A Q&A

Automated Analytical Method Development

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Workflow advantages and future developments.

Who can benefit from automated method-modeling software? Probably more laboratories and research teams than you think—perhaps even your own. That's because all the method-development experience in the world is no match for an automated modeling software package that can eliminate human error, provide a 360-degree view into the design space, and accelerate time to development of a truly robust method. As DryLab Specialist at Molnár-Institute for Applied Chromatography, Arnold Zöldhegyi understands this better than anyone. So, *LCGC Europe* sat down with him to discuss the benefits of the new DryLab/Empower connection in pharmaceutical analysis and to get a peek at future goals and advances for the automation module.

LCGC Europe: What are the benefits of using high performance liquid chromatography (HPLC) modeling software such as DryLab for method development?

Zöldhegyi: The main benefit of modeling software is that it literally illuminates the whole possible design space—a design space that easily consists of more than a million work points or method-parameter combinations. For example, in the case of DryLab, all it takes is 12 distinct input runs to visualize all the chromatographic interactions inside the design space.

Some packages are statistically based and will run numerous experiments, keeping your instrumentation busy day-in and day-out in an automated way. DryLab takes a different approach, probably because it was programmed by two scientists—Lloyd Snyder and John Dolan—who greatly contributed to the understanding of HPLC. A typical statistical package will tell you if your method works or fails, but it won't demonstrate what's going on in your design space the same way DryLab does. DryLab will visualize the interactions of your separation under all possible method conditions so you see precisely which areas your method will work in, which parameters can be varied, and which need strict control.

Some scientists believe following one's intuition is better than using modeling software. Having a hunch and working by trial-and-error may be helpful in some areas, but it is the wrong approach when you're trying to receive marketing authorization for a new drug product. In fact, CROs that do contract method-development work daily—clearly very experienced chromatographers—use DryLab to avoid heading in the wrong direction and to substantiate their decision-making for filings. Modeling software also saves a lot of time wasted in other approaches.

LCGC Europe: How does automated method development relate to Analytical Quality by Design (AQbD), and what advantages does it bring to pharmaceutical analysis?

Zöldhegyi: The term "AQbD" implies a method development that's based on scientific understanding—on HPLC's underlying theories. Because DryLab takes advantage of the absolute accuracy of the laws describing the retention mechanisms in HPLC, you'll only need 12 input runs. Now, adding automation to DryLab further lowers the threshold of using this AQbD software to the level that you'll be using it on an everyday basis.

What then really determines the quality of your DryLab model is the pristineness and reproducibility of your input data. In other words, you can expect a close-to-perfect model if you rule out transcription errors and other slips—which is exactly what automation does.

LCGC Europe: How do the new automation module and its Empower connection facilitate the DryLab workflow, and in what regard does this make the user's life easier?

Zöldhegyi: The automation module connects directly to the Waters Empower CDS, writes the sample sets—making sure that the proper re-equilibrations occur between runs—and then acquires the integrated data from Empower back to DryLab. It does this across the DryLab workflow, which first involves designing and running the 12 input experiments on Empower, then executing and acquiring confirmation runs, and finally running and acquiring robustness verification runs to confirm the robustness assessment.

If you're a subject-matter expert in charge of a separation center that delivers to analytical operations, you've probably set up an SOP that implements the daily use of DryLab. But, not everyone is experienced in method modeling. Here, having the Empower automation really makes life easier, with all data transferring seamlessly across the DryLab workflow.

Not only does the new automation model and its Empower connection facilitate DryLab modeling for less-experienced users, but it also prevents all users from making mistakes when writing method sets, exporting from the CDS, importing to DryLab and copy-pasting additional peak data from spreadsheets. It really brings DryLab's AQbD modeling to your daily routine on all those levels, plus it vastly saves time—your sample set is written with one click.

LCGC Europe: Now, assessing the robustness of an analytical method is one central point of Q12 (LCM). How does DryLab assess method robustness, and how is this process facilitated by DryLab's new automation module?

Zöldhegyi: Robustness is a key performance criterion of analytical methods. The way DryLab has been assessing robustness since we first made the module in 2011 turns out to be in-line with what ICH Q12 recommends.

But the reason for industry to turn to the robustness module is that it gives you a very good understanding of how well your method will perform in routine use, and which areas of your design space it can be run across its lifecycle without facing any out-of-specs. This is highly relevant to many of our customers because their business models depend on their ability to yield profits in a limited window of opportunity. When it comes to analytical development, this means that methods must perform flawlessly in subcontractor labs in regulatory systems across six continents.

So DryLab's robustness assessment works as follows: First, the design space and its chromatographic interactions are modeled based on scientific theory. Then, based on that knowledge, the method-operable design region (MODR) is identified. Instrumentation precision is taken into account including the range of gradient sensitivity, temperature accuracy, pH accuracy, and other specs that could vary such as flow rate. This information is added to the DryLab model to evaluate a work point or workspace's robustness. Once your MODR has been scrutinized, the chromatographer then validates the robustness assessment.

From the systematic way your model has progressed so far, you can see the points in your MODR at which the API will elute earliest and latest, which gives you a range that you can expect in routine use. This will be highly relevant for your system sustainability test. Also, you'll see where in your MODR peaks of interest, for instance, the critical peak pair, will have their lowest critical resolution.

You then take these strategically relevant points from *in-silico* and run them for confirmation with fully automated sample sets written and executed through DryLab's Empower connection, and then acquired from Empower and compared to confirm the model in DryLab.

The whole point of doing this with regard to Q12 is to use the software capabilities of visualizing the interactions going on, and to determine which parameters affect your separation in routine use. This information is gathered and structured in DryLab's knowledge-management document as the scientific basis for your post-approval lifecycle management. Flexible regulatory approaches regarding later changes would derive from, for instance, a downgrading of certain parameters from prior approval to notification.

LCGC Europe: Are you seeing new areas of application in which industry is using DryLab?

Zöldhegyi: We have some amazing customers using DryLab extensively across techniques: ion-exchange, ion-pairing, hydrophobic- and hydrophilic-interaction chromatography and, of course, normal and reversed-phase. We also see a lot of protein analysis with large teams of analytical scientists in the industry using DryLab for separation work on polypeptides and oligonucleotides, and the DryLab workflow being laid down in their SOPs. We see very impressive applications in monoclonal antibody work.

Something new we're seeing is industry companies adding DryLab knowledge-management document to the pharmaceutical-development section of their CTDs. It facilitates approval because it provides all the relevant information that's missing if you only file validation results. Validation results alone do not justify post-approval leeway, which regulators may have granted if you'd turned in documentation of your analytical procedure development.

In this regard, customers filing DryLab's knowledge-management documentation may have the potential to advance the field in the coming years.