ELSIE Supplier Forum

WORKSHOP REPORT

Extractables & Leachables: Sharing Supply Chain Knowledge in the Current Regulatory Environment

12 October 2018 - Göttingen, Germany

Introduction

Sartorius Stedim, Göttingen Germany

The ELSIE Supplier Workshop, *Extractables & Leachables: Sharing Supply Chain Knowledge in the Current Regulatory Environment*, was held on 12 October 2018 in Göttingen, Germany at Sartorius Stedim.

Dr. Rene Faber (Vice President Marketing Filtration Technologies, Sartorius Stedim) welcomed the participants and provided opening remarks. He reflected on the importance of the ELSIE endeavor that "companies should not compete on safety." He noted the importance of the workshop in advancing discussions on enhancing knowledge about components and materials across the supply chain, including understanding risks and customers' solutions. The supply chain does not end with the supplier; rather, competencies should be shared across the supply chain. He mentioned the current lack of a harmonized industry approach to extraction studies, and that such studies are not a tick-box exercise.

The theme for the workshop was information and data sharing across the supply chain, including final product manufacturers. Presentations sparked a number of discussions and ideas about ways to advance knowledge sharing.

Examples of Data Sharing Platforms in the Supply Chain

The database for Not Intentionally Added Substances (NIAS) provides an example of how suppliers are sharing NIAS information in a blinded process, to increase knowledge in the supply chain and to assist in meeting regulatory requirements. The presentation provided much "food for thought" regarding what kinds of information could be effectively shared, barriers to sharing, and potential solutions. Many of the NIAS database users are in the food and food packaging industries. NIAS information is generally from extraction studies using food contact simulants. The data is stored as tables in Excel, providing a simple and familiar platform for users of the database. The data could be used by materials or component producers, and

Participants of the ELSIE Supplier Forum Workshop

possibly by their testing labs. One question discussed was whether such database could be useful in identification of unknowns. Participants noted that the NIAS Database can provide a materials list with reasonably expected NIAS compounds; in cases of unknowns, often CRO labs will have extensive databases that could potentially identify these. Many of the database entries include polyamides and their associated data. The database does not currently include identification confidence levels. Provision of identification level is a point of discussion for ELSIE with respect to data that it is collecting for an ELSIE Knowledge Base.

The NIAS database entries are updated periodically by contributors, including updates to existing materials and uploading of new materials and substances. NIAS lists could be larger than what is represented in the database, depending on the reporting limit.

Participants noted other examples of data sharing through industry databases, such as those used by large retailers and the automobile industry database (IMCD) managed by consortium of auto makers and their suppliers. For the automotive industry there is an understanding of what information must be shared, as well as standardization on how the information is managed and secured.

A participating supplier company noted that their questionnaire to their suppliers is not yet associated with an internal database, although a future goal is to include the supplier information in a supplier portal that would link relevant information. A significant barrier is to convince very large suppliers to respond to the questionnaire. Partnerships along supply chain could be important in driving this sharing model.

Data Sharing and Collection: Practical Considerations

Participants discussed whether the self-updating process would potentially be a barrier to keeping companies interested in contributing data. Accessibility to the right information as well as confidentiality concerns could also be barriers to effective information sharing.

Participants noted the important baseline of quality that food contact risk considerations and materials evaluation can lend to pharmaceutical materials quality and safety considerations.

Participants discussed what kinds of information seems practical and feasible to share, as well as processes that could lower the barriers to sharing. Mr. Hmiel's (Global Director of Regulatory Affairs, Teknor Apex Company) presentation noted some potential limits to data sharing, which may include trade secrets and other company policy considerations. Supplier participants noted that generally they are not able to provide composition information, and that such requests also seem impractical since the key information is what actually is seen as an extractable or leachable. Extraction information could have lower barriers to sharing, assuming supplier has done and supports such testing. In the Borealis case study, the company provided composition information under a confidentiality agreement.

Company culture is large determinant to sharing as well. Specific, rather than vague, requests would be helpful. An honest broker (3rd party), who would assist in confidentiality assurance and blinding would also help. This honest broker model is similar to European food contact model for sharing information, and somewhat similar to the US FDA DMF system. It was note that FDA does ask for composition information in the DMFs, but such information will only be seen by FDA, and not the customers. More companies are aware that data must be traceable and are putting internal programs in place to establish this.

Mr. Hmiel presents on data sharing and collection

Participants discussed the use of tools to predict decomposition as well as extractables and leachables, and noted that expert knowledge would be key to deriving and using this information, not necessarily composition information. Such information could also be culled from the literature. Although not all degradative pathways would be covered, quite a lot of useful information could be found.

Production and processing equipment are also key sources of potential leachables. Elastomers also present a different set of challenges. There are a large number and variety of elastomer grades. Elastomers should be included in these discussions, although the scope of work that could be addressed may at first need to be limited.

Regulatory and Compendial Overview

Dr. Stults (Principal, C&M Technical Consulting) provided an overview of the existing regulatory landscape. Participants then shared some perspectives on regulatory issues and recent developments. For example, it was noted that regulators have asked for statements on specific types of chemical substances from packaging and/or excipients. FDA has recently asked for melamine statements related to polymers, whereas in the past, this request was associated with excipients. In some cases, such information, with respect to polymers, has been hard to obtain from suppliers. A participant supplier noted that his organization had not received such a request and do not ask for melamine information in their own questionnaire's to their suppliers, as this substance would not be expected in the materials they work with. However, his company is seeing questions about optical brighteners, which are used to mask recycled materials, i.e., provides clear blue for PVC.

European and US regulatory expectations for materials differ. In Europe, materials must meet the European Pharmacopoeia (Ph. Eur.) requirements for that material. If there is no Ph. Eur. chapter for a given material, then companies must perform a characterization study, which regulators will review. In the past, USP did not have chapters or requirements for specific materials, but USP 661.1 now provides this. It is still to be seen how FDA will use 661.1 in the review of submissions. The implementation for USP 661.1 and 661.2 is currently 1 May 2020. These chapters will apply to legacy products as well.

USP 661.2 states that if component is tested to 661.2 then don't need to do 661.1 testing. USP 661.1 says that if a material meets 661.2 requirements then material can be used in that component. Whether this material can then be used in a different component, will depend on the application of that component.

USP 665 will be published in the Pharmacopoeial Forum in March 2019. A workshop to discuss the draft will be held at USP on 16 April 2019, and the comment period will end in May.

ELSIE Knowledge Base and Supplier Perspectives

Dr. Egert presents on the ELSIE Knowledge Base Solution

Part of the ELSIE Knowledge Base vision is that the system would include hierarchies of information with relevant tests and results linked to the appropriate levels, e.g., system levels, substance levels, etc. For example, 661.1 testing and results would be at material level, tox papers or regulations at substance level; all within a single integrated system. Dr. Egert (Research Scientist, Boehringer Ingelheim and ELSIE Knowledge Base Chairman) noted that the goal is to establish an effective platform for information flow in the supply chain, and such tool will need to be relational. ELSIE envisions a step-wise approach to Knowledge Base development. This would include collection of extraction study information and linkage to safety information in the first instance; links to method information and information on lab samples if available would also be needed. Modeling could come later, for example, using information that is retrieved from the database. User interface would be web-based.

It was noted the initial prototypes allow to linkages between substances, safety information and materials information (where the substance is found), and includes hierarchies, e.g., generic material families, material grades. Test procedures, references, regulations are also begin collected from the public domain and from ELSIE members.

ELSIE in future could sponsor toxicological and/or extraction studies on substances and materials of concern and include the tests and output in the database.

Some suppliers, like those developing manufacturing systems, are dealing with assemblies of components, which introduces some complexities, including complex supply chains. Thus cross-supplier collaborations and the Knowledge Base project is of value. Compounders have similar situations – multitude of suppliers, multitude of regulations, much extraction information.

Suppliers would be interested in seeing further information, and potential prototypes, on how the ELSIE Knowledge Base is envisioned to work, and would then be in a position to provide further substantive feedback.

It was noted that making the uploading and reporting of information in such a database would help to drive use -- gathering and transferring complex data from a number of different stakeholders, should be made as easy and straightforward as possible.

The Path Forward

Participants noted several areas of mutual interest and agreed value, which ELSIE and the Supplier Forum should advance:

- Continue to share experiences and expertise in how companies are managing and sharing materials related information in the supply chain
- Share prototype examples and information on the ELSIE Knowledge Base with Supplier Forum members to obtain supplier perspectives on the database's function and application
- Discuss sharing of exemplar data from suppliers – identify types of information suppliers would be willing to share; conduct preliminary sharing
- Identify other cross-supplier, and supplier-final product manufacturer collaborative activities that the Forum can develop to assist companies in managing and obtaining value from supply chain information