ACD/Labs Application Note

A Systematic Approach to the Development of Impurity Separation Methods for Drug Development

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CONTENTS

Introduction

Unified Laboratory Intelligence (ULI) is a new category of laboratory R&D informatics that provides a technology framework to improve chemical identification, characterization, and optimization for life science, chemical, energy, consumer products, industrial, and technology industries. ULI is designed to collect and unify chemical, structural, and analytical data as chemical content with context, which enables the generation of intelligence from disparate information within a laboratory environment. In order for any laboratory informatics solution to be implemented successfully and ensure productivity improvements and clear returns, it must first be properly focused. "The most successful strategies are likely to be those that address needs in the context of sub-disciplines."[1] As a result, this application note will focus on the application of ULI within the context of impurity resolution within the drug development process of the pharmaceutical industry.

Within the pharmaceutical industry, the rapid detection, identification, elucidation, and characterization of synthetic or process impurities and degradation products is an intense and comprehensive undertaking. Regulatory agencies including the FDA and ICH mandate dose dependent thresholds for reporting, identification, and qualification of impurities. For example, in the development of a formulated drug substance, the FDA requires that all impurities introduced in the proposed process above 0.1% by area percent need to be isolated and structurally characterized (the requirement can be even lower for drugs with larger doses). Impurities from synthesis, manufacture, or storage are all of interest. Furthermore, in order to develop a robust drug product, degradation products must be characterized with the intent of minimizing their presence (thus preserving the shelf life of the formulated drug product).

The identification, elucidation, and characterization of impurities and degradants in this environment requires a multi-disciplinary approach with good communication and collaboration between various groups. Through the entire drug development process, a wealth of chemical and analytical information must be generated, collected, and documented to facilitate the identification, elucidation, and

characterization of impurities. Furthermore the trend toward a paperless environment facilitates the management, dissemination, and rapid access to such large volumes of accumulated information.

Pharmaceutical Development groups (Pharm Dev or similar variants) are ultimately responsible for the CMC (Chemistry, Manufacturing, and Controls) sections of IND applications and NDA submissions. In general, the groups involved in this process from a synthetic chemistry and data collection and analysis point of view are: (also depicted in **Figure 1**)

- **Process Chemistry**—process chemists are responsible for developing the synthetic route for development candidates. They are expected to collaborate with the groups below to facilitate the identification of impurities or to refine their synthetic route design to eliminate or minimize the presence of these impurities.
- **Analytical Research and Development**—typically responsible for the development of Drug Substance (DS) and Drug Product (DP) specifications, this group will work concertedly with the process chemistry and structure characterization groups to enable impurity profiling and chemical stability evaluation with degradant identification. The "impurity profile" method is developed by Analytical R&D and this method is used to help identify all impurities through each stage of the synthetic route and to help the characterization group decide which impurities require identification. In this group, a significant amount of time, technology, and knowledge is also invested in method development, tests of robustness, and validation.
- **Structure Characterization Group**—typically responsible for performing the structure elucidation and characterization of impurities, in ideal situations, they work in close collaboration with the process chemistry and method development groups to obtain a full sample history ('context') including the synthetic route, experimental conditions, solvents used, pH, temperature, etc. These groups most often work as interdisciplinary spectroscopy teams which bring a wealth of expertise in techniques like mass spectrometry, NMR and optical spectroscopies, and X-Ray Crystallography, amongst others. Elucidating and characterizing impurities in bulk drug substances and formulated drug products are one of their main responsibilities. (**Note**: the Structure Characterization Group is often a part of the Analytical Research and Development Group in some organizations.)

***Figure 1**: A summary of the groups involved in the impurity identification, elucidation, and characterization process in pharmaceutical development.*

In this Application Note, we outline how ULI (Unified Laboratory Intelligence) principles embodied into the ACD/Spectrus Platform are applied to enable active development and management of chromatographic methods and data used for impurity resolution.

It is our assumption that best QbD practices are applied within each of a company's structural units, and that Analytical and Separations labs are equipped with fast and robust chromatographic methods capable of handling the "unknown" of an unexpected contaminant or byproduct. Even in such a perfect scenario, however, the sudden composition changes of a sample cause analytical emergencies and consequent delays. In this document, we suggest a framework of further process enhancements that help reduce this cost which, while always unexpected, is a recurring event in chemistry-driven manufacturing. The end goal is to ensure fast troubleshooting and control of impurities across the complete life cycle of a chemistry product—from its conception to the late stages of manufacturing.

Managing Chromatographic Methods and Data for Faster Impurity Resolution

Extensive method development is both time- and effort- consuming, but there are software aids.

It is not the purpose of this document to provide an overview of modern best practices and software for method development. However, it is important to note that the latest advances do offer significant help, notably by offering efficient peak tracking between numerous samples; by reducing the time required for the systematic method development; and by methodical management of the enormous volume of required data. A few illustrations of how ACD/AutoChrom software helps facilitate method development are provided in Figures 2-5.

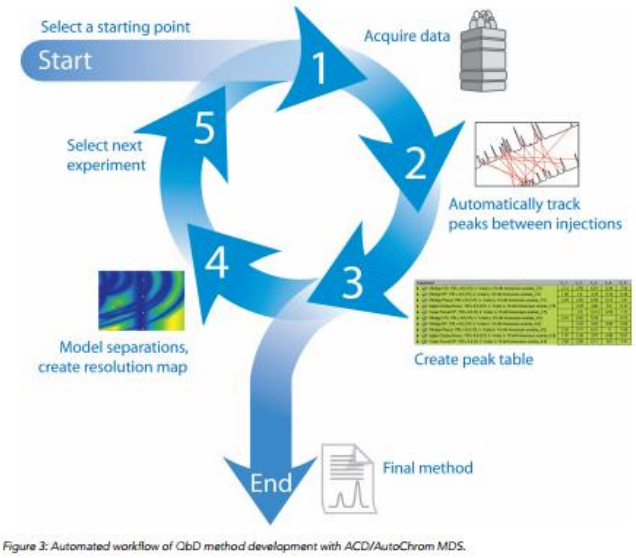
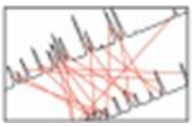


Figure 3: Automated workflow of QbD method development with ACD/AutoChrom MDS.

***Figure 2**: Automated workflow of QbD Method Development with ACD/AutoChrom software.*

> ***"Reliability, robustness, and lifetimes of methods have improved, and at the same time we have reduced the loss of interpretation information and expensive retesting of samples…the QbD approach to method development aided by ACD/AutoChrom MDS (important for method quality) will provide return on investment within a short time."***
>
> ***Rudy Sneyers (Janssen Pharmaceuticals Inc.)[2]***

205.21	API - 309.13	426.11	314.13	416.14	531.09	297.11	300.07	705.22	369.22	414.95
6.76	6.89	9.37	9.79	9.97	10.24	11.28	11.57	13.39	13.6	11.57
5.55	8.71	8.6	10.94	11.01	12.7	13.14	11.79	16.54	14.33	16.66
6.35	9.09	9.3	10.85	11.85	12.82	12.73	11.57	16.13	14.94	15.51
6.6	9.8	9.48	12.26	18.47	13.98	14.64	13.1	18.49	15.85	18.75
7.68	9.77	10.44	10.82	14.72	13.6	14.51	11.67	16.5	19.31	17.48
6.99	9.9	10.34	11.27	14.01	13.15	13.87	11.4	16.01	17.81	16.52
8.04	10.11	10.62	10.84	14.01	13.54	13.83	11.57	16.58	17.11	16.13
8.54	10.75	11.14	12.13	15.94	14.71	15.72	12.93	18.32	20.76	18.87
10.01	10.38	11.79	11.46	16.27	14.55	15.49	12.38	17.65	21.11	18.64
11.54	11.49	13.01	12.9	18.1	15.87	16.95	13.79	19.8	23.1	20.4



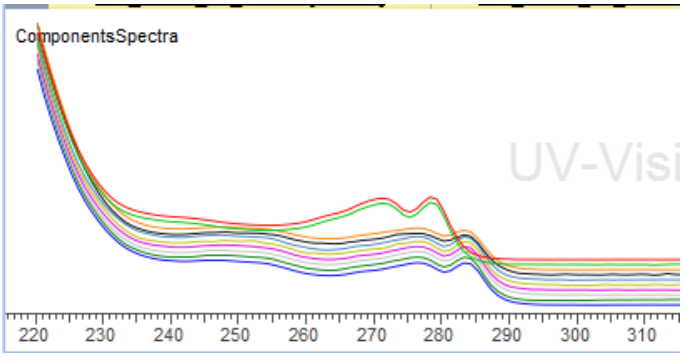
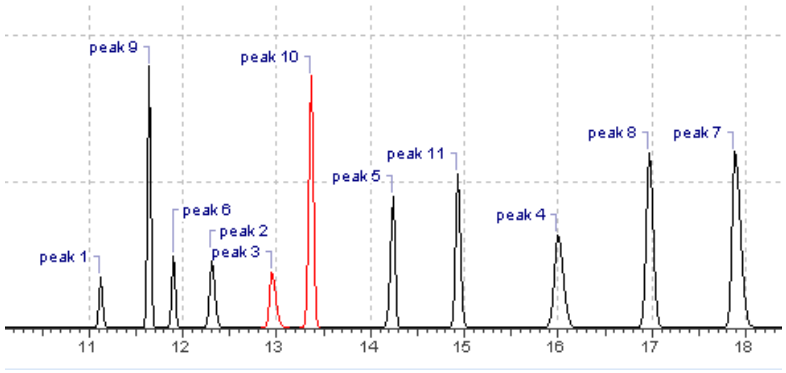


Figure 3: *Software automatically tracks and matches peaks between injections. Sample Table of Peaks after peak tracking, and an Overlaid UV Spectra diagram for the same component from a series of screens at different pH created by ACD/AutoChrom are presented. The peak names are also automatically defined by an LCMS peak tracking algorithm.*

Experiment	Status	Rs Score	Min Rs	Total
Waters Xbridge Phenyl & pH 2.5	Complete	0.634	0.007	16/16
Waters Xbridge C18 & pH 4.8	Complete	0.546	0.318	16/16
Waters Xbridge Phenyl & pH 4.8	Complete	0.731	0.383	16/16
Supelco Ascentis Express C18 & pH 4.8	Complete	0.78	0.099	16/16
Waters Xbridge C18 & pH 7.0	Complete	0.787	0.016	16/16
Waters Xbridge RP18 & pH 7.0	Complete	0.8	0.214	16/16
Waters Xbridge Phenyl & pH 7.0	Complete	0.883	0.728	16/16
Supelco Ascentis Express C18 & pH 7.0	Complete	0.886	0.505	16/16
Waters Xbridge C18 & pH 9.0	Complete	0.909	1.37	16/16
Supelco Ascentis Express C18 & pH 9.0	Complete	0.8	0.286	16/16

Figure 4: *The software ranks the screening experiments by 3 parameters: total number of matched peaks, Minimal Resolution, and Resolution score; and suggests the best experiment for further optimization (blue frame, in this example). Furthermore, the software suggests the best method and the column.*



Advanced features, such as simultaneous pH modeling and optimization for different columns, suggests 5 best methods across all the columns. A sample Predicted Chromatogram at an optimal pH is shown.

In addition to the traditional optimization on the Solvent Ratio resulting in the 3D Resolution Map (here, visualized in the ACD/LC Simulator software), a layer of added success criteria (namely, Resolution, Run Time and k') suggests the project space with optimal Suitability (marked in White on the lower 3D map. The area marked in Orange denotes the areas of unsatisfactory Resolution for the particular project)

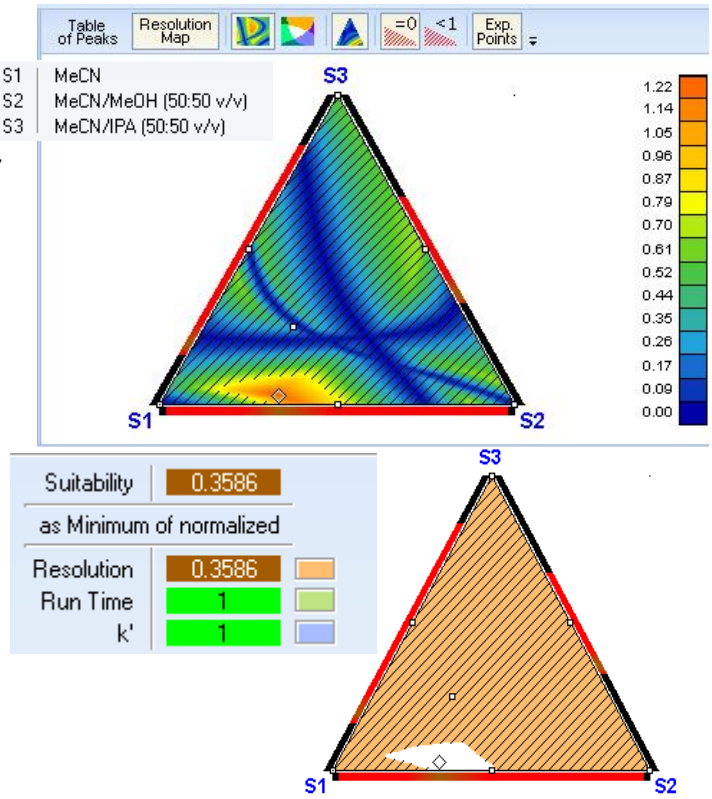


Figure 5: *Optimization information is interactively available on the same screen, allowing scientists to analyze the impact of varying parameters on the separation and method quality.*

The Importance of Complete Chemical Awareness for the Method Development

The ULTIMATE separation method has to be developed with ALL possible chemical scenarios in mind.

It is critical for a chromatographer to have a comprehensive knowledge of the sample's chemistry. As trivial as this statement might be; one will be surprised how often that knowledge is not available to the chromatographer. In the majority of cases, there would be "something new" that makes its way into the process, or new chemical knowledge that is accumulated throughout the lifetime of a product. A change in quality of the starting materials, components, or reagents, synthetic path variations, contaminants, and degradation products are just some of the possible unknown chemical identities a chromatographer has to anticipate. Complete, accessible, comprehensive awareness of the project's chemistry is invaluable for method development success.

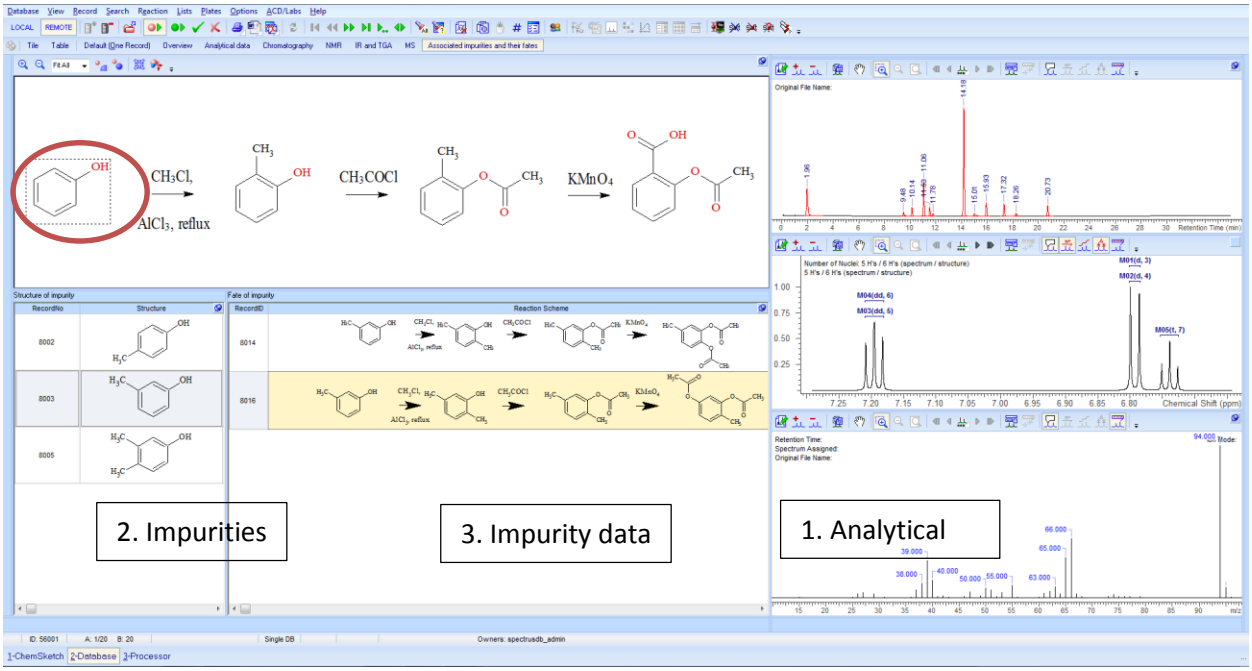


Figure 6: *Above screenshot offers an overview of the chemical reaction, with a table of all associated impurities. "Composite chromatogram" on the top right corner contains all related compounds that can manifest themselves, at any of the stages.*

As users click on a chemical structure (red circle), they can review the analytical data for the chosen compound (1) and associated impurities for that compound in the left hand table (2). As they click on the impurity in that table they can review the known chemical pathway of that impurity in the right hand table (3).

Furthermore, layered behind the chemical image of each impurity is its full chemical record and related analyses: tests, elucidation notes, toxicity measurements, and reports; anything that can be needed for characterization or submission. Noteworthy, measured, or predicted toxicological values can be part of the same display.

Bringing It All Together—An Electronic Platform for Better Methods, Collaboration, and Reporting

Unmistakably and instantly recognizing a contaminant is valuable; knowing WHAT it is, and WHY is invaluable.

What is your process of impurity identification? Is it an educated and tested guess? Is it a rigorous elucidation process? Has it been done before, or do we need to spend valuable time to solve the unknown, under the mounting pressure of manufacturing disruption? At the organizational level, a chemistry portfolio exists for the majority, if not all, of the possible impurities, intermediates, degradants, formulation ingredients and APIs, mixture components, and other suspects. However, this awareness is scattered across teams and departments. ULI software such as ACD/Spectrus is designed to bring them together and incorporate into the method development process.

As discussed in previous sections, a high degree of communication and collaboration between scientists in a multi-disciplinary group is advantageous in helping to develop a drug impurity profile. Having quick answers to questions like, "What was the intended product? What are the starting materials and reagents used? What were the reaction conditions that lead to the formation of a specific impurity? What are some related impurities we've already identified?, etc." can prove instrumental in many areas. However, the unified laboratory platform delivers on the specific needs of the Separations and Method Development teams.

How the ULI Platform Meets the Needs of the Analytical and Separations Specialist

Complete Chemistry Information

Complete information about the chemistry accompanied by the inter-connection between components (reaction schema, degradation path, possible known synthetic variations, etc.) is available (**Figure 6**). Further aids, such as use of physicochemical data (such as pK_a) to assist with prediction, and use of structural information contained within a database to automatically assign main chromatographic peaks (by matching molecular weight to m/z value, for example) also become possible.

Fully Searchable Live Data

ACD/Spectrus ULI platform offers comprehensive, searchable access to the supporting chromatographic and analytical data. Fully Searchable (retention times, spectral parameters, structure similarity are often requested) and "Live" data—but preferably not raw, since processing, connecting, and analyzing numerous past experiments is not feasible.

Knowledge Shared Across Departments

Knowledge accumulated by other people and teams is shared across departments. ULI overcomes the issue of accessibility as time and people have passed, contract organizations changed, experts retired, and details just got forgotten.

Knowledge Sharing for Continual Method Improvement

An electronic venue for knowledge sharing and continual method improvement is provided. A chemical R&D project stretches over a long time period and a variety of separation methods are

developed over its lifetime. In separation sciences, method development is increasingly performed by relatively inexperienced analysts, and as many different stationary phases are used and there is little co-ordination across functions, analyses are excessively long. Unified chromatography access facilitates exchange, standardization for higher performance of resulting method, and faster turnaround. If users have ready access to methods searchable by project or compound, they can avoid having to redo the method development process. If all of the information that was used to develop the method is available to any employee that retrieves the project, then this method can more easily be adapted should the sample profile change during the lifetime of the compound. In addition, structure similarity search and other mining tools can help to potentially speed other method development sessions for related compounds based on past results.

Rigid but Flexible Design Boundaries

Access privileges and quality criteria associated with regulated method development can be put into effect for the entire group.

Predictive Capabilities that come with the Accumulated Knowledge

In chromatography, accumulated knowledge certainly gives way to insight. Better prediction of chromatographic behavior enabled by software product ACD/ChromGenuis, for example, is based on the body of experimental retention times for compounds in the method screens and the knowledge of chemistry parameters, to suggest optimal screens for new compounds. Software can give an idea for a starting point in method optimization or, perhaps even more interestingly, can predict retention times for the structure of a proposed impurity to gain more confidence in structure identification.

Let's picture a scenario of a sudden product change being detected at the manufacturing facility. The chromatographic test that uses the perfectly developed separations method makes that change known. However, a cause of the impurity needs to be identified and resolved before the manufacturing process can resume. If one can instantly access all of the known "LIVE" analysis, starting material data, reaction byproduct analysis, all of the impurities and components researched and noted previously, this costly and intimidating emergency gets an instant head start towards its timely resolution.

Beyond the Separations Lab, throughout the drug development process, and most importantly at the time of submission, progress reports, presentations, and final documentation of the CMC sections for IND and NDA filings are required. Further inspections, plant reviews, and FDA observations also call for in-depth data review and reporting. The preparation of this type of documentation can be very time-consuming, quite costly, and disruptive, as it requires collecting, collating, and combining representative data and chromatograms from various stages of the process. In a typical scenario, it is not unusual for hours/days to be spent searching for/compiling results of a series of specific analytical tests. Even when the desired results are located it might be difficult to understand the context surrounding the data that represents a test. A worst-case scenario involves having to re-acquire data from samples if previous test results cannot be located. In some cases this may even require re-purification of a sample or even worse re-synthesis. Clearly activities such as this can be hugely disruptive and most important costly due to delays in either NDA filing or response to an already existing submission or observation.

The major benefit of using the ACD/Spectrus Platform as a collaboration tool for data and knowledge sharing is its ability to unify the 'live' analytical data from the significant variety of heterogeneous instrument data formats in the typical laboratory informatics environment. As a result, if all the data and its context are stored in one electronic environment, key information can be compiled and combined easily and a report can be generated in the click of a button, saving days/weeks of time in report compilation/creation.

The importance of 'live' data should not go unrecognized. When data is re-accessed and re-evaluated it often will need to be re-processed, re-analyzed, or manipulated in some way. This cannot happen with 'dead' data stored as a PDF, or locked into a specific, proprietary instrument data format. In addition, a 'live' chemical and analytical data collaboration platform, ACD/Spectrus DB, helps compile all of the chemical and analytical information into the context of the life cycle of the drug being developed. As impurities arise, the Process Chemistry, Analytical R&D, and Structure Characterization groups have a platform where they can quickly visualize and assess the context of a given impurity or a particular stage in the process. The ACD/Spectrus Platform enables each scientist to dive deep into the context of the data interpretation where they can evaluate not only the data associated with the chemical structure, but how the data was assigned to the NMR, MS, and Optical data. This knowledge provides in depth chemical context, and serves as a foundation to create a more intelligent informatics environment by leveraging this knowledge to improve the algorithms being used routinely for various structure elucidation efforts.

Conclusion

Data cultures in life science are very heterogeneous, and no single approach can suit the needs of everyone. The most successful strategies are those that address needs in the context of sub-disciplines.[1] Impurity Resolution Management (IRM) is an essential aspect of drug development where Unified Laboratory Intelligence (ULI) can be successfully applied to improve decision-making, reduce time, and decrease cost. As highlighted in this application note, the ACD/Spectrus Platform can serve to help process chemistry groups manage and capture the constantly evolving synthetic route and conditions from lab to pilot to manufacturing activities. Furthermore, it enables the connection of analytical data from different forms of instrumentation to starting materials, intermediates, impurities, and final products to capture process knowledge through chemical context.

To ensure both fast troubleshooting and complete control of impurity information across the complete life cycle of a chemistry product—from its conception to the late stages of manufacturing—companies rely on state-of-the-art separation methods. Specific expertise, cost and time are required to ensure that such methods can catch, address, and help identify an unexpected impurity at any step of the research and manufacturing process. Software helps to not only speed up and optimize the method development process, reducing "the cycle time for data analysis … from more than a week to within a day",[3] but also improves the quality and versatility of each method. Beyond such productivity improvement, greater project- and organizational-level benefits are realized through better knowledge dissemination, access, and reuse. As such improvements are realized, the accumulated corporate Unified Laboratory Intelligence helps fight the "impurity emergency", a costly and always unexpected reality of chemical manufacturing.

[1] Anne E. Thessen and David J. Patterson, Data issues in life sciences, PMC (NIH/NLM), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3234430/, (**November 28, 2011**).

[2] David C. Adams, Sanjivanjit K. Bhal, How Software Can Aid Decision-Making in Chromatographic Method Development, *Chromatography Today*, Feb/March Issue, **2013**.

[3] John D. Stafford, Bryan Castle, A systematic approach to development of liquid chromatographic impurity methods for pharmaceutical analysis, *Journal of Pharmaceutical and Biomedical Analysis*, **2011**.