Cambridge Polymer Group

Material Science in ISO 10993-18 Testing

By Dr. Stephen Spiegelberg

Summary

Chemical risk assessment in medical devices is normally required for new regulatory submissions and is a critical tool in determining the safety of medical devices. This testing follows the requirements of ISO 10993-18 "Biological Evaluation Of Medical Devices - Part 18: Chemical Characterization Of Materials." This application note discusses some of the complexities of ISO 10993-18, and how an understanding of material science plays an important role in data interpretation.

Background

Chemical characterization of materials according to ISO 10993-18 is essentially assessing the chemicals that may leach out of the device when it is directly in contact with a patient, or when leached chemicals contact another component that comes in contact with the patient, i.e., indirect patient contact. In chemical characterization at its simplest, medical devices are extracted in suitable, physiologically relevant solvents, and the extracted compounds are identified and semi-quantitated when they are above a specified level. These compounds are then analyzed by a toxicologist to assess their potential for causing biological harm based on toxicological databases and models.

This extraction collection and analysis is instrument-intensive, requiring sophisticated gas and liquid chromatography systems, inductively-coupled plasma spectrometry systems, and sometimes ion chromatography and gel permeation chromatography. However, although these modern instruments are superb at generating long lists of potential compounds, just possessing these instruments is insufficient to adequately perform a 10993-18 study, particularly on a medical device that contains polymeric components.

Cambridge Polymer Group's ISO 10993-18 Approach

As defined in the standard, a key component of a good 10993-18 study is the initial assessment of the build of materials (BOM). The BOM is a comprehensive list of the materials that are both in the finished product, and that are used to manufacture the device. The device materials include polymeric compounds, fillers, pigments, stabilizing chemicals, metallic components, ceramics, coatings, and packaging materials. Manufacturing materials include contact surfaces that cut, hold, and mold the materials, as well as polishing compounds, release agents, grit blast, lubricants, coolants, cleaning agents, disinfectants, and other materials that come in contact with the device during its manufacture. Our scientists also ask about

process steps which may transform chemicals, which can include temperature, mechanical stress, radiation exposure, and chemical reactions.

This information is used for three reasons:

1. To help identify the suitable extraction conditions for the extraction procedure.
2. To identify potentially-hazardous compounds that may require targeted chemical analysis (e.g., a chemical analysis that specifically looks for a particular compound, rather than a general screening test).
3. To help to identify unknown compounds based on their chromatographic signature.

Items 1 and 2 are performed during the test method development stage of a 10993-18 project. Item 1 relies on a deep understanding of the materials and end-use. Picking the wrong extraction method may generate unrealistic extractions or degrade the device in a manner not relevant for the end-use.

Item 3 is important during the data analysis stage, after extractions have been run through gas and liquid chromatography. Depending on the device, a few hundred compounds may be generated by the instrument and need to be identified. Many of these compounds may not exist in commercial or laboratory-built databases, particularly when these compounds are the result of degradation or chemical reaction. This is the point where experience in material science comes into play.

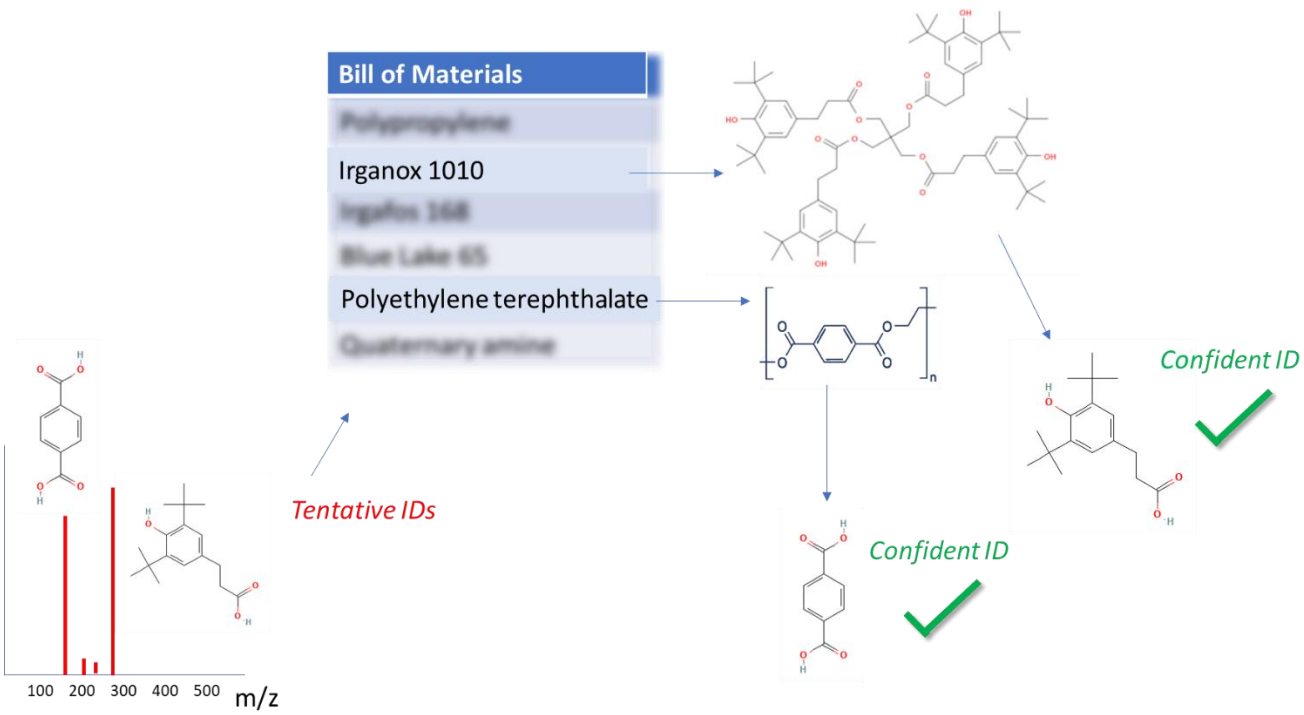

Figure 1: Work flow to improve confidence in compound identification by examining the bill of materials and potential by-products of the BOM constituents.

Cambridge Polymer Group's skilled analytical chemists will gather information about molecular weight and empirical formula from the chromatography, based on the identified peaks and potential adducts, and will consider the strength of the signal in the different detection modes used. They will then look at the BOM and consider the transformation products that may be generated.

Potential chemical structures that match the molecular weight, empirical formula, and BOM are then constructed from chemical databases and considered based on the BOM and transformation products, and how these compounds would

behave in the orthogonal techniques used[1]. Compounds with identification only based on fragmentation pattern or database match to the mass spectrum are assigned a tentative identification. Compounds with identification bolstered with molecular weight, elemental composition, or orthogonal technique information are assigned a confident identification.

An example of this workflow is shown in Figure 1 where compounds identified by chromatography can gain confidence in their identification by considering the bill of materials (BOM) and their expected by-products, along with examination of the results of other analytical techniques used. Confirmed identification is normally assigned when the actual identified compound is also run as a reference compound.

This analysis results in a table of compounds, their identification confidence, and their semi-quantitation based on model calibration compounds, that is then used by our toxicologists to provide a toxicological risk assessment. A key step in this whole process is an understanding of the chemistry of the client's manufacturing process so that identification of unknown compounds can take into account what compounds are likely to be present, and what compounds can be ruled out.

About Dr. Stephen Spiegelberg

Dr. Stephen Spiegelberg is the co-founder of Cambridge Polymer Group. With a career spanning over 25 years, Dr. Spiegelberg has consistently demonstrated an unwavering commitment to ensuring the safety and compatibility of medical devices and materials. At Cambridge Polymer Group, he directs a team of scientists performing contract research, analytical testing, failure analysis, and product development for the biomedical community and other fields. In 2022, ASTM International presented Spiegelberg with the Award of Merit, their highest recognition for distinguished service, for his contributions to the ASTM F04 Committee on Medical and Surgical Materials and Devices. He received his BS in Chemical Engineering from UW-Madison, and his Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology.

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[1] Orthogonal techniques analyze the same compound with different analytical tools to explore different aspects of a compound. This approach is useful to get confirmation about a tentative chemical identification.