ELSIE WORKSHOP
KNOWLEDGE SHARING AMONG SUPPLY CHAIN PARTNERS

12 June 2017
Biogen - Cambridge, Massachusetts

The Extractables and Leachables Safety Information Exchange (ELSIE) consortium held a workshop on *Knowledge Sharing among Supply Chain Partners* 12 June 2017. ELSIE member company Biogen, hosted the meeting at its Cambridge, MA headquarters. This document summarizes the discussions at the Workshop.

The morning session was comprised of presentations and discussions on a wide range of topics related to extractables and leachables given by representatives from ELSIE member companies, USP, Xavier University, and various suppliers (Sartorius Stedim, West Pharmaceutical and Sabic) and the afternoon session was devoted to interactive, round table discussions to address (i) structure of a supplier forum; (ii) mechanisms for data sharing; and (iii) managing global materials certification requirements. This Workshop represents a milestone for ELSIE as an important step toward establishing a supplier forum within the ELSIE consortium.

I. PRESENTATION HIGHLIGHTS

At the outset of the Workshop, ELSIE Vice-Chair, Kim Li (Amgen), provided an overview of the consortium's history and priority activities. Additional presentations focused on mitigation of supply chain risks, maintaining supply chain integrity, the challenges, complexities, and realities of the polymeric supply chain, a summary and update by USP on <665>, <1665>, and <661>, and suppliers' perspectives on the value proposition of supplier engagement with ELSIE.

The Amgen case study demonstrated how information sharing and fostering partnerships with suppliers has the benefit of providing information of value to suppliers, e.g., real-time feedback that would also help suppliers improve their products. Amgen modified supplier agreements to include provision of particular types of supplier data, as well as tighter specifications, and in-process data. Suppliers viewed this as the "price of entry" to do business with the company, realizing the increased value for their customer and their own business. Amgen also presented on some of the "big data" tools they continue to develop to support their partnerships with suppliers.

Xavier University's initiative on good supply practices is focused on both suppliers and final product manufacturers, and includes FDA input. Strong communication concepts are a key focus. The initiative is considering platforms, such as USP, for publishing its recommendations. The importance and power of communication was demonstrated in a comparison between the auto industry supply chain and pharma supply chain in which the auto supply chain tends to be transparent about information and costs while the pharma chain seems to be less transparent. Currently 10 pharmaceutical companies are conducting a feasibility study, looking at internal coordination within companies among, e.g., purchasing, quality, and balancing speed to market with supply chain integrity (safety, efficacy, integrity, compliance). The pilot has demonstrated that understanding self-risk is important.

During the supply chain discussion it was noted that the universe of "medical-grade" polymer suppliers is relatively small, and many downstream suppliers are likely working with the same upstream polymer suppliers. While material suppliers may have a strong data/information package, this data should only be considered a guide since downstream suppliers may be adding additional chemicals or treatments;

the end user will need to consider this and likely conduct further studies. There are also conversion processes and additives introduced at the polymer supply level as well as downstream, depending on the requirements of particular applications, so even with a relatively small universe of resin suppliers, a wide variety of materials are being developed. Composition profiles of natural products used as the base for some components are also very difficult to control. It was noted that downstream suppliers are limited by their own trade secret policies, as well as agreements with their own suppliers and thus are unable to provide extensive information on materials or components, e.g., full extraction profiles, composition information (which pharmaceutical and device manufacturers would like to see), without an alternative agreed legal framework in which to operate.

Dr. Hunt (USP) noted that suppliers do not have to follow USP standards and that these standards are legally applied only to pharmaceutical manufacturers. However, practically speaking, suppliers should follow them given current business and regulatory needs. The previous version of USP <661> (in the USP 38) is now the "current" version; this delay in implementing the new <661.1> and <661.2> chapters is due to revisions that will be made to these chapters including the removal, at FDA request, of the "grandfather" clause excluding legacy products. Early adoption of <661.1> and <661.2> is an option, however, because many companies have already started implementing these chapters. FDA has expressed general support of these chapters (except for the grandfather clause). Current official chapters are in the USP's Revision Bulletin, and will be included in the USP 41 in November 2017.

II. Supplier Engagement with ELSIE – Examining the Value from the Supplier Perspective

The following summarizes the key discussion points, benefits, and questions discussed during the Workshop regarding the value proposition of a proposed supplier forum within ELSIE, providing the opportunity to collaborate and share information:

- Improve understanding of what is achievable by various suppliers
- Consider a member at large from the Supplier Forum that can provide feedback to the Board; suppliers would be contributing funds as well as participation and information
- Share data through the ELSIE Knowledge Base
    - Suppliers indicated willingness to provide data in the Knowledge Base, with some suppliers indicating they would like to use the Knowledge Base for their own research
    - Benefits of sharing physico-chemical information including degradation information, for use in exposure calculations
    - Consider a feature to highlight whether a material doesn't include any compounds that are flagged as problematic in REACH or ROHS, or indicates that materials is USP tested/compatible; or tested according to BPOG protocol
    - Consider including characteristics of "medical grade" in the knowledge base; or use the information to work toward an understanding of medical grade
- Provide a mechanism and forum for joint research
    - Explore how to apply information from one type of study to other studies, e.g., for single-use system component studies, there are numerous materials and devices with diverse uses --

defining extraction conditions is difficult and doing extraction studies on all components is not feasible. Possible to apply same studies from a large filter to smaller filters? There is currently no algorithm for extrapolating from various materials to an entire device.

- Address how packaging interacts with the drug product. Need to balance significant reduction in possibility of leachables with material functionality. Suppliers are interested in being able to assess toxicology information; and many are in need of biocompatibility information. Often ultimate application of a material precludes the use of a material that is easily manufactured.

III. Supplier Engagement with ELSIE – Examining the Challenges and Realities

The following bullets capture some of the key discussion points, benefits, and questions discussed during the workshop around potential challenges and questions raised by suppliers. In the establishment of the new forum, ELSIE will work with suppliers to address the points raised.

- Could bias develop towards materials or vendors based on information provided?
- Exposure of trade secret information
- Implications and assumptions when there is a high degree of uncertainty (when low or no information, assumptions fill void);
- New expectations for change control; new requirements for notification of high risk compounds (e.g., Prop 65 in CA) [how to deal with new information that changes the regulatory status of a compound – need to be certified to more and more compounds in products];
- Prohibiting use of certain raw materials (based on understanding of profile from an unreacted state) – not considering processing, reaction of additives, consequent disappearance of compounds in the non-native state.
- Tracking different levels of conversion of a material through steps in the supply chain in the database will be a challenge.
- Aspects of DMF information could potentially be shared; this might include ingredient information.
- Use of extractables information provided by suppliers. Will end product manufacturers place this information into their submissions, when such information is meant for risk assessment with respect to their particular product, with expectations for further analysis?
- Only experienced personnel should have access to the Knowledge Base, to avoid misuse. Suppliers expressed concerned that customers could, e.g., select materials based purely on data that is not relevant to the actual quality of the material, with un-informed decisions effecting supplier business. Onus and requirement for only SMEs to access data should be put on the Knowledge Base users (not ELSIE).
- Specific "know how" and experience is valuable to suppliers and would be difficult to share.

IV. Small Group Discussion Sessions

The following summarizes output from the small group discussions addressing (i) mechanisms for data sharing; (ii) structure of a supplier forum; and (iii) managing global materials certification requirements.

Mechanisms for Data Sharing

- Extractables data provided needs to be accompanied by appropriate physical-chemical data; which could then be used for, e.g., exposure assessments. Database would be of high value if it included algorithms for, e.g., assessing physico-chemical information. Database would also be of value if it contained qualitative information on extractables, as well as method information.
- Two tiers of data – open public information and "restricted" or proprietary information. Sharing of open/public information and information considered "low risk" by suppliers (which can also include method information or links to method information if publicly available) can be done as a first step; look for gaps and then focus on gaps for areas of sharing proprietary information. Users of a database containing shared information should be able to compare across information pertaining to the same material, i.e., combining or easy cross-referencing of data is needed. A pilot program was suggested that could start with materials considered "low risk" (not latest/greatest).
- Data from recognized protocols would be helpful to include in a database, e.g., data derived according to known methods (e.g., BPOG, USP, other).
- Need data from finished components (packaging, systems, device), which may include n-1 suppliers. It is good to have information from n-2 and other upstream suppliers as well.

Structure of a Supplier Forum

When to Start	▪ Consider a pilot with suppliers for 2017 – Allows participants to ascertain value – Develop agreements and legal documents for forum – Formally establish forum in 2018
Fees:	▪ Established to support forum and remain cost neutral to ELSIE. Since not all Suppliers indicated interest in access to the Knowledgebase, the proposal is to have a separate/optional fee for access to the Knowledge Base.
Interest and Ability to Participate	• Dependent on value proposition to my company • Location and well defined meeting agendas
Types of Members	▪ Suppliers of materials and components that contact Drug Product (include N-1 and upstream) ▪ Suppliers of materials and components that contact Drug Substance ▪ Service Providers ▪ Medical device component suppliers ▪ Exclude Associations comprised of members who are eligible for ELSIE or Forum membership

Value Proposition	▪ Each supplier type (and supplier) has different value proposition for participation ▪ Information sharing and access via Knowledge Base ▪ Best practice and common requirements; economic and business trends; supplier workshop or discussions session sponsorship opportunities. ▪ Joint regulatory engagement ▪ Help define industry standards ▪ Access to customers/end user community – Surveys, webinars ▪ Important to get to "right level" within companies ▪ Establish relationships for cross-promotion and potential collaborations
When/how to Engage Regulators?	▪ Leverage ELSIE relationship with regulators but probably shouldn't seek to have them join "Supplier Forum" ▪ Forum should first be established to determine common areas and consensus viewpoints on activities and priorities ▪ Be sure to engage **internal** quality assurance and control functions

Managing Global Materials / Certification Requirements

- What global compliance statements and standards are truly relevant in the extractables/leachables space; not all are relevant in every situation and shouldn't be "tick" boxes.
- What are "Pharma Grade" and "Medical Grade"? Different definitions exist. Some companies are doing more than others to be "medical grade." Suppliers have adopted standards to meet what they think is medical grade, but this will vary across the industry.
- Animal-origin free/GMP – these are regulations that are definitely requirements
- Minimum requirements today: Change Control Agreements (most important) and Biocompatibility. There are a lot of other requirements from different industries: Chemical, Food, and Medical Device that are not directly applicable or relevant for the pharmaceutical industry. The pharmaceutical industry has utilized these multiple requirements as a starting point only.
- Food contact requirements (21 CFR 177, etc.) are easier, since the formulations are more standard. For pharmaceutical drug products (especially biologics), the formulations are very unique and typically could have a critical effect on leachables.
- Medical Device regulations (ISO 10993) are not relevant to Pharma. Pharma manufacturing needs unique requirements.
- Putting together multiple materials and post-processing (gamma irradiation) makes some of the

earlier raw material testing irrelevant

- For some, even extractable study methods to follow are still not clear: BPOG, USP, BPSA, ASTM, ASME-BPE, etc.
- European Pharmacopoeia 3.1.X – antioxidant limit levels are too high to be relevant for pharmaceutical industry. Suppliers have their own testing and limits.
- Organizations are generally following for Single-Use Systems – BPOG or USP 665; Drug Product Containers – USP <661>; Medical Device – ISO 10993
- Group highlighted that cell toxicity testing needs to be updated to detect leachables that affect cell growth (in bioreactor or for cell therapy). This could be a specific test for biopharmaceutical applications.
- Suppliers are asked by customers to meet/share REACH and ROHS compliance. How relevant are these for the extractables studies arena? Maybe generally relevant to materials quality.