle East
+43 1 333 50 34 0 • analyze.emea@thermo.com

Netherlands
+31 76 579 55 55 • analyze.nl@thermo.com

South Africa
+27 11 570 1840 • analyze.sa@thermo.com

Spain
+34 914 845 965 • analyze.es@thermo.com

Switzerland
+41 61 716 77 00 • analyze.ch@thermo.com

UK
+44 1442 233555 • analyze.uk@thermo.com

USA
+1 800 532 4752 • analyze.us@thermo.com

www.thermo.com

Thermo Fisher Scientific, San Jose, CA USA is ISO Certified.

©2007 Thermo Fisher Scientific Inc. All rights reserved. Microsoft is a registered trademark of Microsoft Corporation, Oracle is a registered trademark of Oracle Corporation. All other trademarks are the property of Thermo Fisher Scientific Inc. and its subsidiaries.

Specifications, terms and pricing are subject to change. Not all products are available in all countries. Please consult your local sales representative for details.

BR62225_E 12/09S

Thermo SCIENTIFIC