An Impurity Control Strategy Using Impurity Mapping with Dynamic Purge Factor Determinations for Drug Substance Development

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PURPOSE

API process development is tremendously challenging and needs to support Quality by Design (QbD) principles, to ensure that medicines are safe and efficacious. To achieve these goals, control strategies must be developed which comprehensively assess, classify, and report process route development. Process mapping and determination of impurity fate and purge lies as the foundation of this. While scientists have developed processes to gather this information across batches per impurity, it remains a tedious manual process.

OBJECTIVE

Here we provide an overview of a software application, Luminata™, developed to address the data management and knowledge-sharing challenges faced by project teams in process development.

METHOD

Analytical data collected for Agomelatine, a CNS agent synthesized by the six stage process route illustrated in Figure 1, was used in this work.

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 Series with an Agilent VWD G1314B UV detector, acquiring spectra at 210 nm.

Figure 1—The process route for the synthesis of Agomelatine.

Color-coding of intermediates (green) and impurities (yellow) easily visualizes molecular composition at each stage. The connected analytical data enables the software to not only calculate chromatographic ‘Area % values’ for each entity (these values are populated in the batch data table as LC/MS data is attached), but also to use that data to dynamically build real time purge factor calculations.

RESULTS

A full ‘map’ of the synthetic route along with impurities and intermediates was created in the software for x batches of the API (Agomelatine). All relevant reference and experimental LC/MS data were connected to the various stages and entities to consolidate process information in a single repository.

Figure 2—Summary view of process route, associated impurities, and connected LC/MS data for synthesis of Agomelatine, in Luminata. The resulting ‘process map’ enables easy visualization of the impurities at each stage of the route, easy comparison of molecular composition across reaction steps, and mapping of impurities (including genotoxic impurities if present) within the synthetic route (Figure 3).

Figure 3—The process map for synthesis of Agomelatine in Luminata, clearly visualizes molecular composition at each stage. Color-coding of intermediates (green) and impurities (yellow) facilitates review.

Dynamic Purge factor Calculations

The foundation of dynamic purge factor calculations in the software is appropriately defined connections between the entities at each stage or synthetic step. The software recognizes unchanged carry-over and transformations between entities as arrows are drawn. The LC/MS data is used in the background to automatically build corresponding purge factors (see Figure 4).

Figure 4: A—Connection of impurities from stage 2 to stage 3 (connected by green arrow) results in automatic calculation of cumulative carryover where DL is the detection limit and QL the quantitation limit.

Carryover is calculated using Area % values for two consecutive stages:

In addition to calculating cumulative carryover amounts for the fate of particular impurities (e.g., from stage 3 to stage 5 in Figure 4), the software will also compare different batches within a total record set, if an impurity has been spiked into several processes in varying amounts e.g., 1 %, 3 %, and 5 %, one cumulative carryover table can be built with specific stages from each spiked amount (see Figure 5).

Figure 5—Automatically generated cumulative carryover table for two process batches with 1% and 3% spiked impurity amounts.

CONCLUSION

Large quantities of data are generated in route development for an API. While scientists have designed processes that allow them to understand and document the fate and purge of impurities, this routine work still involves manual calculations from data that is often distributed across a variety of systems.

Luminata enables project teams to develop control strategies more efficiently and support decision-making by automatically calculating purge factor directly from the LC/MS data within the same environment.

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