

Lancaster Labs develops extractables database for LC/MS analysis

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The FDA has been focusing effort into evaluation of potential adulteration of drug products due to contact with packaging and closure systems, sample delivery devices and components utilized in the manufacturing of the product. Packaging includes components such as vials, caps and stoppers. Drug delivery devices include nebulizers, syringes, medical devices and various types of inhalers. Components utilized during the product manufacturing process include filters, tubing, fittings, connectors, bioprocess bags, bioreactors, etc.



In an effort to assist our customers with identification of extractable compounds detected by LC/MS analysis, Lancaster Laboratories has developed a non-volatile compound database.

Extractables are compounds that can be extracted from a component under extreme conditions such as the presence of harsh solvents or elevated temperatures. Leachables are compounds that leach into the drug product from a component through direct contact with the formulation under normal storage or manufacturing conditions. Both extractables and leachables represent possible contaminants of a drug product and therefore need to be evaluated.

Sources of extractable and leachable compounds include antioxidants, antiozonates, UV stabilizers, plasticizers, processing aids, accelerants, coatings, elastomers, inks and vulcanizing agents.

- Antioxidants, antiozonates and UV stabilizers are compounds that are added to polymers to deter possible degradative processes. Exposure to heat, ozone and oxygen can result in differing types of degradation within plastics.
- Plasticizers are compounds added during the manufacturing of plastics to make the plastic softer and improve its flexibility.

- Processing aids are utilized to increase the flowability of plastics.
- Accelerants and vulcanizing agents are compounds utilized in the curing process of rubbers.
- Elastomers are utilized in the manufacture of rubber products allowing them to be relatively soft and deformable.
- Extractable studies are performed to determine which of these compounds can be extracted from a defined component under harsh conditions.

Extractable studies often involve incubation of components in solvents of varying polarity under

high temperature. The resulting extraction solutions are subject to a variety of analytical techniques to characterize the extractable profile. The analytical techniques utilized include gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/mass spectrometry (LC/MS). Components can also be subjected to an acid digestion and analyzed for inorganic extractables by inductively coupled plasma analysis (ICP).

GC/MS analysis consists of two different types of sample introduction: headspace (used for the evaluation of volatile compounds) and direct injection (used for the characterization of semivolatile compounds). GC/MS utilizes electron impact ionization producing a mass spectrum displaying a unique fragmentation pattern for each compound of interest. These mass spectra can be compared to various commercially available databases to assist with the identification of the compound. Databases utilized at Lancaster Laboratories include the NIST98K and Wiley databases.

LC/MS is utilized to evaluate extracted solutions for non-volatile compounds. LC/MS utilizes various soft ionization techniques that result in a mass spectrum primar-

ily displaying the molecular peak. Modes of ionization for LC/MS include electrospray and atmospheric pressure chemical ionization. Currently, no commercial databases are available to assist with the identification of LC/MS generated mass spectra.

Lancaster Laboratories has purchased a variety of standard materials based off compounds commonly used in the manufacturing of various components utilized in the pharmaceutical industry. Lancaster Laboratories has generated mass spectra for all of the purchased standards, including various antioxidants, antiozonates, UV stabilizers, processing aids, plasticizers and brighteners. The database currently consists of greater than 100 compounds. Lancaster also has a vast array of mass spectra from various other compounds utilized in manufacturing where standard material may not be available.

All extractable compounds have been analyzed utilizing electrospray ionization in both the positive and negative modes along with atmospheric pressure chemical ionization in the positive mode. Unknown extractable compounds mass spectra generated by LC/MS analysis will be compared to the

Lancaster Laboratories generated database to assist our scientists with identification of the extractable. While the database will assist Lancaster Laboratories scientists in determining identification of unknown compounds, the Lab cannot guarantee identification during the course of the extractable leachable study.

If a customer would require further work be performed to attempt identification of unknowns, then the Lab would recommend utilizing either its LC/MS Time-of-Flight or LC/MS Orbitrap technology to determine an accurate mass of the unknown.

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