

MDCPSS SUMMER NEWSLETTER

President's Message

Dear Members,

Greetings and welcome to the Medical Device and Combination Product Specialty Section's (MDCPSS) summer newsletter. It's an honor to serve as your 2016-17



MDCPSS President. As president I have three goals: First, to improve the visibility of our Specialty Section both inside and outside of SOT. Second to provide you with meaningful webinars, useful ToXchange postings, and worthwhile SOT meeting activities. And third, to continue to grow our membership by reaching out to students, international members, and members of allied specialty sections.

To begin, I'd like to introduce our new Executive Committee: Barb Henry (Vice President), Alan Hood (Past President), Taylor Builee (Vice President-Elect), Shawn Deng (Secretary/ Treasurer), Sherry Parker (Councilor), Whitney Christian (Councilor), Daniel Lou (Graduate Student Representative), and Monica Pombo (Postdoctoral Representative). I also wish to thank the following individuals whose terms ended in April: Greg Erexson (Past President), Jim Kleinedler (Secretary/Treasurer), Sandra Chang (Postdoctoral Representative), and Kevin Trout (Graduate Student Representative). We're truly grateful for the terrific job they all did!

Activities so far this year include a January webinar and several events at the SOT Annual Meeting. The webinar was presented by Wim De Jong from the Netherlands'

Centre for Health Protection at the National Institute for Public Health and the Environment. Wim's presentation was entitled "SCENIHR Opinion on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices." This webinar was timely, very interesting, and well-attended. If you missed it, the slides and a recording are available on the MDCPSS website.

At the 55th SOT Annual meeting held in New Orleans there were 6,812 attendees, including many of our members. We sponsored three activities at the meeting: a poster session, a medical device biomaterials workshop, and a member reception.

At the reception, which was funded by American Preclinical Systems, we presented two student travel awards, a best abstract award, and an award for best published paper. New Orleans was warm, fun, and fascinating with lots of tasty food and good times. This coming year we'll be presenting more webinars and sponsoring symposia at the 2017 SOT meeting. We'll also be periodically sending out email blasts about other events and posting items of interest on our ToXchange bulletin board.

Please check the MDCPSS website regularly for additional information and updates on our activities. Also, don't hesitate to contact me or any other Executive Committee members with ideas, feedback, and suggestions to help us accomplish my three goals. We're excited about the coming year and hope you'll help us make it a success.

Sincerely,

Kelly Coleman

MDCPSS President

kelly.p.coleman@medtronic.com

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Medical Device News and Events

FDA (CDRH) Releases New Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" June 16, 2016.

The final guidance is the update to the 2013 draft guidance, and supersedes the Blue Book Memorandum #G95-1 "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,'" dated May 1, 1995. The link to the Guidance is provided at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm348890.pdf>.

Overall, the Guidance places greater emphasis on risk assessments used to determine the strategy for biological evaluations, chemical characterization, specific testing considerations (e.g., cytotoxicity, sensitization, hemocompatibility, pyrogenicity, implantation, genotoxicity, carcinogenicity). Considerations for color additives have been removed and are now provided in a separate draft policy (see below). A webinar to review the new Guidance was given on July 21, 2016. When available, the webinar will be available on the FDA website <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm507235.htm>.

FDA (CDRH) Presents Draft Policy for Color Additives in Medical Devices.

A webinar was presented on February 12, 2016, and slides are still available at <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm411063.htm>

The FDA's current policies include regulatory requirements for the use of color additives in medical devices and recommendations for manufacturers who want to market a device that contains a color additive. Recommendations in the new draft policy include characterization of leachable color additives from medical devices, and investigations prompted by biocompatibility testing failures, and changes to extracts noted during biocompatibility testing (i.e., color changes, presence of particulates) related to color additives. Investigations include identification, quantification and analysis of risk for leachable color additives and related impurities.

OFFICERS

(2016-2017)

Click on names

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Sherry Parker

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MDCPSS Website

MDCPSS EC

Newsletter Editors

Sherry Parker

Whitney Christian

Alan Hood

MDCPSS EC



Combination Product News

Recent USP<661> and Related Chapter Revisions and Changes

Contributed by Dr. Barbara Henry

The objective of USP<661> is to provide tests, test procedures and acceptance criteria for plastic materials of construction used in packaging systems for pharmaceutical products. The intent of this testing is to ensure that materials of construction selected for study are well-characterized. Non-volatile residue, residue on ignition, and buffering capacity, are less useful as indicators of safety and quality and thus are no longer included in the revised chapter. Introductory information contained in USP <661> includes four subchapters described below.

USP<661.1> Plastic Packaging Systems and Their Materials of Construction

Ingredient information can be obtained more readily than extractables information and can be used to forecast extractables. Materials of construction are characterized for their polymer additives (ingredients), for the purpose of material screening and selection.

USP<661.1> also establishes the concept of relevant metals, where a relevant metal is one which is a known component of the plastic material or could potentially arise from the plastic's starting materials, additives, or manufacturing residuals. USP<661.1> requires that plastic materials of construction be tested for those metals that are relevant to that material (e.g., those listed in European Pharmacopeia). Consider also metals that the user or vendor can reasonably conclude may be present in the material due to its composition and manufacturing process. (See USP<233> for more details on metal analyses.)



USP<661.2> Plastic Packaging Systems for Pharmaceutical Use

USP <661.2> requires that all packaging systems be demonstrated to be safe by performing a chemical assessment. <661.2> references the relevant USP Chapters (<1663> for extractables and <1664> for leachables), thereby providing users with a means for designing and implementing effective, efficient, and more or less customized extractables or leachables assessments that comply with regulatory requirements.

USP<1663> Assessment of Drug Product Extractables Associated with Pharmaceutical Packaging / Delivery Systems

USP<1663> is an informational chapter intended to present and describe the best demonstrated scientific practices for accomplishing an extractables assessment. This chapter presents and describes in detail the critical dimensions of an extractables assessment, including the critical dimensions of an extraction study, which is required in order to create extractables profiles. An extraction study has two critical dimensions: laboratory generation of the extract (extraction) and testing the extract (characterization). In addition, chapter discusses how to assess the completeness of an extractables assessment, and presents two examples of extractables profiles (along with extraction and analytical characterization parameters), which were generated for materials characterization purposes.

Chapter <1664> is intended to present a framework for the design, justification, and implementation of assessments for drug product leachables derived from pharmaceutical packaging and delivery systems. Leachables assessments typically include leachables (migration) studies, which are laboratory investigations into the qualitative and quantitative nature of particular leachables profiles over the proposed shelf-life of particular drug products. It provides detailed recommendations regarding the design of leachables studies, leachables characterization, establishing a leachables-extractables correlation, and considerations in

Combination Product News (Cont.)

developing leachables specifications and acceptance criteria. The discussion of leachables characterization includes best-practice recommendations for: analytical thresholds and their application, analytical method requirements, drug product sample preparation for leachables analysis, analytical techniques, and quantitative leachables method validation.

USP<1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging Delivery Systems

Chapter <1664> includes a detailed discussion of the use of simulation studies for leachables assessment used when it is not analytically feasible (due to challenging thresholds) to successfully discover and identify all actual leachables in a drug product leachables study. In a simulation study, the drug product formulation has been replaced with a simulating solvent that mimics the formulation, the conditions of contact have been accelerated to increase both the concentrations of probable leachables and the rates of their migration into the simulating solvent, and the test article can be the complete packaging and delivery system or separate components of that system.

USP<1664.1> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems: Orally Inhaled and Nasal Drug Products

USP<1664.1> describes the leachables assessment rationale for orally inhaled and nasal drug products (OINDP), along with details on the application of leachables thresholds and best practices to the various OINDP dosage form types. <1664.1> addresses specific considerations for leachables in metered dose inhalers (MDIs), nasal sprays, dry powder inhalers (DPIs) and inhalation solutions, suspensions, and sprays. Chapter <1664.1> is intended to bring into USP's general chapters specific best practice recommendations of the Product Quality Research Institute (PQRI) related to leachables in Orally Inhaled and Nasal Drug Products (OINDP), including the first safety-based thresholds for leachables characterization and safety qualification.

USP<1665> Toxicological Assessment (No draft is currently available.)

USP <1665>, a general chapter, addresses the toxicological safety assessment of extractables and leachables. It provides a framework for performing a toxicological safety assessment, consistent with existing regulatory guidance. It is not expected to provide specific protocols or specifications, nor delineate every situation in which a toxicological safety assessment is required.

USP<87> Biological Reactivity – *In Vitro*, and, USP<88> Biological Reactivity – *In Vivo*

Finally, note that this Stimuli article acknowledges that chemical assessment should be augmented by biocompatibility (biological reactivity) testing. It is expected that plastic materials of construction meet the requirements of the *in vitro* biological activity tests (see USP chapter <87>). In addition, if it is desired that a particular material of construction or plastic system be designated as a member of a specific USP plastic class, then the appropriate biological testing specified in USP chapter <88> (Biological Reactivity – *In Vivo*) is necessary and appropriate. [Keep in mind that requirements specified is ISO 10993 include consideration of *in vivo* testing beyond USP<88>.]

USP<661.3> Draft, Comments due July 31, 2016 (Excerpts from draft)

It is likely that raw materials, production intermediates, process streams, APIs, and DPs will contact one or more plastic components of the manufacturing suite during the manufacturing process, resulting in process-related impurities (PrIs). The potential for PrIs to alter a quality and/or safety attribute of the contacting entity and also the Drug



Combination Product News (Cont.)

Product (DP), if the PRLs persist through the manufacturing process, is addressed in this chapter. This chapter is applicable solely to those that involve liquid process streams and process intermediates due to the expected increased degree of interaction with liquids. Plastic materials and components used in both Multiple Use Systems and Single Use Systems must be suitable for their intended use and should: be compatible with the pharmaceutical product and all process intermediates and process streams, be composed of materials that are safe for use with the pharmaceutical product and all process intermediates and/or process streams, and perform properly. These plastic manufacturing components and systems are considered to be chemically suited for their intended use with respect to safety if they: are constructed of well-characterized materials as in <661.1>, have established general physiochemical properties and biocompatibility (biological reactivity), and, have been established as safe by means of the appropriate chemical testing, such as extractables or leachables profiling and toxicological assessment of the test data.

Chapter <661.3> states that the potential for Process Related Impurities to persist and potentially adversely affect safety of the process output must be assessed using a two-stage approach consisting of:

- an Initial Assessment, which examines whether demonstration of equivalence with a comparator component or system can be established which would allow acceptance of the component without further characterization. If equivalence cannot be established between the component under consideration and the comparator, then a Risk Assessment should be conducted.
- a Risk Assessment establishes 3 levels of risk (per <661>): low (Level A), moderate (Level B), and high (Level C). (Details of test requirements are in Table 2 of the chapter.) All risk levels require testing for identity as specified in 661.1. Components in the highest-risk category (Risk Level C) must be more rigorously characterized.

Also included in this draft chapter is a standard extraction protocol based on a minimum set of extraction conditions to simulate the broad range of aqueous fluids that may be encountered in the production of both pharmaceutical and biopharmaceutical manufacture: water, low and high pH, salt concentration, an organic solvent, and 0.1 N hydrochloric acid for extractable metals. See section 5.2 for more details.

USP<661.4> Plastic Medical Devices Used to Deliver or Administer Pharmaceutical Products (No draft is currently available.)

This summary was prepared from the USP Stimuli article “USP Plastic Packaging General Chapters: An Overview” by USP Packaging, Storage, and Distribution Expert Committee members, Dennis R. Jenke and Daniel L. Norwood, and from USP chapters, drafts and briefing documents. Please refer to the USP chapters for the most up to date revisions.

Membership Update

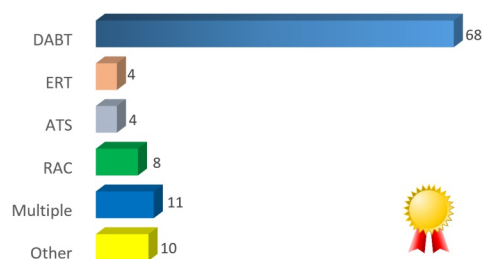
Contributed by Daniel Luo: The MDCPSS was formed in 2009 with 51 founding members. Since then we've grown steadily and now have 157 members.

Our members come from industry, government, consulting and academia. From those who have indicated their sectors, ~65% are in industry positions, ~15% are in consulting, ~10% are in academia, and ~10% are in government related positions.

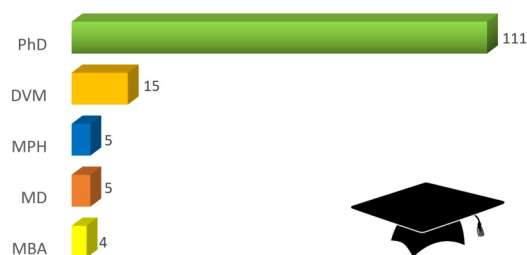
Educational backgrounds range from BS degrees to those with MBAs, MPHs, PhDs, DVMs, and MDs.

Membership Update (Cont.)

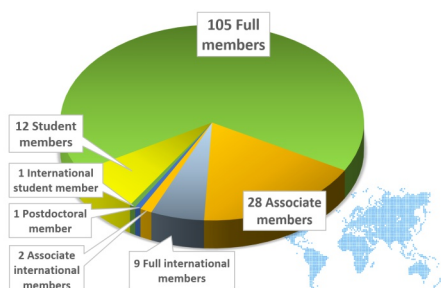
Our Members: Certifications



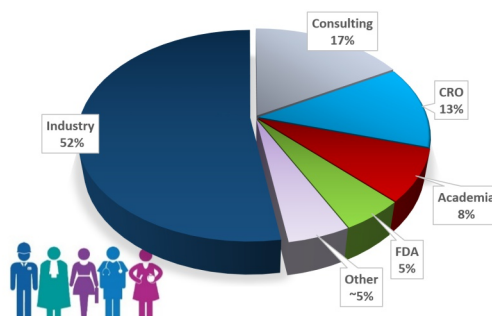
Our Members: Education



Our Members: Membership Types



Our Members: Sectors



Treasury Update

2016 Net Assets

Jan	2016	\$24,675
Feb	2016	\$22,675
March	2016	\$19,356
April	2016	\$19,356
May	2016	\$19,356
June	2016	\$23,432

2016 MDCPSS Sponsors

Medtronic
Kelly Coleman
Ethicon
American Preclinical Services
WL Gore & Associates
WuXi AppTec

Contributed by Dr. Shawn Deng: MDCPSS had a successful year in member registrations and net assets, with modest expenses. Thanks to a strong year of support from sponsors, MDCPSS net assets remained stable throughout the year. The MDCPSS Executive Committee thanks all this year's sponsors for helping to make MDCPSS 2016 activities possible. Please consider making a tax deductible donation in any amount to support MDCPSS.

MDCPSS accepts donations by check or credit card. Checks can be sent to SOTHQ, and other forms of payment may be completed by email or phone with the help of Raul A. Suarez (raul@toxicology.org) at SOT Headquarters 703.438.3115 x1461. All donations should include donor's name, contact information, amount of donation, plus payment information and sent to the Medical Device and Combination Product Specialty Section, Society of Toxicology, 1821 Michael Faraday Drive, Suite 300, Reston, VA 20190.

Global Regulatory Updates

Consensus on Endocrine Disrupting Chemical Identification Criteria in the European Union

Contributed by Dr. Whitney V. Christian

In April 2016, Germany's Federal Institute for Risk Assessment [Bundesinstitut für Risikobewertung (BfR)] organized an international workshop to discuss the identification of endocrine disruptors. Twenty three expert scientists and four observers from the European Commission (EC), the European Food Safety Authority, and the European Chemicals Agency took part. The outcome was the generation of an accord on the criteria for identifying the hazard potential of endocrine disrupting chemicals (EDCs), which was outlined in a final report released on May 4th, 2016 entitled "***Scientific Principles for the Identification of Endocrine Disrupting Chemicals – A Consensus Statement***".¹ As the regulation of EDCs will be influenced by this Consensus Statement, the Medical Device Industry could be impacted considering that some chemicals routinely used in medical devices, like plastic monomers (e.g., BPA) and phthalates (e.g., DEHP), may be considered EDCs in certain circumstances.



The Consensus Statement officially acknowledges the WHO definition that "[a]n endocrine disruptor is an exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub) populations." The term "adverse effect" was defined as "[a] change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences." Further, the term "intact organism" reflects that the adverse effect is observable in a test animal, epidemiologically, or clinically, but does not mean that the adverse effect must be demonstrated in an intact test animal, as a validated alternative test (e.g., *in vitro*) may be adequate.

Of note, endocrine disruption as a hormone/receptor-mediated phenomenon is discussed within the Consensus Statement. In homeostasis of the programming role of postnatal development with emphasized. Although also lead to adverse effects, the fetal basis of adult-onset Statement acknowledges evidence of disrupting the during specific stages of relationships and dose-particular, disruption of the proper endocrine system and, in turn, the hormones during prenatal and consequences later in life is hormonal interference in adult life can this brings credence to the concept of disease. In so doing, the Consensus that regulatory action can be based on programming function of hormones development although dose-response thresholds may not be clearly defined.

"A chemical that falls under several regulatory systems would have only one [risk] assessment, which would be accepted by all of the regulatory systems."

This evidence, however, may be hard to obtain because exposures during critical windows of susceptibility are challenging to reconstruct, making it difficult to discern the existence of causal relationships. With that, the Consensus Statement calls for the further development of internationally validated test systems (especially, non-animal assays) for the identification of EDCs, admitting that suitable model systems and assays for several specific modes-of-action have not been established. These test systems should be developed in mind of their use in regulatory decision-making as well as current sources of uncertainty, including non-monotonic

Global Regulatory Updates (Cont.)

dose-response relationships and low dose effects. Furthermore, although sources of uncertainty exist, the establishment of criteria for the identification of EDCs and the regulation of EDCs is possible without resolving them.

For EDC identification, the Consensus Statement emphasizes that consideration should be given to the timing of exposure relative to life stage and that transient indices or effects may not necessarily indicate adversity. In addition, it is recognized that adverse effects may appear to arise from endocrine disruption but may arise through non-endocrine modes-of-action (e.g., secondary effects to a separate toxic event); such effects are not considered appropriate for EDC identification. Further, endocrine activity itself does not necessarily classify a compound as an EDC, and also, potency is not a relevant factor for EDC identification. The latter point is significant because it indicates that a potency threshold is not permitted for the identification of an EDC; rather, a weight-of-evidence approach that evaluates adversity as well as mode-of-action must be utilized.

Although hazard identification is the focus of the Consensus Statement, additional criteria for EDC risk assessment are also mentioned. The Consensus Statement endorses the One Substance – One Toxicological Assessment philosophy: *“A chemical that falls under several regulatory systems would have only one [risk] assessment, which would be accepted by all of the regulatory systems. This does not necessarily imply that the regulatory decision would be the same, which would depend on a number of considerations.”* To conduct this risk assessment, a dose-response assessment, exposure assessment, and risk characterization, considering potency, susceptible sub-populations, and the severity and reversibility of effects, is required. In turn, emphasis is placed on closing knowledge gaps pertaining to exposure assessment, epidemiological studies, modes-of-action, and test method/biomarker development. In particular, resolution of the issues surrounding non-monotonic dose-response relationships and the absence of effect-thresholds is called for, as normal hormone-mediated effects in humans are threshold-dependent without the existence of low level effects.



The Consensus Statement was offered as advice to the EC, which then carried out an impact assessment analyzing the options for defining EDC identification criteria in the context of regulatory policy-making, as requested in the Plant Protection Products Regulation (EC) 1107/2009 and the Biocidal Products Regulation (EU) 528/2012 (EU pesticides and biocides laws, respectively). The impact assessment was published on June 15th, 2016,^{2,3} and the EC adopted the WHO definition as

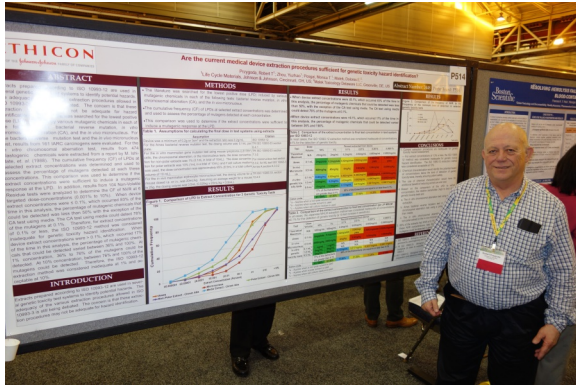
criteria for identifying EDCs with the modification that an EDC *“has an endocrine mode of action”* that can be causally linked to *“an adverse effect relevant for human health”*.⁴

References

1. “Scientific Principles for the Identification of Endocrine Disrupting Chemicals – A Consensus Statement” Outcome of an international expert meeting organized by the German Federal Institute for Risk Assessment (BfR). 2016. <http://www.bfr.bund.de/cm/349/scientific-principles-for-the-identification-of-endocrine-disrupting-chemicals-a-consensus-statement.pdf>.
2. European Commission Impact Assessment “Defining criteria for identifying endocrine disruptors in the context of the implementation of the plant protection products regulation and biocidal products regulation”. 2016. http://ec.europa.eu/health/endocrine_disruptors/docs/2016_impact_assessment_en.pdf
3. European Commission Executive Summary of the Impact Assessment “Defining criteria for identifying endocrine disruptors in the context of the implementation of the plant protection products regulation and biocidal products regulation”. 2016. http://ec.europa.eu/health/endocrine_disruptors/docs/2016_impact_assessment_annex_en.pdf.
4. Draft Annex to the Commission Delegated Regulation (EU) “Setting out scientific criteria for the determination of endocrine disrupting properties and amending Annex II to Regulation (EC) 1107/2009”. 016. http://ec.europa.eu/smart-regulation/impact/ia_carried_out/docs/ia_2016/c_2016_3752_anx_en.pdf.

SOT 2016 Annual Meeting

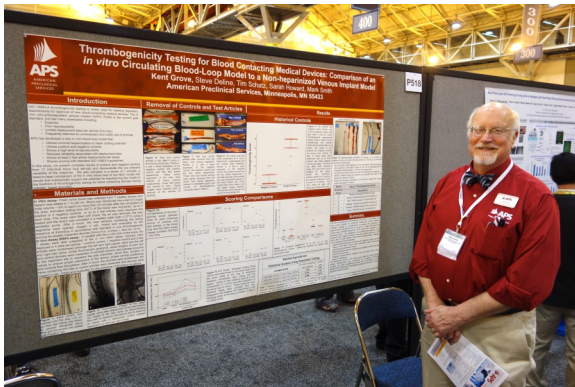
Poster Session: Photos provided by Kelly Coleman



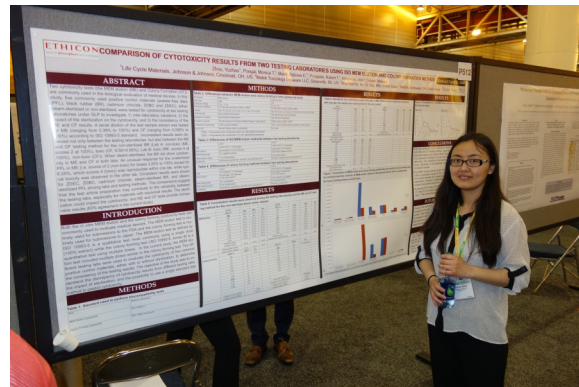
Bob Przygoda



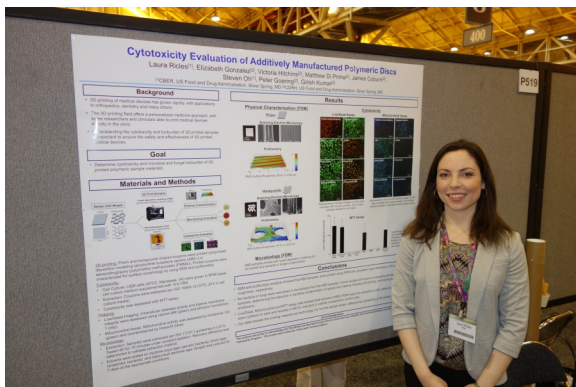
Frances Hsia



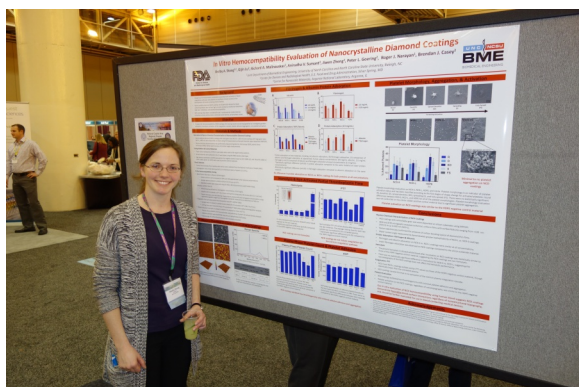
Mark Smith



Yuzhao Zhou



Laura Ricles



Shelby Skoog

SOT 2016 MDCPSS Reception

Photos provided by Kelly Coleman



Best Overall Abstract

F. Hsia, N. Goud, A. Andrews, H. Schwanz,
Boston Scientific



Best Published Paper

K.P. Coleman, L.R. McNamara, T.P. Grailer, J.A.
Willoughby, D.J. Keller, P. Patel, S. Thomas, and C.
Dilworth (2015)



Student Travel Award

Alex Nguyen, North Carolina State University



Student Travel Award

Emily Martell, University of Rhode Island



**Special Thanks to APS for Sponsoring
our Reception**

SOT 2016 MDCPSS Reception (continued)



MDCPSS Mission

The objectives of the Medical Device and Combination Products Specialty Section of the SOT are to:

- Provide an international focus group for toxicologists working in the area of medical devices and combination products including a device component.
- Promote the development of new experimental methods for the evaluation of medical devices.
- Sponsor scientific and educational programs that emphasize current developments and issues in the toxicological evaluation of medical devices.
- Promote proactive communication and interactions among toxicologists in government regulatory agencies, regulated industry, and academia regarding current issues in medical device toxicology.
- Stimulate interest in medical device safety as a career path for new toxicologists.