ChromaDex CONNECTION

analytics consulting ingredients standards

Tech Tip 0026 - *cGMP Reference Standard Requirements*

In 2007, the U.S. Food and Drug Administration released the final rule for Current Good Manufacturing Practices (cGMPs) for Dietary Supplements (21 CFR Part 111). The cGMPs establish requirements for the manufacturing, labeling, or holding of Dietary Supplements to ensure their product quality.

> ***Subpart A – General Provisions***
> *Quality means that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition, and limits on contaminants, and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration…*

Since the use of reference standards and reference materials in the analytical testing of dietary supplements directly affects the quality of such dietary supplements, it is not surprising to see that the cGMPs have requirements for the selection of reference standards.

> ***Subpart J – Production and Process Control System: Requirements for Laboratory Operations***
> *Section 111.315, What are the requirements for laboratory control processes?*
>
> *You must establish and follow laboratory control processes that are reviewed and approved by quality control personnel, including the following: (d) Use of criteria for selecting standard reference materials used in performing tests and examinations*

It is important to note that the cGMPs do not establish the criteria by which you should select reference standards neither do they require the use of compendial reference standards. Instead, they do require that you establish appropriate selection criteria yourself. An effective means of complying with this provision is by establishing and following a Standard Operating Procedure (SOP) for the selection of reference standards and reference materials for use by your analytical laboratory department.

It is up to each company to establish their own procedure and requirements for the selection of reference standards. As a reference standard supplier, we would like to make some suggestions for your consideration. These criteria are of top importance to include in your SOP:

- Extent & suitability of characterization of the reference standard
- Supporting documentation provided with the product
- Vendor's reputation & supply history

Extent & Suitability of Characterization

The purpose of a reference standard is to calibrate instruments and quantify samples so arguably the most important consideration for reference standard acceptance criteria is the extent and suitability of the characterization process used by the reference standard supplier. Your main concern should be that the vendor has adequately tested their product to ensure its identity and total purity. Suitable analytical techniques used in each case can vary by compound but an orthogonal approach, where

each property is measured by complimentary techniques, should be used to ensure complete characterization. Reference standard suppliers should willingly supply details on how they test and verify the characteristics of their products. Appropriate analytical techniques that can be used in reference standard characterization include:

Identity Verification

- Nuclear Magnetic Resonance (NMR)
- Proton & Carbon NMR
- 2-Dimensional NMR spectroscopy
- Mass Spectroscopy Analysis (MS)
- High Performance-Thin Layer Chromatography (HP-TLC) for Botanical Materials

Total Purity Calculation

- High Performance Liquid Chromotography (HPLC)
- Gas Chromotography (GC)
- Karl Fischer water titration
- Headspace GC for residual solvent content
- Proton & Carbon NMR
- 2-Dimensional NMR spectroscopy
- High Resolution MS
- Quantitative NMR (qNMR)
- Elemental analysis (CHN)

Several analytical techniques that are appropriate for fine chemical testing such as chemical titration, single spot Thin Layer Chromatography (TLC) and Loss on Drying (LOD) are not considered fit for purpose in the characterization of reference standards due to their greater inherent error.

Although not strictly required, showing that a selection of products from a reference standard vendor are comparable to compendial reference standards can be an effective component of your selection criteria. For this reason, ChromaDex has performed traceability testing on a select group of reference standard lots and provides that data free of charge to our customers wishing to show compendial traceability as part of their selection criteria. In addition, ChromaDex offers a select group of chemical reference standards that are fully verified by a trusted pharmacopoeia, the American Herbal Pharmacopoeia (AHP). These products have been confirmed by this independent third party group and carry the AHP-Verified mark.

ChromaDex utilizes an orthogonal approach to reference standard characterization. We offer three product grades with varying levels of testing to suit the technical and budget requirements of our clients. More information on ChromaDex product grades and which analytical techniques are used can be found in Tech Tip 1: Reference Standard Product Grades.

Supporting Documentation

A certificate of analysis (COA) should be provided by your supplier for each reference standard lot they produce and this documentation should be automatically provided with each purchase. This COA not only provides information about the material but it ideally should give transparency of the entire

characterization process, testing performed, test method used, and data obtained and results calculated for the specific lot in question. Reference standards should also be supplied with expiration dates and storage recommendations. If the vendor does not provide certificates or those certificates and data are presented in an opaque manner, this is cause for concern.

ChromaDex believes in full disclosure and transparency of our characterization process. We include details and results on the product COA for the analytical methods used to test each batch. We offer three product grades with their varying levels of testing and appropriate uses clearly explained in Tech Tip 1: Reference Standard Product Grades. Please contact us if you have any questions about or product grades or certificates of analysis.

Vendor's Reputation & Supply History

An assessment of the reference standard vendor's reputation in the market is an important indicator of the suitability of their products for use in your quality testing. For vendors with large product lines, it can be important to consider each product line or brand independently. For instance, you should pay attention to which products are designated as reference standards as opposed to fine chemicals for general laboratory use. If the vendor does not market their product for your use as a reference standard or reference material, that should be a cause for concern and further investigation. Similarly, the vendor's history of supplying quality reference standards to your company can be an important factor.

ChromaDex is a trusted source for phytochemical reference standards since our founding in 1999. Designation between reference standards and fine chemicals are clearly made in our literature. We offer three product grades with their appropriate uses clearly explained in Tech Tip 1: Reference Standard Product Grades. Please contact us if you have any questions about or product grades or certificates of analysis.

We hope that this Tech Tip has been helpful to you in establishing your procedures. Our core competency is the isolation, development, and characterization of phytochemical reference standards for the Dietary Supplement industry. We also offer cGMP consulting services to further guide you in your compliance process. Please contact us for further assistance and any questions you may have.