Single-Use News L-e-t-t-e-r-s

December 2014

This periodic newsletter serves as a central resource for information and updates on the exploding role of Single-Use Technologies in the World of Bioprocess Science and includes regular contributions from the following important "lettered" sources (in alphabetical order):

ASME-BPE (American Society of Mechanical Engineers-BioProcessing Equipment), **ASTM INTERNATIONAL**, **BPOG** (BioPhorum Operations Group), **BPSA** (Bio-Process Systems Alliance), **ELSIE** (The Extractables and Leachables Safety Information Exchange), **PDA** (Parenteral Drug Association), **PQRI** (Product Quality Research Institute), and **USP** (U.S. Pharmacopeial Convention)

[See Page 3 for a brief description of each.]

SUT TOWN HALL UPDATE

Seventy-seven industry suppliers and end users attended the *Town Hall Forum on Standardization of Single-Use Systems* at last month's BioProcess International Conference and Exhibition in Boston, MA. The session was led by a panel of six industry professionals who represented the lettered organizations from this newsletter.

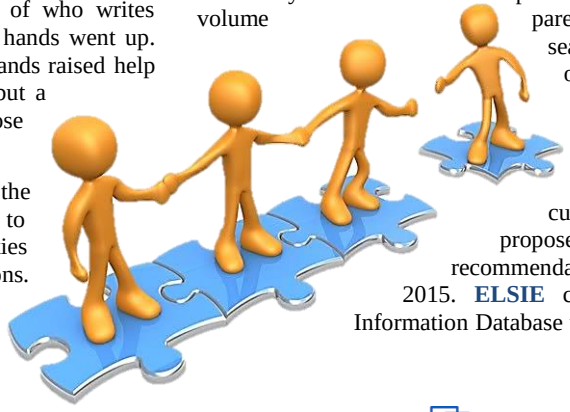
A call for volunteers went out once again during the town hall session, and the balance of the presentation and subsequent discussion focused on current SUT-related collaborations amongst the lettered organizations.

The debate was lively and the response was very positive. In fact, the format of the presentation prompted the creators of this newsletter to change the layout on the second page to better reflect how these organizations are making strides together as opposed to solely highlighting each individual organization's SUT activities.

One of the most important points of the session emphasized the need to collaborate as an industry in order to develop greatly needed standards and guidelines for the SUT community before the government has to step in and do it instead.

There is also a great need for "fresh horses" within these organizations which would create an impetus for this effort by way of novel ideas and new energy. During the Town Hall meeting, Jay Ankers, Chair of the ASME-BPE asked the audience for a show of hands of who writes standards as part of their day job? At least four dozen hands went up. Then Mr. Ankers asked how many of those with their hands raised help write standards for these volunteer organizations? All but a few hands went down. As Mr. Ankers pointed out, those numbers should be equal and they are not. □

Prior to the Town Hall session, representatives of the lettered organizations met in a closed door summit to discuss current SUT-related collaborations and activities amongst and between all of the volunteer organizations. This meeting resulted in a table depicting past, current and future guides, papers, and other tangible results. □



SUT ALIGNMENT UPDATES

LEACHABLES & EXTRACTABLES

Members participating in the Town Hall panels have discussed the need to separate the terms Leachables and Extractables, because they are not always addressed in tandem.

USP is working on the development of several compendial standards: <661.1> for Plastic Materials of Construction, <661.2> for Plastic Packaging Systems and <661.3> for Manufacturing Systems. To support these mandatory chapters, <1663> Assessment of Extractables and <1664> Assessment of Drug Product Leachables are also being developed. **PQRI** is currently developing Recommendation for Leachable & Extractable in Parenterals, which directly references USP and discusses evaluating data. Collaborative activities of PQRI participants from industry, academia and government regulatory agencies have resulted in recommendations for threshold and best demonstrated practices for leachables in orally inhaled and nasal drug products. This guidance has provided manufactures a high level strategic process to assess and qualify the safety of extractables and leachables. In 2009, a work plan was approved for extrapolating these same concepts for Parenteral and Ophthalmic Drug Products (PODP) with considerations of factors i.e. dose, duration, patient population, materials and product characteristics of PODP. The scope of the PODP project includes evaluation of materials commonly found in prefilled syringe systems, small and large volume parenterals, and ophthalmic/blow fill seal containers. These same principles of good science can also be translated to disposable systems in the absence of defined and specific regulatory guidance. Chemists and toxicologists are currently concluding research to propose methodology. The recommendations document is planned for 2015. **ELSIE** continues to populate the Safety Information Database with safety information extractables

toxicology. Additionally, **ELSIE** has prepared three papers on evaluation of results from a controlled extraction study Pilot Program. These papers are expected to be published shortly. The **BPOG** Extractables team is working to make their user requirements and rationale more widely available and a full paper on this effort can be found in the November 2014 edition of *Pharmaceutical Engineering*. They hope this will clarify as many points as possible and help suppliers work with their requirements. An effort on end user practices for leachables is expected to be released this year. **BPSA** has actively worked with **BPOG** in an as-yet unsuccessful attempt to produce a consensus document representing the interest of suppliers as well as users and continues to work closely with **ASTM** in development of a consensus standard. **ASTM** members have formed a working group *WK43975 New Practice for Determining and Characterizing Extractables used in Single-Use Applications*. The goal is to "provide a standardized approach for determining the most likely extractables profile from materials used in Single-Use applications, including (the chemicals, the conditions, and) the assays for these materials" (www.astm.org). **ASME-BPE** is also further developing it's standard on Leachables and Extractables published in 2014 to expand more specific requirements for extractables testing, in accordance with ASTM WK43975. **ISPE**'s annual meeting in 2014 focused, in party, on standardization of extractables/leachables assessments.

SUT SUPPLY CHAIN

BPOG has made a cGMP Expectations presentation to **BPSA** as well as a presentation at BioProcess International on the topic of supply chains in SUT. They continue to conduct webinars and write papers on this topic as well. **ASTM**'s biannual meeting last May included a workshop focusing on production and supply chain issues related to raw materials--predominantly Single-Use systems. Nearly 100 individuals representing end users, suppliers and consultants attended this session. A follow-up to this meeting took place last October.

PARTICULATES IN SUT

At **BPSA**'s July 2014 International Single-Use Summit, they issued *"Recommendations for Testing, Evaluation, and Control of Particulates in Single-Use Process Equipment"* which was developed by Subject Matter Experts from both the supplier and end user sides of the bioprocess industry—in order to meet a need. This informative document not only helps readers to characterize and quantify types and levels of particles in Single-Use systems and components, but it also recommends procedures for minimizing these types and levels. In addition, the document offers a look ahead to the future and what the industry should expect by way of improvements in particle control in order to protect the health and safety of pharmaceutical patients. At this time, there is still an industry need for collaboration on the methods to detect particles in the SUT fluid path, which **BPSA** has formed a task group to address. **BPOG** will be looking to work with **BPSA** to close many aspects of the GMP expectations gap. **ASME-BPE**'s 2014 Standard contains several SUT-specific items including Non-Mandatory Appendix N. The goal of Non-Mandatory Appendix N is to provide guidance to manufacturers and end users of bioprocess equipment that will allow them to develop and manufacture products and systems that meet particle acceptance criteria such as standardized hygienic union dimensions, steam through connections, and product/process contact as it relates to system boundaries and facility design. **ASME-BPE** is considering publishing a standard which will reference the **BPSA** particulate paper. Looking ahead, **ASME-BPE** has initiated discussions with **ASTM** regarding testing protocol for particulates in Single-Use systems. **ASME** has also aligned its definition of "Product & Process Contact Surface" definition with **ISPE**'s new Baseline Guide in the 2014 edition. **ASTM**'s work group WK43742 is writing a draft standard entitled *New Practice for Characterizing Particulates Burden from Single-Use Systems*. **USP** has issued acceptance limits for visible and sub-visible particles. These can be found in <787> *Subvisible Particulate Matter in Therapeutic Protein Injections*; <788> *Particulate Matter in Injections*; <790> *Visible Particulates in Injection*; and <1790> *Visual Inspection of Injections.*

CHANGE NOTIFICATION

BPOG and **BPSA** share the same position about the need to standardize supplier change notifications. BPSA is forming a task group to define levels of change and to provide a standardized template for suppliers to streamline the change notification process and facilitate the implementation process for users. **ASTM** is currently working on development of a change notification standard similar to E2500 *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.* **ISPE** published an article in the May 2014 edition of Pharmaceutical Engineering entitled *Change Notifications for Single Use Components: Criteria from an End User Perspective*. The article offers risk-based and science-based methods to catalog stages of changes in SUT manufacturing methods and raw materials.

CHANGE CONTROL

ASME-BPE addresses Change Control and Change Notification in their standard to the extent that it is required as part of their ASME Certification Program, currently in place for Stainless Steel Tubing and Fittings.

SUT SYSTEM INTEGRITY

ASTM created *WK43741 New Practice for Testing Integrity of Single-Use Systems* which seeks to develop a standardized approach for SUT vendors to use throughout the lifecycle of the SUT component. It is intended to help the supplier measure an SUT system's integrity based on risk assessment and can be applied to all categories of SUT components. **BPSA** has formed a task group to assist **ASTM** in developing a standard for best practices to test Single-Use bags. **USP** <1207> *Sterile Product–Package Evaluation* provides an overview of "leak test" methodologies (also termed technologies, approaches, or methods) as well as "package seal quality tests" useful for verification of sterile product package integrity. More detailed recommendations for the selection, qualification, and use of leak test methods are presented in three subchapters that address these specific topics: 1) <1207.1> *Package Integrity and Test Method Selection*; 2) <1207.2> Package Integrity Leak Test Technologies; and 3) <1207.3> *Package Seal Quality Test Methods*.

CONNECTORS

With stimulus and support from BPSA, **ASME-BPE** formed the Polymeric Hygienic Unions Task Group which is similar to their Metal Fitting Task Group.

SUT DESIGN VERIFICATION

ASTM had produced SUT-specific *WK46541 New Guide for Specification, Design and Verification of Single Use Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment* which is complimentary to the very successful standard for traditional equipment – E2500-07. It is intended to be used by suppliers, sub-suppliers and end users of SUT and takes into consideration the unique traits of Single-Use components and their rising popularity in the biopharmaceutical industry. **BPOG** continues to offer consensus support to ASTM in the development of SUT Design Verification standards. □

***General SUT activities that do not fall into the categories above are also being addressed. You can read more about these in the upcoming January 2015 Special Report published by BioProcess International entitled:* The Single-Use Watering Hole: Where Innovation Needs Harmonization, Collaboration and Standardization.** □

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A brief description of the major organizations involved in Single-Use Technologies can be found below. Please visit their websites for a broader description of their industry involvement, a list of their upcoming meetings and events, and volunteer membership information.

ASME-BPE (American Society of Mechanical Engineers - BioProcessing Equipment Standard) www.asme.org
The ASME-BPE Standard is intended for design, materials, construction, inspection, and testing of vessels, piping and related accessories such as pumps, valves, and fittings for use in the biopharmaceutical industry. This standard (www.asme.org/products/codes-standards/bpe-2014-bioprocessing-equipment) also provides requirements for Single-Use Systems and components.

ASTM International www.astm.org
ASTM International develops international voluntary consensus standards similar to the ASME BPE. Twelve thousand ASTM standards are used around the world to improve product quality, enhance safety, facilitate market access and trade, and build consumer confidence. ASTM International includes more than 30,000 of the world's top technical experts and business professionals, representing 150 countries. Working in an open and transparent process and using ASTM's advanced electronic infrastructure, ASTM members deliver the test methods, specifications, guides, and practices which support industries and governments worldwide.

BPOG (BioPhorum Operations Group) www.biophorum.com
BPOG consists of experts from biopharma drug substance operations who meet and work together at fact-to-face meetings in the U.S. and Europe on a regular basis. They have 19 member companies with over 500 participating representatives. BPOG has established best practices on a wide range of quality, engineering and organizational topics central to the challenge of mastering a biotech drug substance operations. BPOG is made of up exclusively of end users.

BPSA (Bio-Process Systems Alliance) www.bpsalliance.org
The BPSA is an industry-led corporate member trade association dedicated to encouraging and accelerating the adoption of Single-Use manufacturing technologies used in the production of biopharmaceuticals and vaccines. BPSA facilitates education, sharing of best practices, development of consensus guides and business-to-business networking opportunities among its member company employees.

ELSIE (The Extractables and Leachables Safety Information Exchange) www.elsiedata.org
ELSIE was formed in 2007 with the core objective of establishing a comprehensive database which provides a jointly-developed and credible source of safety information on extractables and leachables as well as extraction profiles and standardized study protocols for a range of materials commonly used in pharmaceutical, biological and device applications and processes (e.g. container closure systems, devices, manufacturing/processing, etc.).

PDA (Parenteral Drug Association) www.pda.org
PDA is the worldwide leading provider of science, technology and regulatory information and education for the pharmaceutical and biopharmaceutical industries. Founded in 1946 as a nonprofit organization, PDA now has over 9,500 members worldwide. Using their expertise, these members are committed to developing scientifically sound technical information for practical uses in order to advance science and its regulations.

PQRI (Product Quality Research Institute) www.pqri.org
The Product Quality Research Institute (PQRI) is a non-profit consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality and development. PQRI provides a unique forum to focus critical thinking, conduct research, exchange information, and propose methodology or guidance to pharmaceutical companies, regulators, and standard setting organizations.

USP (U.S. Pharmacopeial Convention) www.usp.org
The USP is a scientific nonprofit organization that sets standards for the quality, purity, strength, and identity of medicines, food ingredients, and supplements. USP's drug standards are enforceable in the United States by the Food and Drug Administration (FDA). These standards are also used in more than 140 other countries.

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