

# Reference Standards in API Drug Development Manufacturing

Key processes for proper API filtration to prevent cross-contamination in final product

By Ed Price, President, [PCI Synthesis](#)

While the [API manufacturing](#) industry continues to grow and evolve, with the goal of developing new drugs extracted from natural products or synthetically produced drug substances, one thing remains unwavering: the product must be as pure as possible to ensure its safety in patients.

To ensure quality APIs [reference standards](#) are used to help ensure the identity, potency, quality and purity of drug products and drug substances. This is accomplished by analyzing the substance against its qualified reference standard, so the accuracy of reference materials is essential to the manufacture of quality APIs.

The U.S. Food and Drug Administration (FDA) defines a reference-standard material as a "highly purified compound that is well characterized." One of the international standards-setting organizations, the [U.S. Pharmacopeia \(USP\)](#), defines reference-standard materials as "highly characterized specimens of drug substances, excipients, reportable impurities, degradation products, compendial reagents, and performance calibrators."

Reference-standard materials can be broadly categorized as the following

- Assays—used to determine potency for active pharmaceutical ingredients (APIs) and salts.
- Degradation products—used to identify and possibly to quantitate degradation products.
- Process impurities—used to identify and possibly quantitate process-related compounds.
- Resolution—used to determine assay performance or impurity method qualification.

Reference standards can be compendial, referred to as Primary Reference Standard, or a highly characterized in-house standard or a Secondary Reference Standard. Primary Reference Standards can be obtained from the standards-setting Pharmacopeias, such as the USP or EP.

Here at PCI Synthesis, we regularly synthesize and qualify materials as reference standards for a variety of projects, such as the following:

- To quantitatively determine the product assay.
- To detect impurities in the sample.
- For releasing raw materials.
- For in-process monitoring.
- As a retention time reference marker.
- For stability studies.

Reference-standard materials that are synthesized and supplied by the sponsoring client or through another third-party are always evaluated by PCI Synthesis in order to ensure the integrity of the substance, regardless of what testing already took place. The reference standard must be of the highest purity possible and may require further purification to be considered one.

## How Reference Standards are Qualified

Primary Reference Standards are designated substances that are widely acknowledged to have the appropriate qualities within a specified context. Its value is accepted as long as the substance is being stored and used according to instructions on the API's label.

While in-house reference standards are first evaluated for purity, if the purity is not acceptable then it is further purified until an acceptable level is obtained.

Once the chromatographic purity is acceptable then the substance is further characterized by MS, FTIR, C-NMR, H-NMR and [elemental analysis](#). This data, along with residual solvent content, residual inorganic analysis, moisture content, etc. is used to qualify a substance as an in-house reference standard.

Once this is accomplished, a full report and Certificate of Analysis (COA), along with the appropriate data and documentation is then issued for each in-house reference standard.

There are many processes – governed by the FDA, as well as in-house standards – that companies manufacturing APIs and other substances must go through. Perhaps one of the most critical of these is developing complete reference standards. This provides the benchmark for purity and safety which is the benchmark for medicines sold in the U.S.

On our blog, we have plenty of articles about various aspects of API manufacturing, ranging from [“The Role of Calibration in Ensuring Safe Measuring Instruments for API Manufacturing”](#), [“Do's and Don'ts of API Technology Transfer in Phases 1, 2 and 3 Clinical Trials”](#) and [“Internal Auditing: A Sound Business Practice to Ensure Successful Project Outcomes in cGMP Manufacturing.”](#)