Applying QbD in Process and Impurity Control Strategy Development

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Introduction

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 informatics platform innovation; particularly to support reduction of data abstraction, data assembly, and human data preparation.

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 a new software application (Luminata™)[1] developed specifically to address these platform innovation needs.

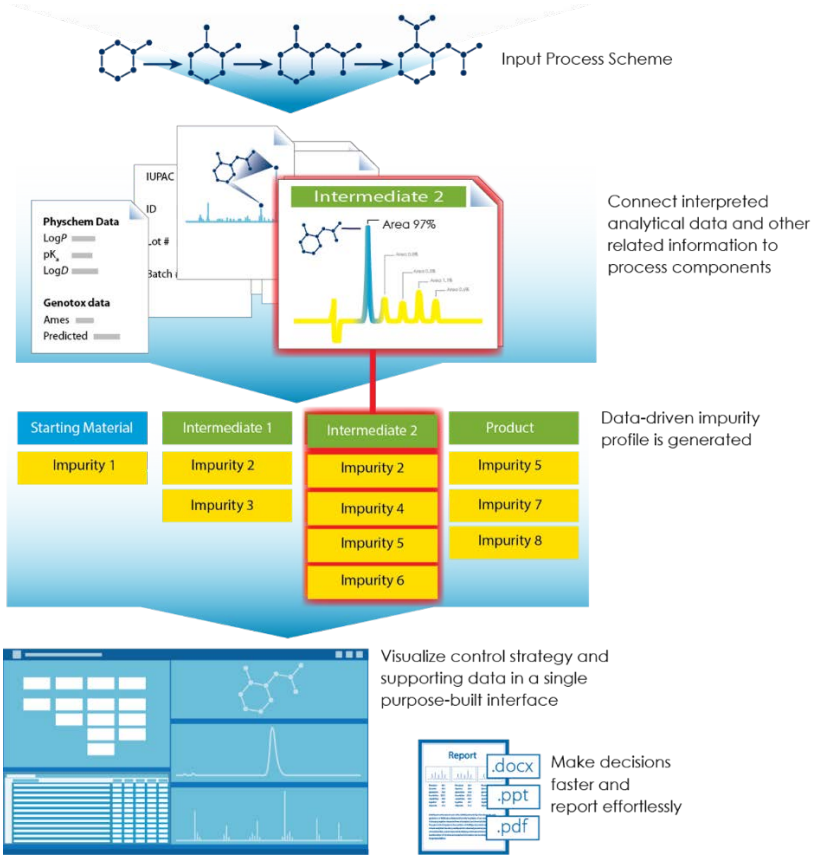

Figure 1 The workflow of Luminata—software designed for management of impurity data

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.

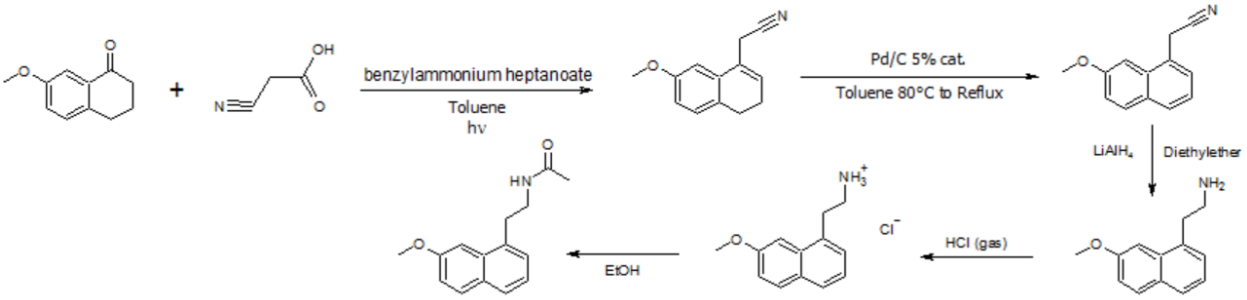

***Figure 2**—The process route for synthesis of Agomelatine.*

Analytical data was collected on an Agilent-1200-Series with an Agilent VWD G1314B UV detector, acquiring spectra at 210nm; 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, the column used was a Zorbax Eclipse XDB C18 5um - 4.6 x 150mm.

The software application Luminata™ (v2017.1), based on the ACD/Spectrus Platform, was used to manage the analytical and chemical data.

Results

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

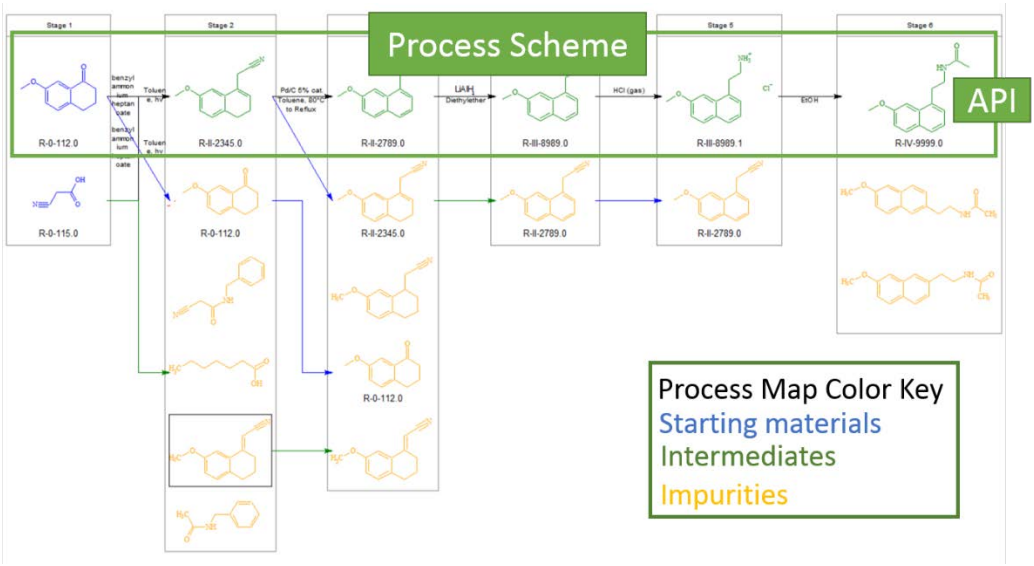

Figure 3 *The process map for synthesis of Agomelatine in Luminata provides easy visualization of molecular composition at each stage.*

Connection of live analytical data with chemical entities enables fast confirmation of the veracity of numerical and textual interpretations or processed results without having to open separate applications. The accuracy of automatically calculated % area values for quantitation of impurities may easily be assessed with direct access to the chromatogram. The identity of individual chemical structures is easily confirmed with the ability to review interpreted mass spectra and labelled 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.

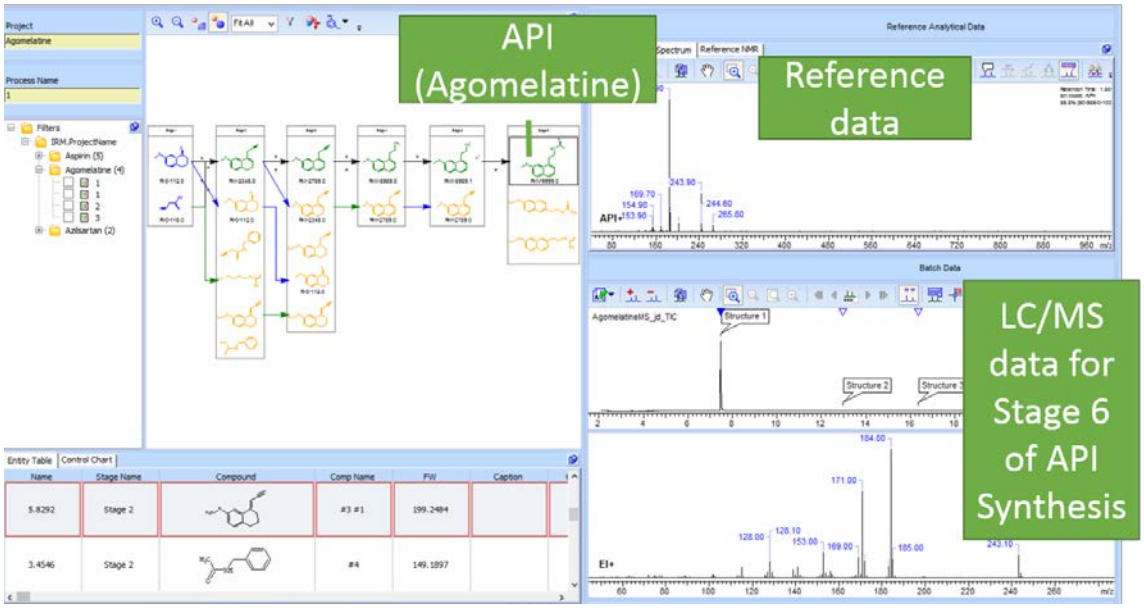

Figure 4 *Luminata enables visualization of all data in a single interface. Drag and drop assembly of live LC/UV/MS data with each stage ensures data integrity and efficient data management.*

Assembly of all process related information—the context of the experiment, expert interpretations, and decisions resulting from it—in one application ensures access of up-to-date information to the entire project team (Figure 4). Permissions allow teams to search, review, and/or edit data. Luminata maintains a 'line-of-sight' from a finished batch to individual stages, and between batches to facilitate quick decision-making (Figure 5). It enables rapid assessment and decision-making around the effectiveness and efficiency of impurity control measures in accordance with QbD principles.

Figure 5 *Automatically generated summary tables track molecular entities and their corresponding levels. Area % values are generated directly from analytical data for easy comparison. Results export directly to Word or Excel.*

While not investigated in this study, data for modified routes, on different scales, and for investigations around alternative catalysts and reagents for the same API endpoint can also be managed efficiently.

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

References

1. Luminata, version 2017.1, Advanced Chemistry Development, Inc., Toronto, On, Canada, www.acdlabs.com/Luminata, 2018.

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