APPLICATION NOTE

ACD/LABS [ADVANCED CHEMISTRY DEVELOPMENT, INC.]

Applying QbD in Process and Impurity Control Strategy Development

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Introduction to QbD and Impurity Control

Global regulatory authorities continue to push Quality-by-Design (QbD) on pharmaceutical groups and their supporting corporate informatics infrastructure. Effective leveraging of QbD in risk mitigation requires an informatics platform that does not rely on data abstraction, simplifies data assembly, and reduces the need for human data preparation.

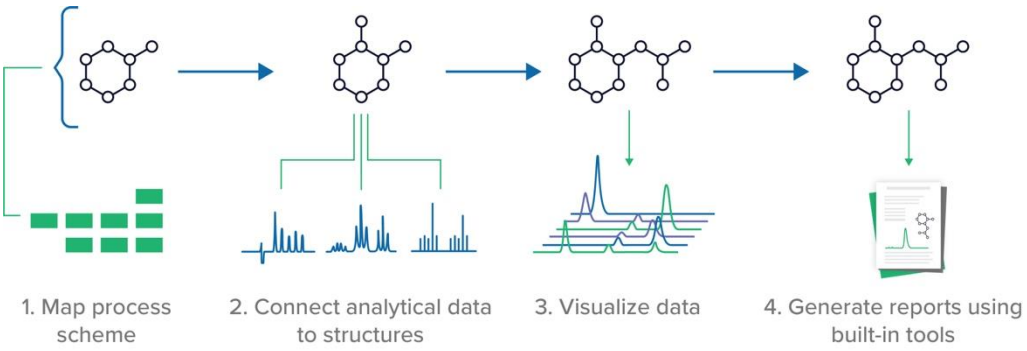

***Figure 1**. The workflow of Luminata—software designed for management of impurity data*

Informatics software for impurity control should optimally provide users with the ability to construct “process maps.” The platform should also allow the user to visualize the wide variety of related spectroscopic and chromatographic data in a single environment for each stage and substance for efficient and informed decision-making.

Here we provide an overview of how Luminata can be used to address these needs.

Method

Analytical data collected for Agomelatine, a CNS agent synthesized by the six-stage process route illustrated in Figure 2, was used in this work.

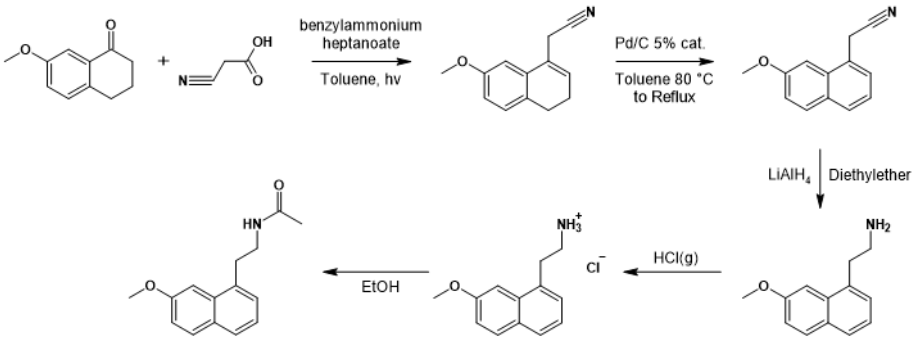

Figure 2. The process route for synthesis of Agomelatine

Analytical data was collected on an Agilent-1200-Series with an Agilent VWD G1314B UV detector, acquiring spectra at 210 nm, and an Agilent 6110 Quadrupole API-ES Mass Spectrometer, collecting low-resolution spectra in a mass range of 45-1000Da.

Isocratic separation was performed with pH 4.5 buffered ammonium formate/ACN (35:65). The flow rate was 1.2ml/min with a run time of 50min, and the column used was a Zorbax Eclipse XDB C18 5um - 4.6 x 150mm.

The software application Luminata, based on the ACD/Spectrus Platform, was used to manage the analytical and chemical data.

Results

Using the process route imported into Luminata, all the LC/MS data can be connected to each process stage. Impurities, whether carry-over from a previous step or new, may be inserted as text labels until the structure is identified and verified. The resulting 'process map' enables easy visualization of the impurities at each stage of the route and comparison of molecular composition across reaction steps (Figure 1). Compilation of the chemical information enables users to review the reproducibility and robustness of the process between batches.

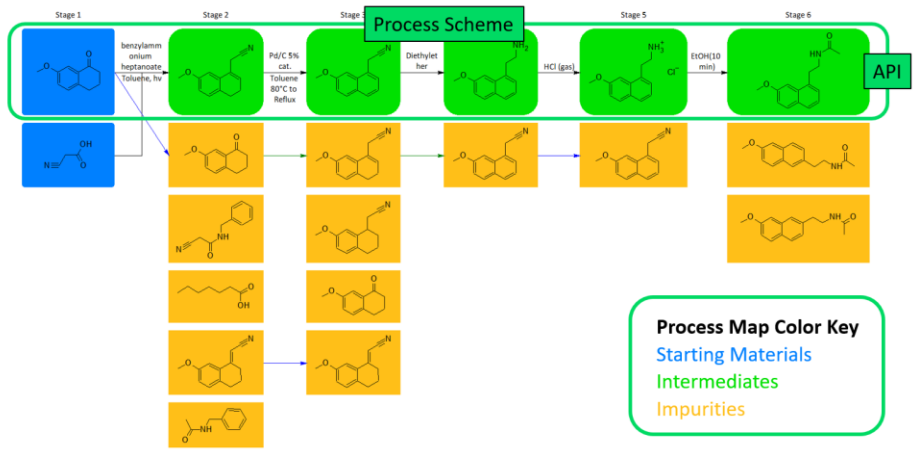

Figure 3. Luminata's process map provides easy visualization of molecular composition at each stage

Connecting live analytical data with chemical entities enables confirmation of interpretations or processed results without opening separate applications. The accuracy of automatically calculated % area values of each impurity can be assessed by accessing the chromatogram. The identity of each chemical structure is easily confirmed with the ability to review interpreted mass spectra and labeled chromatograms with a single click.

Once a structure is identified, the software automatically replaces text labels with structures, eliminating the need for manual data transcription and saving time. Consolidating all process-related information in one application ensures the entire project team has access to up-to-date information. Team members can search, review, and edit data, providing effective collaboration and project management.

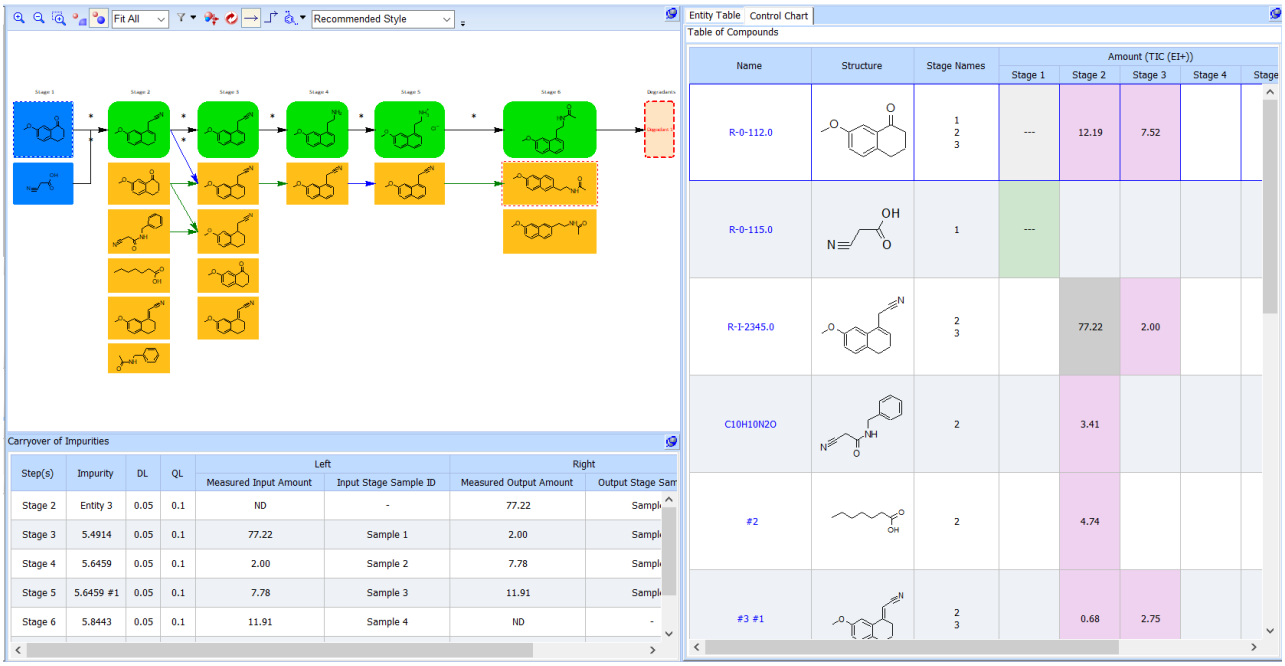

Figure 4. *Automatically generated summary tables track molecular entities and their corresponding levels.*

Luminata maintains data for each stage of the process for each batch, which facilitates detailed analysis and quick decision-making (Figure 4). Users can quickly assess the effectiveness and efficiency of impurity control measures following QbD principles.

Conclusions

Dynamic visualization of assembled and aggregated information preserves data integrity while supporting decision-making. Luminata effectively supports process and impurity control strategy development by enabling:

- Risk assessment pertaining to impurity onset, fate, and purge
- Comparative assessment of different control strategies

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