Case Study

Accelerating Impurity Identification and Characterization at Eli Lilly

Scientists use analytical instrumentation, electronic laboratory notebooks, and specialized software for impurity identification and management.

ACD/Labs

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Introduction

The identification and characterization of impurities in pharmaceutical drugs is critically important to ensure that their presence will not evoke any form of adverse response, either pharmacological or toxicological, in a patient taking the medication. Furthermore, attention must be made to the impact impurities can have on the production process and formulation.[1]

Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the International Congress on Harmonization (ICH) have established rigorous guidelines for the identification of extraneous compounds in pharmaceutical agents throughout the development process and post-marketing. Generally, for drugs dosed at ≤2g/day, impurities present at ≥0.10% require isolation and structural characterization. For drugs dosed at >2g/day, the threshold for isolation and identification is lower at 0.05%.[2]

FDA and ICH guidelines further state that, "The specification for a new drug substance should include a list of impurities."[3] Furthermore, "the applicant should summarize the laboratory studies conducted to detect impurities in the new drug substance," and "a registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities."[4]

Complying with the guidelines requires the collaboration of three drug development chemistry functions, in addition to regulatory bodies, stability and forced degradation, and toxicology groups:

> Process chemistry – scaling up the development of an optimal synthetic route that maximizes yields, is cost-effective, safe, environmentally aware and minimizes the presence of impurities for the drug substance from laboratory scale to manufacturing scale.
>
> Analytical method development – development of specifications and optimization of analytical method (or series of analytical methods) are intended for us in assessing material quality and/or stability.
>
> Impurity Isolation, identification and structure characterization – development of specifications and optimization of analytical method (or series of analytical methods)that are intended for use in assessing material quality and/or stability.

At Eli Lilly, these three groups work individually and collectively to ensure the identification and characterization of impurities during drug development is performed accurately and quickly. The scientists that direct impurity identification and characterization utilize analytical instrumentation, electronic laboratory notebooks and specialized software from ACD/Labs to meet the daily challenge.

Data Collection

Collecting the analytical data needed to identify and characterize an impurity begins in the analytical labs. ACD/Labs software can import raw and processed data from instruments across analytical laboratories—chromatography, mass spectroscopy, optical spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy. This gives each scientist the flexibility to use the software in a manner that best meets his specific needs and workflow.

Scott Bradley, Principal Research Scientist, (Small Molecule Design and Development), preprocesses data with the instrumentation software, but he uses ACD/Labs software for structure elucidation and characterization from that point forward. ACD/Labs software enables Scott to attach a proposed chemical structure and provides him with the

A Systematic Approach to Development of Liquid Chromatographic Impurity Methods for Pharmaceutical Analysis

A September 2011 article by John Stafford et al. in the Journal of Biopharmaceutical and Biomedical Analysis describes a rational approach to high-performance liquid chromatography (HPLC) impurity method development. A suite of ACD/Labs software tools and a clearly defined workflow enable the strategy (see Figure 1). "The software provides full instrument control with automated sequence execution, automated signal processing with reconciliation between detectors and test preparations, retention modeling and predictive simulation of chromatographic separations, and a single user interface that allows the user ready access to the project data."[5]

Experiments were performed using an Agilent 1200SL series liquid chromatography system equipped with a binary pump, vacuum degasser, auto-sampler, column thermostat, column and solvent switching valves, diode array detector (DAD), quadrupole mass spectrometric detector (MSD) with multimode source, and ChemStation software. Instrument control, detector signal processing, peak tracking, data analysis/visualization, and component retention modeling were accomplished using ACD/Labs software.[6]

"The procedure offers a common starting point for both active pharmaceutical ingredient and drug product methods. The workflow is tailored to match the specific needs of a project based on phase of development. The use of sample mixtures and the specificity of MS and UV detection dramatically reduces experiment cycle time by more than 80%."[7]

convenience of doing the assignment and the associated record keeping. This is unique functionality not available from instrument vendor software, and it enables Scott and his associates to build a knowledgebase by capturing the 'live' data required for interpretation of the impurity.

John Stafford, (Research Scientist), Small Molecule Design and Development, uses the software to automate all of the experimental data collection from instruments. "It's very easy to just go into the lab, put the software on the instrument, and then start things running."

Chad Hadden, (Research Scientist), (Small Molecule Design and Development), uses the instrument vendor software to preprocess data, but uses ACD/Labs software to process and interpret it. According to Chad, "It aids my structure elucidation process, and it gives me features that the [instrument] vendor software does not."

Impurity Identification and Characterization

The heart of ACD/Labs software is its ability to improve the effectiveness and efficiency of impurity identification and characterization. John, Scott, and Chad have all seen significant improvements at Eli Lilly since the software has been deployed.

John's group uses the software to process the data from the experiments and match peaks across different experiments. "We tried doing that manually for a year or two before we acquired the software, and it was a very difficult task." The software enables his group to put more components in a mixture so they can make fewer injections across a set of experiments. According to John, "We then rely on the software to help us pull out the desired information in the Mass Spec and the diode array signals." John, along with others in the group, authored a journal article in 2011 (see sidebar at left) that describes and quantifies how a rational approach combining hardware and software significantly improves HPLC method development.

Scott has noticed changes in the way scientists in his team now pursue structure elucidation and characterization. "Some have made substantial workflow changes—from a manual process using paper printouts, pencils, and rulers to a computerized process. Even those that used some level of rudimentary computerization now enjoy greater convenience and a much higher level of confidence. Software has improved productivity across the operation."

Chad says, "I use the software to process and analyze data; by analyze I mean the whole impurity identification capability using NMR prediction capabilities to elucidate the structure." Chad also appreciates that ACD/Labs lets him work the way

he chooses, "It doesn't require a change in my workflow. It also matches the way I think, and [ACD/Labs] NMR Workbook has facilitated my process tremendously."

According to Scott, the software goes beyond just streamlining operations and actually helps in the "craft" of structure elucidation. "Assigning and recording a peak and having multiple displays and tracking gridlines make it much easier to find correlations than when you're relying on paper, pencils, and rulers. Things don't get lost in the cracks, and everything is accounted for. You're not forgetting what you've done and having to go back and redo it. It helps tremendously."

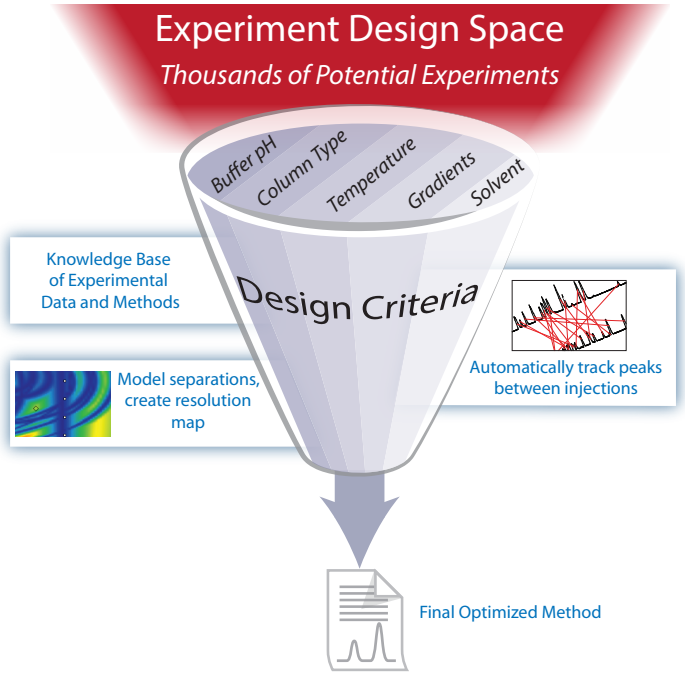


Figure 1. The software assisted approach for method development and optimization.

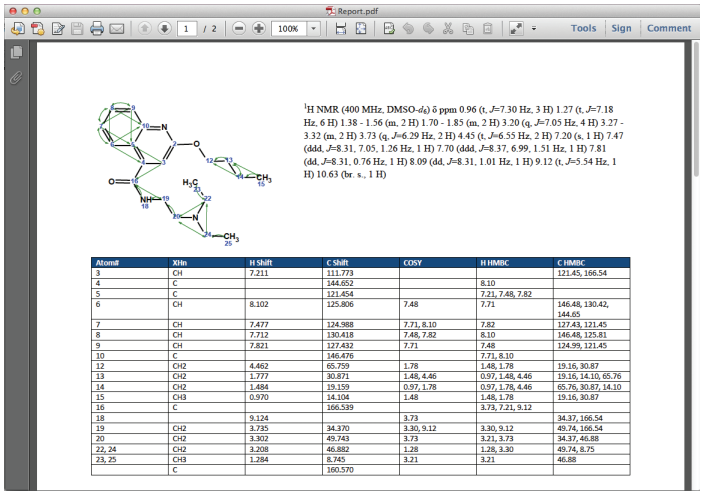
Collaborating and Reporting

John describes how the collaboration process flows from his method development group to the characterization group. "Individual project scientists will be conducting experiments, and as they see a new impurity they will try and get initial information about it using a nominal mass or, sometimes, an exact mass instrument. They will review results in consult with other chemists on the project to see if they can propose a structure. If they want to identify it further, they will either try and make it synthetically or try to isolate it. From this point, it will be sent to the characterization group for mass spectrometry and nuclear magnetic resonance analysis to characterize the structure."

Scott's group, in turn, uses ACD/Labs software to support collaboration. "We directly display the structure we propose, without any interim steps, from [ACD/Labs] elucidation along with the associated data in order to collaborate with chemists in other departments. When everyone is satisfied with the structure, we can quickly generate a report and place it in the ELN [electronic laboratory notebook] for distribution to all chemists across the organization." Each chemist can then append the report within his or her ELN and associate it with the sample. "We've received very positive feedback on this process."

According to Scott, this process saves considerable time and effort. "Before the software, most people had their own system. One popular system was to draw the structure in PowerPoint, enlarge it to the size of the page, type in the chemical shifts of the protons and carbons next to each assigned proton or carbon, and then manually draw arrows showing correlations—which is quite labor intensive."

Chad finds that using ACD/Labs workbook templates across departments ensures consistency for interpretation and reporting. "Because our group is viewed as problem solvers, the initial information we receive varies widely between two extremes: Sometimes we receive the entire synthetic route with lot numbers, ingredients and other detailed, relevant information. Other times, someone comes to us and says, 'Here's my impurity; can you tell me what it is?'"



Atom#	XHn	H Shift	C Shift	COSY	H HMBC	C HMBC
3	CH	7.211	111.773			121.45, 166.54
4	C		144.652		8.10	
5	C		121.454		7.21, 7.48, 7.82	
6	CH	8.102	125.806	7.48	7.71	146.48, 130.42, 144.65
7	CH	7.477	124.988	7.71, 8.10	7.82	127.43, 121.45
8	CH	7.712	130.418	7.48, 7.82	8.10	146.48, 125.81
9	CH	7.821	127.432	7.71	7.48	124.99, 121.45
10	C		146.476		7.71, 8.10	
12	CH2	4.462	65.759	1.78	1.48, 1.78	19.16, 30.87
13	CH2	1.777	30.871	1.48, 4.46	0.97, 1.48, 4.46	19.16, 14.10, 65.76
14	CH2	1.484	19.159	0.97, 1.78	0.97, 1.78, 4.46	65.76, 30.87, 14.10
15	CH3	0.970	14.104	1.48	1.48, 1.78	19.16, 30.87
16	C		166.539		3.73, 7.21, 9.12	
18		9.124		3.73		34.37, 166.54
19	CH2	3.735	34.370	3.30, 9.12	3.30, 9.12	49.74, 166.54
20	CH2	3.302	49.743	3.73	3.21, 3.73	34.37, 46.88
22, 24	CH2	3.208	46.882	1.28	1.28, 3.30	49.74, 8.75
23, 25	CH3	1.284	8.745	3.21	3.21	46.88
	C		160.570			

Figure 2. An example proof of structure characterization report generated by ACD/Labs software.

"The main collaboration tool [across the organization] is the Electronic Laboratory Notebook," says John. The original investigating scientist will have his or her experiments, and as the process evolves he or she will reference associated information. "Eventually, this information will be pulled together to create a report for a regulatory submission. It [the report] is placed in a library system and linked to lab notebook references in terms of where the materials came from, where the work was done, and other relevant information."

Audit Trail

Scott states that while the reports his group provide are not usually included in the new drug application (NDA) to the FDA, they are a critical part of the audit trail. "For example, the reports we supply to analytical chemists generally end up as an attachment in their ELN, but are not submitted directly as part of the NDA. But, if the FDA question aspects of the NDA related to the structure, the report can be provided. Furthermore, the report can be traced back to our notebook, which includes the associated data and elucidation process, and this information can quickly be provided as confirmation of the particular impurity, thereby avoiding a delay in the approval process."

Expanding Capability to Process Chemistry

ACD/Labs software was recently deployed to organic process chemists, and while it is too early to quantify improvements, Chad believes it will be valuable to have everyone, "talking apples-to-apples." According to Chad, "I can help in any way, shape, or form, if everyone is using the same thing."

Enterprise Search, Retrieval and Reuse of 'live' Data

Scott views the ability to store assigned spectra and NMR data in an easily accessible database as a major advantage of ACD/Labs. "When someone submits a new sample, we can compare the structure with prior, similar samples within the software." Because the structure is associated with 'live' data, "You can zoom, you can hover over an atom and see the chemical shifts—it's a lot more useful than just comparing it with a static word or pdf document. We can also go back in and change assignments as we learn more about a structure, and that's incredibly convenient."

Chad would like to see a centralized database of impurities accessible by chemists across all departments—process chemistry, analytical, and structure elucidation and characterization. "I can't tell you how many times, over the past 15 years, someone has said, 'we have a new impurity,' when, in fact, we've just characterized something like that, and it's only different by a double bond."

Conclusion

ACD/Labs software is a critical component of a system that helps Eli Lilly accelerate the accurate identification and characterization of impurities in the active pharmaceutical ingredient (API) and the final drug product. Scott cites the convenience of doing the assignment and the associated record keeping, automated reporting, and the ability to store assigned spectra and NMR data in an easily accessible 'live' database as the greatest value to his group. According to John, "Overall the increased throughput and automation are the two things that have really helped our workflow." Chad emphasizes that the software allows him to do things much faster; things that would take much more time if he didn't have it. "Reporting, the structure elucidation through [ACD/Labs] Workbook, doing the assignments, synced spectra, tables—all of this [capability] saves me a tremendous amount of time."

About Advanced Chemistry Development, Inc. (ACD/Labs)

ACD/Labs is a cheminformatics company that develops and commercializes solutions in support of R&D. Our solutions are used globally in industries that work with small molecules including pharma/biotech, chemicals, consumer goods, agrochemicals, petrochemicals, academic institutions, and government organizations. We provide integration with existing informatics systems and undertake custom projects including enterprise-level automation. 2014 marks our twentieth anniversary of helping organizations accelerate R&D and leverage corporate intelligence. ACD/Labs also provide worldwide sales and support with offices in N. America, Europe, and Asia.

For more information, please visit www.acdlabs.com.

About Eli Lilly and Company

Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism.

For more information, please visit www.lilly.com and http://newsroom.lilly.com/social-channels.

Endnotes

[1] Gary E. Martin, "A Systematic Approach to Impurity Identification," Richard J. Smith and Michael L. Webb, ed., Analysis of Drug Impurities, Wiley-Blackwell; 1 edition (April 30, 2007), 124.

[2] Guidance for Industry: Q3A Impurities in New Drug Substances, Revision 2, Attachment 1: Thresholds, U.S. Department of HHS: FDA, CDER, CBER and ICH (June 2008), 11.

[3] Guidance, 5.

[4] Guidance, 4.

[5] John D. Stafford, Todd D. Maloney, David P. Myers, Jose M. Cintron, and Bryan C. Castle, "A systematic approach to development of liquid chromatographic impurity methods for pharmaceutical analysis," Journal of Pharmaceutical and Biomedical Analysis, Volume 56 Issue 2 (September 10, 2011): 281.

[6] Stafford, 281 – 282.

[7] Stafford, 291.