Cambrex

Case Study
Analytical Services

Successful control strategies – Part 2

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Building quality into the product through range finding studies.

Insight into impurities: Formation, fate and purge

Demonstrating control over the manufacturing process is a key element of the Quality by Design (QbD) model. In Part I of 'Successful control strategies', we discussed Cambrex's capabilities in determining CPPs and PARs to pinpoint manufacturing steps that require tighter control. We continue our discussion of these late-stage QbD studies by exploring the importance of fate and purge studies, which measure the ability of the process to remove impurities and provide evidence of their removal. Often these studies are run in parallel because they generate related data; fate and purge studies can expose other CPPs or indicate the downstream removal of a CQA from a drug substance.

"While CPP and PAR range finding studies seek to understand their effect on the process as it relates to end product quality, here we use the process to understand the fate of impurities during each step in the process and where they are removed," explains Dr. Daniel Kirschner, Executive Director of Analytical Services at Cambrex. Fate and purge studies also reveal how specifi cations at different process stages relate to each other, which is critical to understanding the formation of impurities throughout the manufacturing process as a whole.

ICH Q11 emphasizes the importance of understanding impurity formation:

"For chemical entity development, a major focus is knowledge and control of impurities. It is important to understand the formation, fate (whether the impurity reacts and changes its chemical structure), and purge (whether the impurity is removed via crystallization, extraction, etc.) as well as their relationship to the resulting impurities that end up in the drug substance as CQAs. The process should be evaluated to establish appropriate controls for impurities as they progress through multiple process operations."[1]

Quality is our competitive edge.

At Cambrex, quality drives the process to produce results that stand up to regulatory filing.

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,200 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.

Each of these late-stage QbD studies contribute to readiness for commercialization. The body of data generated by fate and purge studies supports the justifi cation of impurities in an NDA. They also provide clients directions for adjusting their process to manage an impurity, including residual solvents or genotoxins, or the evidence that they are purged naturally as a result of the reactions in the process.

Invaluable payoff: Setting precise specifications

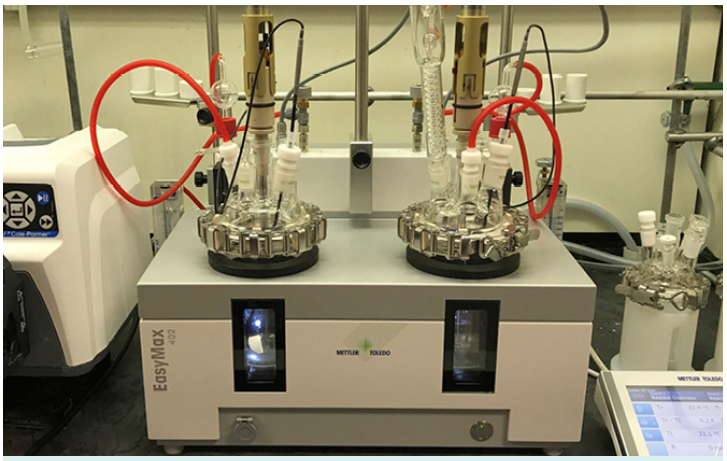
A successful fate and purge study requires close collaboration between the client and the CDMO at the onset. These experiments require careful design and execution, and extensive information is required up front, including a list of known impurities. At the same time, a thorough, small-scale tech transfer must be performed to reproduce the process.

Once known impurities are synthesized, our chemists qualify them as reference standards so that they can be spiked into the manufacturing process and traced throughout each step. Typically, impurities are followed for at least two reaction steps, but in some cases, an impurity is followed all the way through the process to the final drug substance.

Data is collected at each step in the process to determine any change to the impurity, including a change in its con-centration, whether it altered in formation, or if it was purged from the process. If the impurity undergoes a chemical transformation, the newly formed impurities are also independently tested. The scale and magnitude of these studies varies widely. Since all of these steps are repeated at multiple stages in the process for multiple impurities, fate and purge studies often create an extensive matrix of data points.

Validated methods are standardly used at Cambrex to provide reportable values, but our experts possess analytical dexterity to develop ad hoc methods for unique situations. For example, after spiking an impurity, a downstream measurement may require analyzing an extraction solution that is not typically measured. Cases like these require experienced chemists to adapt a method that has been demonstrated as suitable for intended use.

Large data sets are generated from calculating the percentage of purge at different time points, and these are ultimately translated into specifications for each step. The practical endpoint for the client is a broad set of precise specifications for the entire process to achieve expected quality of product. With control over the process, manufacturers can set specifications up front for starting material and intermediates rather than relying on batch data.



Cambrex is equipped with state-of-the-art technology to simulate complex synthesis during analytical studies. The EasyMax workstation allows accurate control of each reaction during synthesis and measurement of intermediates and by products. Our team of cross-disciplinary experts apply thorough analysis to determine fate of impurities at each step of the process.

Forecasting obstacles: Preventing downstream costs

In addition to informing chemists about the fate of material during the manufacturing process, fate and purge studies also prove the capability to detect the impurities in the process and control them, which is a key component of the QbD model. Equipped with better knowledge of the process, our scientists can predict whether impurities will pose a barrier to producing a clean product and manage specifi cations accordingly on the front end. In some cases, the specifications are narrowed in order to control impurities and their derivatives in subsequent steps, but the reverse scenario can also occur. For example, a higher percentage of an impurity in starting material might be justified if validated methods show that it is purged away during the process. Stretching the allowable limit of an impurity may save the client signifi cant cost in securing starting material with less stringent purity standards.

Determining the levels of residual solvents during fate and purge studies can also be a cost-saving asset for clients. Following solvents through the manufacturing process and demonstrating that they are removed in the final API eliminates the need for testing the end product for the presence of numerous solvents. Similarly, by demonstrating that a potential genotoxic impurity (PGI) is not carried through to the fi nal product, clients don't have to invest resources to develop and commercialize a method to prove that the PGI does not exist in their drug substance.

Optimal end product: Mapping a path for quality

Fate and purge studies challenge the process by deliberately spiking known concentrations of impurities to determine how well they are purged from the process. The value of these experiments is to allow broader understanding of the manufacturing process and how impurities are inherently removed so that chemists can set optimal specifi cations for starting material and intermediates.

It's not uncommon for clients to skip this step in development to avoid the time and resources devoted to such a complex analysis of their process. However, drug developers can reap large rewards from investing in studies that satisfy QbD requirements. Not only does the data feed directly into regulatory filings, the opportunities uncovered during these studies to optimize the process can deliver time and cost savings. Range fi nding studies yield more than just data points. They point us toward the best route to achieve optimal quality in drug products.

Make your investment count.

Eliminate downstream testing by investing in quality development.

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