Cambrex

Case study
Analytical services

Qualified reference standards: Setting the standard for product quality

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The impact of quality reference standards on manufacturing success.

Input versus output: The value of qualified reference standards

Drug producers face increasing stringency from regulatory authorities to substantiate the purity of drug products and to demonstrate control of impurities. Qualified reference standards play a critical role in providing validated benchmarks to satisfy regulatory requirements pertaining to purity. Additionally, they equip manufacturers with information they can apply to solve issues and to assess the impact of changes to the manufacturing process.

As drugs progress toward IND and NDA filing milestones, qualified reference standards must be produced in quantities sufficient to support analytical and process development studies. When drug manufacturers are navigating the competing pressures of time and budget limitations alongside regulatory constraints, they may undervalue the benefit of applying thorough and rigorous characterization efforts early in the development pipeline.

An experienced CDMO can connect the value of investing in qualified reference standards to the impact on final product quality. Profiling impurities allows manufacturers to isolate and identify them if problems arise. Armed with an accurate understanding of an impurity and its specific characteristics, they can design a solution to fix a problem without retracing steps to characterize the impurity. For APIs, creating a qualified reference standard allows manufacturers to reliably assess the purity and identity of subsequent batches. Or, consider the IR absorption spectrum of a substance, which provides conclusive evidence of its identity. Differences observed in the spectrum of a sample compared with the reference standard may be the first indication of a novel polymorph. Awareness of differences from reference standards allows strict monitoring throughout production to achieve uniform purity. The output of the manufacturing process is directly tied to the input. By investing in qualified reference standards early on in development, Cambrex customers gain an edge in later problem solving to act swiftly with well-informed decisions.

Confidence in continuous quality.

Qualified reference standards demonstrate quality throughout the entire process of drug development.

About Cambrex

Cambrex is **the** small molecule company that provides drug substance, drug product and analytical services across the entire drug lifecycle. Enjoy working with our experts to accelerate your small molecule therapeutics into the market.

With over 35 years' experience and a growing team of over 2,000 experts servicing our global clients from our sites in North America and Europe, we are tried and trusted in branded and generic markets for API and dosage form development and manufacturing.

"Analytical methods are the foundation for acquiring product knowledge. It is critical to develop and qualify a series of methods useful for characterizing product attributes such as structure, purity, chemical modifications and biological activity. Early in development, it is unlikely that a recognized reference standard already exists, so an in-house primary reference must be made and fully characterized through the development of analytical methods and tools."

Q6A 2.11 reference standard

A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing. For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and/or controlled, and purity should be measured by a quantitative procedure.

Clearing hurdles: Integrated capabilities

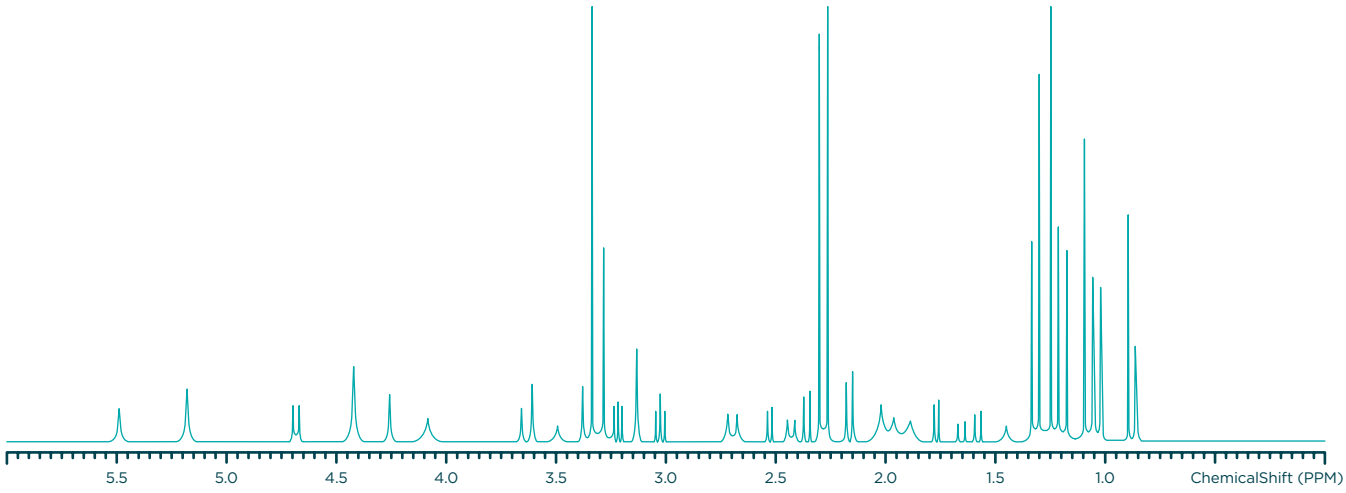
Delivering qualified reference standards requires close collaboration. During the process, there are many iterations of cycling results between process chemists and analytical chemists. Newly observed impurities that arise during process development trigger new isolation, analytical characterization and synthesis efforts. As impurities are isolated and synthesized, process chemists must consult with analytical teams for characterization studies. Cambrex has expert chemists with a wide range of expertise under one roof to perform each step of identifying impurities, executing synthesis rapidly and performing full characterization.

In this case, a client required a reference standard for a newly observed impurity in order to perform quantitative analysis during the development process. Our integrated team of experts quickly identified the impurity, synthesized the reference standard on a 10-gram scale, and developed a custom analytical method to characterize the impurity. Because the impurity was the result of a small change to a large molecule, separation of the impurity was challenging. Furthermore, the impurity was unstable under the initial analysis conditions, so the team modified conditions to perform accurate quantitative analysis without degradation of the impurity.

Integrated capabilities.

When analytical teams and process chemists are neighbors, there is no physical barrier to delivering quick solutions.

Each case presents unique challenges, but Cambrex's compliant facilities are equipped with top-notch technology to deliver validated data for determining potency and releasing future batches of material with reliable consistency. Our strict protocols and thorough analyses give confidence in the accuracy of the results and stand up to the rigor of regulatory requirements. With analytical teams just a few doors down from our process chemists, our facilities are designed to minimize delays caused by physical separation of different teams. A Certificate of Analysis (COA) is delivered with all our reference standards, including detailed reports from the experiments to support regulatory filings.



A newly observed impurity required specialized separation conditions to successfully separate it from the closely related API. Cambrex experts further developed conditions to avoid degradation of the impurity to allow proper quantitative analysis.

Benchmark for success: Impact on regulatory filing

While reference standards provide solid benchmarks for comparing different lots of APIs, impurities, and intermediates, their proper selection and qualification also influence regulatory filing. Qualified reference standards provide proof of continuous quality of starting material and drug substances, and allow monitoring of other substances including excipients, impurities, and byproducts throughout the entire process. They enable drug makers to demonstrate with confidence that the properties of any given material are consistent across multiple manufacturing campaigns and provide a reference point for comparison during any stage of the process.

A reliable fingerprint for your API provides an accurate assessment of the similarities or differences between multiple batches. Purity of each manufactured batch of material is determined by direct comparison with a qualified reference standard. At Cambrex, we leverage our LIMS to create an efficient process for characterizing all reference standards that are relevant to each particular manufacturing process. Successfully generating well-characterized reference standards helps protect large capital investments in drug development. From steering pre-clinical decisions to post-marketing regulatory inquiries, Cambrex gives clients a high degree of confidence that material is fully characterized to accurately compare against various lots of material, develop meaningful specifications, and fulfill regulatory requirements.

Authors

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