Residual Solvents: the Neglected Quality & Safety Attribute

By Joy Joseph

ChromaDex®

10005 Muirlands Blvd, Suite G, Irvine, CA 92618
+1-949-419-0288 | sales@chromadex.com

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All three versions of the US good manufacturing practices (FDA 21 CFR Parts 110, 111 and 211) require that ingredients used in the production of finish products and finished products themselves be controlled and tested for limits of contamination. In this writing we will specifically address the current lack of attention to the identity and testing for residual solvents in ingredients and products within the Dietary Supplement industry.

Residual solvents, as defined by the US Pharmacopeia, are organic volatile chemicals that are used to produce or are produced in the manufacture of drug substances, dietary ingredients or excipients and in the preparation of finished products, both pharmaceutical and dietary supplements. Often these chemicals are not completely removed by the manufacturing processes utilized to produce finish products. Thus some level of residual solvents may be present in both the ingredients and finished products and their presence should be measured and justified.

Since residual solvents are not usually present to provide a benefit to the consumer, they should be removed to meet product specifications and good manufacturing practices. Remaining amounts present should be supported by safety data published by a qualified authority. Because they do not provide a benefit to the consumer and are not a part of the quality attributes, residual solvent levels are classified as contaminants and impurities.

Qualified authorities such as the United States Pharmacopeia, Canadian Natural Health Products Directorate, European Compendia, Chinese National Institutes for Food and Drug Control, the Australian Government Therapeutic Goods Administration, the Japanese Compendia and the International Pharmaceutical Excipients Council have published requirements for assuring product quality, specifically including references to limits testing for the presence of residual solvents.

Much effort has been invested by the scientific community in the research of residual solvent toxicity and development of guidelines for their limits, yielding a considerable volume of various publications on the topic. Residual solvents have been categorized as either Class 1, 2 or 3 depending on their individual toxicity profiles and acceptability of use. Risk assessments have been performed to determine tolerable daily intakes (TDI) and exposure limits of toxic chemicals by the International Program on Chemical Safety (IPCS). The World Health Organization and other national and international health authorities and institutes use acceptable daily intakes (ADI) for their guidelines. Permitted daily exposure (PDE) that is defined as a pharmaceutically accepted intake which should not to be confused with acceptable daily intake, since the ADI and the PDE can be different for the same chemical. All of the compendia have copies of these lists available for use in determining testing strategies.

Despite clear requirements and guidance from a wide array of regulatory and compendia sources, we repeatedly find that residual solvents testing is not adequately performed in the dietary supplement industry. Companies can choose to perform the testing in their own quality control laboratory or through the use of qualified contract testing laboratories. However, our work consulting with our clients as well as discussions with other industry contacts, shows that a lack of residual solvent testing remains very common in the industry.

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One of the reasons that residual solvent analysis is not being routinely performed may be due to the complexities of identifying the most appropriate test method for particular solvents. The 2014 USP Official Compendia speaks to analytical procedures for determining identity and quantification of residual solvents in the General Chapter <467>. In this chapter a procedure is provided for identification, control and quantification of residual solvents. The procedure addresses optional modifications, recognizes other appropriate validated procedures that may be employed and addresses potential precautions that may cause errors in reporting result. Other compendia, as well as the 2008, ICH Impurities, Guideline for Residual Solvents, have also addressed testing challenges.

While the USP and other compendia provide options for testing based upon acceptable standards and limits in order to reduce the overall laboratory testing burden, under no circumstance is it acceptable to ignore residual solvent identity and quantity in ingredients and finished products. Current focus by FDA investigators has been on assurance that correct ingredients are being used that meet prescribed quality standards and residual solvent requirements have not yet been addressed as a high priority. This may be due in part to the fact that USP and other compendia suggest that the quality be primarily addressed by the manufacturers of ingredients since they are the ones required to have approval for the solvents used in products for human or animal consumption. However, in the USP Dietary Supplement Compendia, there are a number of monographs for botanical extracts that call for residual solvent testing.

Laboratories need to be adequately equipped with instrumentation and qualified scientist who are capable of implementing compendia test methods or developing validated methods that will provide accurate data identifying and quantifying those impurities that may be contaminating products intended to be ingested that could be sources of toxicity. While gas chromatography is suggested as the preferred method in most cases, analytical techniques and chemist competence both play a role in achieving valid test results. Valuable information can be found in multiple publications with solutions to the influences from physicochemical properties of the various solvents and on the proper use of head space analysis, both of which usually present problems for analyst.

As the Food and Dietary Supplement good manufacturing practices continue to evolve and the Food Safety Modernization Act finalizes the proposed regulations for a safe supply chain, more emphasis will be placed upon these processing and contaminant controls. These activities undoubtedly will move limits testing for residual solvents into a more prominent place in testing for quality attributes.

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