

MDCPSS WINTER NEWSLETTER

Dear Members,

Thank you for your support of the Medical Device and Combination Product Specialty Section (MDCPSS). The past six months on the Executive Committee (EC) have just flown by! Early in the EC term, we received five requests to sponsor events at the 2018 SOT Annual Meeting in San Antonio: two continuing education (CE) courses, and three workshops. Like all Specialty Sections being asked to endorse a proposal, the EC ranked the proposals and provided comments and endorsements to the Program Committee so that they had a better appreciation of the importance of each proposal to our disciplines and constituents. One of those CE classes and one workshop were approved by the Program Committee. (More details are provided in this newsletter.) Considering that there are 27 specialty sections (SS) now in SOT and a limited number of CE courses and workshops each year, this was great news! Starting at the 2018 Meeting, the SOT Scientific Program Committee will be implementing a new pilot program: A Guaranteed Proposal Acceptance (for the SS). On a three-year rotation schedule, nine SS will be guaranteed each year to have their #1 proposal included in the SOT Annual Meeting program in 2018, 2019, or 2020. To determine the rotation schedule, the Specialty Sections were ranked from largest to smallest, grouped by relative size (large, medium, small) and then assigned to Annual Meeting years (2018-2020) in descending order of size in a group. For the MDCPSS, our "guaranteed" year is the 2019 Annual Meeting. So start thinking now about an issue or topic to develop for the MDCPSS guaranteed proposal for 2019!



As a SS we have more to be thankful for in our very enthusiastic and dedicated EC. Through the efforts primarily of **Kelly Coleman**, our membership is at an all-time high of 171. The **Continuing Education Course AM06, "In Vitro Testing: Tales from the Real World"** at the upcoming SOT Annual Meeting in San Antonio is largely due to the efforts of Kelly. In addition, not only does Kelly influence his employer to support the MDCPSS with donations, but Kelly himself is an individual contributor to our \$20,044 balance! Although his term as Past President/Councilor will expire at the end of April, we're counting on Kelly to remain active in the MDCPSS and to keep us up to date on acceptance of in vitro and alternative methods in toxicology, ISO TC 194 activities and ways to reach out to new potential MDCPSS members.

If the Energizer Bunny was a toxicologist, it would not be half as motivated, efficient and productive as our Vice President, **Taylor Builee**! Taylor has been very committed to our Awards, Program, and Outreach Committees. Taylor was key to organizing, scheduling, and receiving SOT funding for the two recent webinars: **Quantitative Structure Activity Relationships: An Overview** (November 14, 2017, Speaker: Dr. Prachi Pradeep, US EPA/ORISE) and **Regulations, Standards and Practices for Biocompatibility & Toxicology Assessment in China** (October 13, 2017, Speaker: Chenghu Liu, Director, Biological Evaluation Department, Shandong Quality Inspection Center for Medical Devices Jinan, China). Taylor is always coming up with new ideas, volunteering to submit funding applications, reminding us of deadlines, and moving us forward. Taylor (and Kelly) pushed for the \$500 increases (now \$1500 each) for our two student travel awards. Taylor continues to be an efficient and enthusiastic EC member who will make a great President in May!

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Sherry Parker takes her VP-Elect position on the EC seriously, even when Hurricane Irma hit her home state of Florida: rather than miss a meeting due to the storm-related issues, she joined the EC meeting teleconference from a hotel! We are grateful for her safety as well as her contributions to the MDCPSS. Sherry is co-chairing the 2018 MDCPSS workshop on extractables & leachables (“**Matching Methods to Markets: Balancing Regulatory Expectations and Technical Challenges**”) with me. Sherry works on the Newsletter and Mentoring Committees, is one of the ISO TC 194 members charged with revisions to ISO 10993-17, and brings the laboratory service provider perspective to our EC discussions. In May, Sherry will move up to the VP position of our EC.

Xiaomin (Shawn) Deng was key in arranging the CFDA webinar in October (with Taylor). Given that the webinar took place in the middle of the night for this speaker, Chenghu Liu, located in China, Shawn's liaison help was much appreciated. In addition, he has done a great job managing our finances. Shawn has been a volunteer and contributor to the EC and the MDCPSS activities wherever needed. He has kept a willing spirit despite the relocation of his family during the fires that ravaged Northern CA. We wish his family continued strength and look forward to continuing to work with Shawn through May 2018 (unless he'll run for office again).

Whitney Christian, one of the EC Councilors, moderated the successful October CFDA webinar. He has been deeply involved in the Program Committee and is working to bring about a webinar on the gas pathway device guidelines, among other topics. His contributions to the Newsletter are always substantive and informative, such as the extensive overview of the EU Medical Device Directive in our **last newsletter**. Whitney is committed to the future growth of the MDCPSS as evidenced by his leadership of the Mentoring Committee and the organization and planning of multiple mentorship activities at our upcoming SOT meeting in San Antonio. Reach out to him and help support new toxicologists in the MDCPSS. We will miss Whitney as his Councilor term expires May 1, 2017...unless we can persuade him to run for office again!

Megan Hahn, a Councilor, was new to the EC this year but she quickly became involved in the Newsletter, Program, and Outreach Committees. Megan put this newsletter together never complaining that it has been like herding cats! It is a tough and thankless job to produce the newsletter so if you find it at all informative, do pass that along to Megan (and Sherry and Whitney who work on the Newsletter Committee as well).

Monica Pombo, our Postdoctoral Representative, will be leaving her EC office May 1, 2018 after completing her postdoc. She will be working soon on the Awards Committee to select recipients for the five awards given by the MDCPSS: best published paper, and, best overall abstract (deadline January 6, 2018); best poster (deadline February 17, 2018); and two student travel awards (deadline January 25, 2018). For award descriptions, see <http://www.toxicology.org/groups/ss/MDCPSS/awards.asp>. We hope to persuade Monica to stay active within the MDCPSS and consider running for one of the positions opening up.

If you have admired the beautiful MDCPSS poster displayed in the Specialty Section areas at the SOT, mention it to **Daniel Luo**, the MDCPSS Graduate Student Representative. Daniel works on the Membership and Outreach Committees and comes up with new ways to reach graduate students in toxicology and share information about the type of toxicology our membership practices. Because we are a small SS, getting the word out that toxicology is an integral part of the multi-billion dollar device industry is crucial and we thank Daniel for his efforts.

Take a moment to explore the **MDCPSS webpage** on www.toxicology.org. Look through the list of webinars and download the slides or listen to the webinars. Check out the references included, which contain lists of free software available to assist you in your research and work. Volunteer to help a committee. Attend the MDCPSS reception and sponsored events at the 2018 SOT Annual Meeting. Share your ideas for webinar and program topics with any of the EC officers. We want to be relevant and help our members with shared tox issues. And don't forget to renew your SOT and MDCPSS membership now!

Thank you on behalf of the MDCPSS EC,

Barb Henry

MDCPSS President
bhenry@wlgore.com



MDCPSS Webinars

MDCPSS, along with IVAMSS, co-sponsored a two-part webinar held April 10, 2017:

1. "ISO 10993-1 Biological Evaluation—The Risk Management of Unstudied Extractables and Leachables (E&L) Impurities in Medical Devices and Combination Products"

Webinar speaker was Kim Li, PhD, DABT, MPH, Amgen Inc.

Abstract: In 2016, the FDA issued final guidance on the use of ISO 10993–1 “Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process.” The guidance describes a framework whereby chemical characterization of device materials and the toxicology assessment of the extractables and leachables (E&L) impurities may reduce certain biocompatibility testing requirements.

The chemical characterization of the device materials and components is often a comprehensive profile with known as well as tentatively identified structures (TIS). TIS may result from degradation and/or fragmentation of the chemical additives and processing aids used in the production of polymeric materials. The polymeric materials of construction in medical devices are also common materials of construction for bioprocess materials and primary containers that have direct contact with drug product. Therefore the widespread use of polymeric materials underscores the need for a holistic approach in the evaluation of leachables in combination products. Protein therapeutics are more susceptible than chemically synthesized drug products to the leachables that may impact product safety and quality.

While the risk assessment of known chemical compounds is well established based on the known toxicity endpoints (e.g. target organ toxicity, mutagenicity, carcinogenicity and reproductive/developmental toxicity), TIS are unstudied chemicals for which the current risk assessment practices and threshold concepts may not apply. However, it is neither practical nor technically feasible to conduct animal testing on TIS. On the other hand, biocompatibility tests using extracts as described in ISO 10993–12 do not have the specificity nor sensitivity offered by chemical characterization and toxicology assessment of the E&L profiles of the test materials.

This presentation will examine the science- and risk-based decision analysis to integrate the current threshold concepts with in silico tools for the screening of TIS impurities. The presentation will discuss the three different modules of Toxtree (IdeaConsult): in vitro mutagenicity (Ames test) prediction, Cramer classification for systemic toxicity and protein binding alerts. When integrated into a systematic analysis, these modules offer understanding of the chemical reactivity and toxicity for the TIS, which may form the basis to reduce certain unnecessary biocompatibility testing.

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MDCPSS Webinars (cont.)

2. "Animal-Specific Modelling for the 3R in Preclinical Assessment: A Bone Drugs Example

Webinar speaker was Marco Viceconti, Executive Director, Insigneo Institute for In Silico Medicine, The University of Sheffield and Sheffield Teaching Hospital NHS Foundation Trust

Abstract: There is a growing societal pressure toward the Reduction, Refinement, and Replacement (3R) of animal experimentation in most developed countries, primarily motivated by ethical considerations. But there is also a growing concern that the approach used to test the safety and the efficacy of products potentially affecting human health needs some serious revision: a 2014 report of the Tufts Center for the Study of Drug Development suggests that the cost to take to the market a new drug today exceed US\$2.5bn; most of these money is spent during the clinical assessment, but it is probably the preclinical assessment to be blamed most, if (according to Pharmaceutical Research and Manufacturers of America) out of five compounds cleared in the preclinical phase, only one will survive the clinical trials. This means that pre-clinical trials, which are mostly based on animal experimentation, are wrong four times out of five, and this is clearly unacceptable.

Under these combined pressures, the drive for the 3R is combining with the need for the development of Non-Animal Alternatives that not only help to solve this delicate ethical conundrum, but also improve our ability to predict safety and efficacy of a new product before it is tested on humans. There are other industrial sectors that develop products potentially hazardous for human health; if a large airliner crashes, or a nuclear power plant blows, hundreds if not thousands of lives can be at risk, and the environmental damage could eventually affect many more. But in none of these sectors it is conceivable to evaluate safety by trial and error, which is at the basis of the preclinical testing of products affecting human health. These products are most entirely tested through laboratory experiments, and the massive use of modelling and simulation. However, until recently no human health products regulator would even consider in a submission evidences obtained with modelling and simulation.

Here we present the results of a research funded by the UK National Centre for the Reduction, Refinement, and Replacement of animal experimentation (NC3R), where a well establish murine model widely used to test preclinically the efficacy of bone drugs was critically revised using animal-specific modelling based on longitudinal imaging. The methods developed were able to reduce of 63% the number of animals required to achieve statistical significance. But more important, the possibility of observing the effect of the drug being tested over large anatomical volumes, and over time in the same animal non-invasively, has put in serious question the need for a series of interventions that if removed would significantly refine this animal experiment. Last, we will present some preliminary results where animal-specific models are used to partially replace animal experimentation altogether, using an approach call in silico augmented study. We will conclude by suggesting that animal-specific modelling, when combined with human-specific model could produce conclusive evidences on non-animal alternatives are better suited than animal models in predicting the response in humans.

A recording of the webinar and a copy of the slides are available on the MDCPSS Website:

<http://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp>

MDCPSS Webinars (cont.)

MDCPSS hosted a webinar entitled “Regulations, Standards, and Practices for Biocompatibility & Toxicology Assessment in China”, held October 13, 2017.

Webinar speaker was Chenghu Liu, Biological Evaluation Department, Shandong Quality Inspection Center for Medical Devices, Jinan, China

Abstract: The purpose of this webinar is to help participants learn about evaluating biocompatibility of medical devices in China. In recent years, the China Food and Drug Administration (CFDA) has released several important policies and regulations that impact local medical device submission and registration. At the same time, local biocompatibility evaluation standards have also evolved to align with advances in the global ISO 10993 standards. Technical Committee 248 of the Standardization Administration of the People's Republic of China (SAC) is currently based at the Shandong Quality Inspection Center for Medical Devices and is chartered with establishing local biocompatibility standards. The current Chinese GB16886 standards were adopted from the ISO 10993 standards and are essential for biocompatibility evaluation in China. In addition, China has also developed specific test method standards to supplement the GB16886 standards. This webinar will provide an overview of the current status and future trends in biocompatibility evaluation, regulatory requirements, and best practices in China.

This webinar is available on the MDCPSS website:

<http://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp>



MDCPSS hosted a webinar entitled "Quantitative Structure Activity Relationships: An Overview", held November 14, 2017.

Webinar speaker was Dr. Prachi Pradeep, US EPA/ORISE

Abstract: Chemical risk assessment is often limited by the lack of experimental toxicity data for a large number of diverse chemicals. In the absence of experimental data, potential chemical hazard is often predicted using data gap filling techniques such as quantitative structure activity relationship (QSAR) models. QSARs are theoretical models that relate a quantitative measure of chemical structure to a physical property or a biological effect. QSAR tools are a widely utilized alternative to time-consuming clinical and animal testing methods, yet concerns over reliability and uncertainty limit application of QSAR models for regulatory chemical risk assessments. The reliability of a QSAR model depends on the quality and quantity of experimental training data and the applicability domain of the model. This talk will describe the basics concepts and best practices in QSAR modeling, principles associated with validation of QSAR models, summary of available QSAR tools, limitations and challenges in the acceptance of QSAR models within a regulatory framework, and the current status and prospects of QSAR modeling methods in the medical devices community.

This webinar is available on the MDCPSS website:

<http://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp>



2018 SOT Annual Meeting



Sunday, March 11, 2018

- 8:15 am - 12 pm: Continuing Education Course AM06, "In Vitro Testing: Tales from the Real World", Convention Center, location TBD.
- 1:15 - 5 pm: Continuing Education Course PM10, "Evaluation of Leachable Substances from Materials with Applications in Foods and Pharmaceuticals: Science- and Risk-Based Approaches", Convention Center, location TBD.

Monday, March 12, 2018

- 8 - 9 am: MDCPSS Executive Officers Meeting, Hilton River's Edge Cafe & Patio Bar.
- 5 - 6 pm: MDCPSS Mentoring Event, location TBD.
- 6 - 7:30 pm: MDCPSS Evening Reception, location TBD.

Wednesday, March 14, 2018

- 8:00 - 10:45 am: Workshop, "Matching Analytical Methods to Markets: Balancing Regulatory Expectations and Technical Challenges", Convention Center, location TBD.

Date & Time TBD

- Poster Session, Medical Devices
- Poster Session tour mentoring event



Continuing Education AM06, In Vitro Testing: Tales from the Real World

Chairperson(s): Kelly Coleman, Medtronic PRL, Minneapolis, MN; and Amy Clippinger, PETA International Science Consortium Ltd., Norfolk, VA.

Primary Endorser: In Vitro and Alternative Methods Specialty Section

Other Endorser(s): Medical Device and Combination Product Specialty Section, Regulatory and Safety Evaluation Specialty Section

Advances in science and technology have paved the way for a paradigm shift in toxicity testing. We now have the opportunity to more efficiently evaluate substances and better protect human health and the environment by using approaches grounded in human mechanisms rather than animals. Acute toxicity tests—namely, skin and eye irritation, skin sensitization, and systemic (oral, dermal, and inhalation) toxicity—are commonly conducted on medical devices, pesticides, industrial chemicals, pharmaceuticals, cosmetics, and other substances. Thus, it is important to implement rigorous

2018 SOT Annual Meeting (cont.)

alternative acute toxicity-testing approaches that will protect human health and the environment while reducing the time, cost, and animal use associated with traditional toxicity testing. The goal of this course is to teach attendees about existing in vitro, in chemico, and in silico acute toxicity tests and how they have been successfully applied in integrated approaches to evaluate the toxicity of a wide range of substances. Other approaches, such as the use of waivers or the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) mixtures equation, will be discussed. The presentations also will highlight the remaining challenges that need to be overcome before alternative methods can be implemented globally and accepted by regulatory agencies. This course will be of interest to toxicologists from diverse sectors, including those from the chemical, pharmaceutical, medical device, and personal care product industries, along with others who want to learn more about currently available non-animal tests and how to use them.

Continuing Education PM10, Evaluation of Leachable Substances from Materials with Applications in Foods and Pharmaceuticals: Science- and Risk-Based Approaches

Chairperson(s): Greg L. Erexson, AbbVie, North Chicago, IL; and Kim L. Li, Amgen Inc., Thousand Oaks, CA.

Primary Endorser: Medical Device and Combination Product Specialty Section

Polymeric materials commonly used in food and pharmaceutical manufacturing and packaging components are known to leach chemical substances into the final products. The leachable substances may present potential safety risks to consumers and patients. The goal of this course will be to provide an overview of scientific and technical considerations relevant to the assessment of leachable substances covering historical and current context on patient safety and product quality, collaboration between chemists and toxicologists, best practices for deriving chemical-specific safety limits, and use of in silico QSAR tools to advance the 3R principle to replace, reduce, and refine animal testing. This course will provide a comprehensive overview of the risk assessment process for leachable compounds from food contact and pharmaceutical materials.

Workshop, Matching Analytical Methods to Markets: Balancing Regulatory Expectations and Technical Challenges

Chairperson(s): Barbara Henry, W.L. Gore & Associates Inc., Elkton, MD; and Sherry Parker, WuXi AppTec Inc., St. Paul, MN.

Primary Endorser: Medical Device and Combination Product Specialty Section

Today, regulators, supply chain partners, and customers want to know what is in the products they buy that might harm them. From a risk assessment perspective, the absence of clear consensus and regulatory guidance for chemical characterization of medical devices, drug-device combination products, and their components delays commercialization of life-benefiting technology, leads to increased animal testing as a clearly-defined path to market, and is expensive. This session will seek to open the dialogue on the challenges and potential paths forward for manufacturers of medical devices, device-drug combination products, and manufacturers of components to those industries. The first presenter will briefly compare several extractables and leachables (E&L) approaches, including

2018 SOT Annual Meeting (cont.)

ISO 10993 and those by the United States Pharmacopeia, Product Quality Research Institute, the US Food and Drug Administration (US FDA), the Extractables Work Group of the BioPhorum Operations Group, and the Bio-Process Systems Alliance. Once the stage is set, the next presenter will focus on ISO 10993 -1, -17, and -18 acknowledging the importance of chemical characterization of medical devices, as well as the current lack of sufficient detail to plan extraction, analysis, and interpretation for risk assessment. Proposed revisions to the standards and guidance will be discussed. Remember the expression “garbage in, garbage out”? In order to have high-quality risk assessments, the data must be high quality. The next topic will be the essential collaboration between the chemist and toxicologist in the design, execution, and interpretation of E&L studies. Knowing what the product is made with, manufacturing steps, potential contaminants, residuals, and impurities helps the toxicologist identify potential chemicals of concern, which the chemist will then need to find and quantify using appropriate solvents, extraction conditions, and analytical techniques. How low should you go (limit of detection) to support the risk assessment for the intended use of the product? When to be aggressive in extractions and when to use “kinder and gentler” extractions simulating clinical-use conditions of products will be addressed. This topic will end with risk assessment approaches, including handling of unknown chemicals and use of the Threshold of Toxicological Concern (TTC) for a permanently-implanted medical device and a drug-device combination product. Now, that the opening presentations have shared a collaborative plan of attack for E&L, does it matter which lab does the analysis? Inter-laboratory variability related to compound identification and quantitation, including equipment sensitivity and the available chemical library, will be discussed by the next presenter. Disparity in the number of reported compounds among four test laboratories for the same test articles, despite the same extraction solvents, conditions, and analytical techniques, will be shared. Considerable quantitative and qualitative differences potentially impacting the risk assessment will be discussed. The final presentation will provide light at the end of this complex and complicated tunnel by sharing US FDA expectations of E&L studies for medical devices and combination products. The presentation will include LODs, LOQs, sensitivity, extraction methods, and the interpretation of qualitative, semi-quantitative, and quantitative data, as well as issues frequently encountered. To close out the session, the panel will answer audience questions regarding lab selection, unknowns, use of the TTC, Cramer Classes, and in silico approaches. This session will feature information and provocative discussions that will be transferable to other E&L applications and should be of interest to contract labs and manufacturers of parts intended for use in medical devices, pharmaceutical processing, or single-use systems, as well as regulators.

See more at: <https://www.toxicology.org/events/am/AM2018/scientific-sessions.asp>



Executive Committee Positions Now Available!

In keeping with the election cycle, four executive committee positions are available in 2018-2019. Please consider nominating a candidate (including yourself!) by submitting a biosketch to Barb Henry (bhenry@wlgore.com) by December 22, 2017. [Follow this link for further information.](#)

- VP-Elect (4 year cycle with Executive Committee)
- Secretary/Treasurer (2 year term)
- Councilor (2 year term)
- Postdoctoral Representative (1 year term)
- Graduate Student Representative (2 year term)



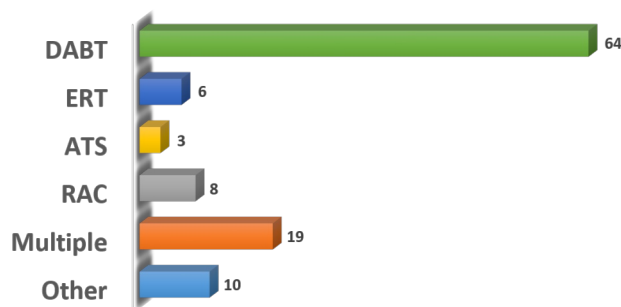
Membership Update

Contributed by Daniel Luo:

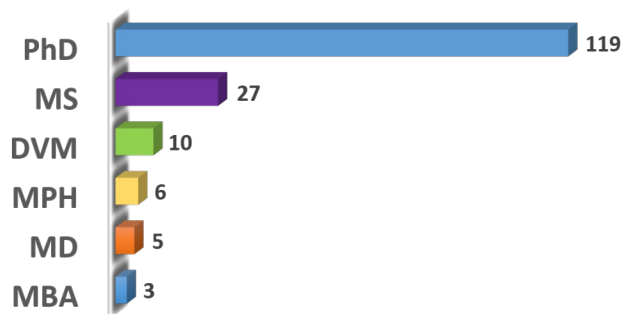
The MDCPSS was formed in 2009 with 51 founding members. Since then we've grown steadily and now have 171 members.

Our members come from industry, government, consulting and academia. From those who have indicated their sectors, ~52% are in industry positions, ~17% are in consulting, ~6% are in academia, and ~9% are in government related positions. Educational backgrounds range from BS degrees to those with MBAs, MPHs, PhDs, DVMs, and MDs.

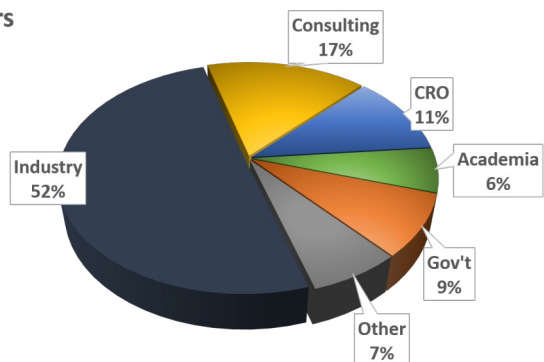
Certifications



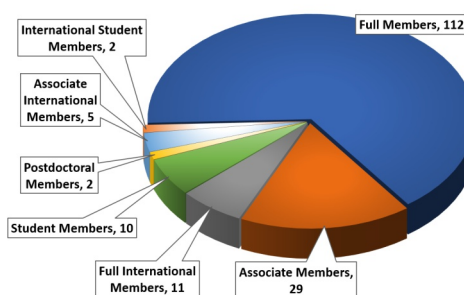
Education



Sectors



Membership Types



Treasury Update

2017 Net Assets

Aug	2017	\$20,044
July	2017	\$20,044
June	2017	\$20,044
May	2017	\$15,834
Apr	2017	\$15,834

2017 MDCPSS Sponsors

Edwards Lifesciences
WL Gore & Associates
Fidelity Charitable
Medtronic
Kelly Coleman

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 maintained stable throughout the year. The MDCPSS Executive Committee thanks all this year's sponsors for helping to make MDCPSS 2018 activities possible. Please consider making a tax deductible donation of 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 by phone directed to Raul A. Suarez (raul@toxicology.org) at SOT Headquarters (703) 438-3115 x1461. All donations should have the minimal information, donor's name, contact information, amount of donation and payment information directed to the Medical Device and Combination Product Specialty Section, Society of Toxicology, 11190 Sunrise Valley Drive, Suite 300, Reston, VA 20191.

ISO 10993 TC 194 Meeting Update

by Kelly Coleman

The 28th meeting of ISO Technical Committee 194 was held from October 16th–20th in Seoul, South Korea. The meeting was jointly organized by the Korean Ministry of Food and Drug Safety (MFDS), the Korea Testing & Research Institute (KTR), and ISO/TC 194. Eight working groups (WG) conducted sessions during the week that were attended by approximately 100 delegates, including 28 from the United States. Key discussion items and recommendations are presented below.

WG 2 Degradation aspects related to biological testing

The WG 2 session was chaired by Dr. Scott McNamee (United States) and attended by 14 experts from 6 countries.

At this meeting, comments on ISO TS 37137-1 were reviewed and addressed. Also, comments were reviewed for Committee Draft (CD) 10993-9 and CD 10993-15. All the comments were addressed, and the documents are ready for circulation as Draft International Standards (DIS).



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ISO 10993 TC 194 Meeting Update (cont.)

WG 6 Mutagenicity, carcinogenicity, and reproductive toxicity

This session was chaired by Dr. Albrecht Poth (Germany) and attended by 19 participants from 7 countries. Comments received for a working draft on ISO/TR 10993-33 Guidance on tests to evaluate genotoxicity - Supplement to ISO 10993-3, were discussed and resolved. Dr. Rosalie Elesbru (United States) provided a presentation on the chapters of ISO 10993-3, which are not recognized by US FDA. The following tasks were agreed to: Revision of part 10993-3, asking for a New Work Item Proposal (NWIP) circulating with a latest draft by March 31, 2018; Inclusion of the revised ISO/TR 10993-33 in an informative annex of ISO 10993-3; and after publication of the revision of ISO 10993-3, withdrawal of ISO 10993-33:2015.

WG 8 Irritation and sensitization

The WG 8 session was chaired by Dr. Wim de Jong (the Netherlands) and attended by 20 experts from 9 countries.

The results of the in vitro irritation round robin study (RR) were presented by the convener Dr. de Jong. Twenty laboratories and institutions from around the world participated in the RR study, which was a great success with an overall predictivity of irritant activity in medical device extracts ranging from 95-100%. Based on these results a NWIP was submitted and accepted to draft a standard on the use of the reconstructed human epidermal (RhE) model for determination of irritant activity (ISO 10993-23). Dr. Reiko Kato (Japan) presented information of one of the positive biomaterials (Y-4) that is now available from the Hanto Research Institute as positive control material for irritation testing. Dr. Jae-Sung Kwon (South Korea) presented plans for evaluating the reconstructed human cornea model to determine the eye irritation potential of medical devices.

It was decided to extend the scope of ISO 10993-23 to deal with both in vitro and in vivo irritation testing. In addition, a NP was recommended to revise ISO 10993-10 into a standard for only sensitization testing. This will lead to two separate standards, one dealing with the biological evaluation of medical devices regarding sensitization testing (10993-10), and the other dealing with irritation testing (10993-23). WG 8 agreed to convene at an interim meeting at Delft, The Netherlands in April/May 2018.

WG 10 Local effects after implantation

This session was chaired by Dr. Arne Hensten (Norway) and attended by 14 experts from 10 countries.

Dr. Sharlene Dai (United States) shared information regarding the implantation endpoints from a manufacturer's point of view.

The delegates reviewed the revised ISO 10993-1 to see whether the ISO 10993-6:2016 implantation endpoints were in line with its latest version. Some discrepancies were identified that need to be addressed. The consensus was that this does not require a revision of the ISO 10993-6 at present, and should await the regular 5-year review. However, the delegates considered that these differences should be subjected to a gap analysis and wished to have the results presented at the next ISO/TC 194 meeting. WG 10 agreed to schedule a half-day meeting in 2018.

ISO 10993 TC 194 Meeting Updates (cont.)

WG 11 Allowable limits for leachable substances

Working Group 11 met on three days and was chaired by Dr. Alan Hood (United States). The first session was attended by 44 experts from 12 countries; this was joint meeting with WG 6 and WG 14. During this meeting, the TTC Technical Specification (TS) was discussed and the delegates voted to move it forward as a Working Draft (WD). The remainder of the session was a presentation by Dr. Hood on the integration of Parts 17 and 18, which included: (1) when to initiate a toxicological risk assessment, (2) the use of TTC for deriving an analytical evaluation threshold (AET), and (3) utilization of mg/device material characterization data to estimate a maximum exposure dose based on worst-case assumptions.

The second session was attended by 27 experts from 11 countries. During this meeting, the delegates agreed that PDTS 29741 Development of Tolerable Intake (TI) values for Di(2-ethylhexyl)phthalate (DEHP) is not needed and voted to cease its development. Dr. Nicholas Martin (France) presented an update on ISO 10993-7:2008 Ethylene oxide sterilization residuals. WG 11 recommended that this document be forwarded to ISO/CS for circulation as a DIS. Dr. Hood presented proposed updates to ISO 10993-17:2008 Biological evaluation of medical devices – Part 17: Methods for the establishment of allowable limits for leachable substances. The WG agreed the need for changing the name of the standard to Toxicological Risk Assessment for Medical Devices, and suggested modifications to proposed updates for the writing group to consider.

During the third session, Dr. Hood, Dr. Kelly Coleman, and Dr. Sherry Parker (United States) continued presenting proposed updates to ISO 10993-17. Attending delegates discussed or suggested modifications to proposed revisions. The WG agreed that the writing group should continue updating Part 17 and that a NWIP should be submitted no later than December 1, 2017. WG 11 also agreed to work with WGs 8, 12, and 14 to organize an interim meeting in April/May 2018.

WG 12 Sample preparation and reference materials

The WG 12 session was chaired by Mrs. Anita Sawyer (United States) and attended by 18 experts from 8 countries. The working group discussed results and comments from the Systematic Review of ISO 10993-12:2012; 14 Standard Bodies voted to confirm ISO 10993-12:2012, while two Standard Bodies voted to revise/ amend with comments.

Dr. Molly Ghosh (United States) led the discussion of FDA's comments. The major points were the suggestions to exclude use of this standard for chemical characterization and risk assessment, and deletion of parts section 10 and Annexes C and D dealing with exhaustive and exaggerated extractions for hazard identification. There was also a discussion of appropriate extraction solvents for a biological and chemical testing, in which the solvents listed in the WG 15 Round Robin protocol and ISO/CD 10993-18 were compared.

Based on the Systematic Review comment discussion; the desire to harmonize with ISO 10993-1, ISO 10993-17, and ISO 10993-18 currently undergoing revision; and that the WG 15 Task Force's Round Robin investigating the adequacy of current ISO 10993-12 extraction conditions is planned to have results early in 2018, the WG decided to proceed with a simplified NWIP with no change in scope. The WG worked on the structure and content of an outline of the proposed revision to be included in the

ISO 10993 TC 194 Meeting Update (cont.)

NWIP. The WG plans to initiate revision work and have an interim meeting in conjunction with other ISO/TC 194 WGs in Delft in May 2018.

WG 14 Material characterization

After the initial joint session with WGs 6 and 11, WG 14 met on two subsequent days. These sessions were chaired by Dr. Ted Heise (United States); the first of which was attended by 28 experts from 10 countries. The convenor, Dr. Heise reported that the ISO/WD 10993-19 (ISO/TC 194/WG 14 N 42) has been revised by the writing team to address comments from WG experts. WG 14 recommended that the revision of ISO 10993-19 be balloted as a Draft Technical Report (DTR).

WG 14 spent the balance of its scheduled time deliberating on open issues related to the CD of ISO 10993-18. Topics covered included recently added definitions, a revised Figure 2, clauses 5.1, 5.3, 7, and 8, and annexes C and E. The WG recognized that validation of analytical methods for ISO 10993-18 is in most cases not possible, and otherwise not practical. Accordingly, it was considered appropriate for the standard to specify that methods shall be qualified for their intended purpose.

The WG also recommended that: (1) An ad hoc group (AHG) on Analytical Method Qualification be formed that would draft text on the necessary elements for qualification of analytical methods used in chemical characterization; (2) A second CD of ISO 10993-18 be submitted by January 5, 2018 with an 8-week balloting period, and (3) A project extension of 9 months be requested for updating ISO 10993-18.

The working group proposed to hold an interim joint meeting with WG 8; provisionally during the last week of April 2018, in Delft, The Netherlands.

WG 15 Strategic approach to biological assessment

The WG 15 session was chaired by Dr. Jon Cammack (United States) and attended by 42 experts from 15 countries.

Mr. Robert Geertsma (The Netherlands) introduced an update on standardization in tissue engineering; other experts provided input as well.

Dr. Kelly Coleman, Task Force (TF) 11 Chair, provided an update on progress in alternatives for animal testing, including: (1) A presentation at the 10th World Congress on Alternatives and Animal Use in Seattle, Washington, USA, 2017-08-24; (2) Outcome of literature searches and best practice information on in silico methods potentially applicable for medical device risk assessments; and (3) A brief summary of WG 8's in vitro irritation RR study. It was recommended that TF 11 work with AAMI to develop a strategy for presenting the RR results to FDA.

Mr. Byron Hayes (United States) led a discussion of ISO/TS 37137-1 and ISO/TR 37137-2.

WG 15 thanked the ad hoc group for the work done on the revision of these two documents and recommended that this ad hoc group be disbanded and the work be allocated to WG 2.

Mrs. Anita Sawyer provided an update from the WG15 ad hoc group that developed a round robin

ISO 10993 TC 194 Meeting Update (cont.)

proposal to evaluate extraction methods and conditions and it was agreed that Mrs. Anita Sawyer will give a further presentation at the next meeting of WG 15 in Berlin, 2018

During the discussion of any other business, the topic of leachables from medical devices with the potential for endocrine disruption was introduced by Dr. Albrecht Poth.

WG 15 recommends that the topic of leachables from medical devices with the potential for endocrine disruption be presented and discussed at the next meeting of WG 15 in Berlin, 2018. Dr. Cammack and Dr. Poth will coordinate the presentation(s) and discussion of the topic for WG 15 in Berlin, 2018.

Plenary Session

On the last day of the ISO/TC 194 meeting a plenary session was held during which the convenors presented the brief minutes of the respective working group meetings. ISO/TC 194 chairman, Dr. Albrecht Poth, led this session. Subsequently, a meeting of the European mirror committee on biological evaluation of medical devices, CEN/TC 206, was chaired by Dr. Wim de Jong.

FDA MDDT Program

FDA Program to Modernize Device Evaluation

by Jeffery Brown, PETA

The new [Medical Device Development Tools \(MDDT\) program](#), finalized by the U.S. Food and Drug Administration Center for Devices and Radiological Health (FDA CDRH) in August 2017, aims to reduce the regulatory burden faced by medical device sponsors by promoting the development of tools that streamline the review process. Importantly, this program provides a clear pathway for companies to receive agency approval to use non-animal methods in place of animal tests that are routinely required or recommended by CDRH reviewers.

In brief, CDRH uses this program to determine whether a test method is “qualified” as an MDDT for use within a tightly defined context of use (COU). The program guidance recognizes three broad tool types that are fit for development as MDDTs, including non-clinical assessment models (NAM) that predict in vivo device performance. As the guidance makes clear, NAMs include in vitro models that can replace animal testing.

Once a test method is qualified, the agency and its reviewers accept the use of the tool without the need to reconfirm its suitability within the COU. Although this approach is similar to the familiar process of method validation, the agency’s guidance points out that “[q]ualification, as described in this guidance is intended to increase predictability in device evaluation and regulatory decision-making by making it clear to prospective sponsors that FDA accepts assessments from an MDDT in support of demonstrating safety, effectiveness, or performance of a medical device, without need to reconfirm suitability and utility of the MDDT, when used within the qualified context of use.

Qualification also improves efficiency in the regulatory process because a qualified MDDT can be used by multiple sponsors across multiple medical device development programs.”

FDA MDDT Program (cont.)

How do MDDT projects begin?

CDRH encourages industry consortia and other stakeholders to work together to identify tools that can be used for multiple products within a common COU, in part to avoid the resource intensiveness posed by validating NAMs on a case-by-case basis. Once stakeholders have identified a NAM that can replace an animal test, they submit an application to CDRH that describes the tool and its COU, along with a proposed plan to demonstrate that the tool performs as intended. The agency consults with submitters throughout the application process to ensure that the proposed plan is satisfactory before any new testing is carried out. After the agency accepts an application, submitters follow the approved plan and share results with the agency. If the strength of evidence supports use of the tool within its COU, the agency considers the tool qualified as an MDDT. After qualification, the agency and its reviewers accept the use of the tool without the need to reconfirm its suitability within the COU.

An MDDT project example: developing a NAM to replace an in vivo biocompatibility test

Medical device companies that market personal lubricants routinely evaluate products using the rabbit vaginal irritation test (RVI). A number of reconstructed human vaginal tissue models are commercially available, but none have been validated for use with personal lubricants as replacements for the RVI.

[CDRH accepted an MDDT project proposal](#) that aims to do just that. The Institute for In Vitro Sciences, in collaboration with a consortium of personal lubricant manufacturers, the Consumer Healthcare Products Association, and the PETA International Science Consortium Ltd., submitted the proposal to evaluate in vitro irritation testing with reconstructed human vaginal tissue models as a NAM to replace the RVI. To do so, the results of in vitro irritation tests will be compared with existing RVI test results for the lubricant products contributed by the industry consortium. The tool's COU is restricted to personal lubricants with formulations similar to those evaluated during the agency-approved tool evaluation plan. If the project is successful and CDRH qualifies this in vitro irritation test as an MDDT, any device sponsor interested in marketing a personal lubricant with a formulation that falls in the tool's COU will be able to use the in vitro irritation test in place of the RVI in regulatory submissions.

Candidates for future MDDT projects

Medical device sponsors are likely aware of [non-animal methods](#) that have been validated to replace animal tests for products other than medical devices and device extracts. These methods are ideal candidates for development under the MDDT program, especially those that may replace routinely used animal tests including:

- Reconstructed human epidermis (RhE) models to replace the rabbit skin irritation test.
- RhE models to replace the guinea pig maximization test.
- Monocyte activation tests to replace pyrogen tests that require rabbits or horseshoe crabs.
- In vitro screening panels to replace in vivo acute systemic toxicity tests.



FDA MDDT Program (cont.)

In some cases, studies underway independent of this program are generating data that may support qualification of an MDDT NAM. As an example, a [round robin validation study](#) has been conducted to assess the suitability of RhE models as a replacement for the rabbit skin irritation test during the evaluation of medical devices. Data from this validation study would be ideal to prepare as an MDDT proposal. Ultimately the list of possible MDDT projects is long and limited only by the interest of companies and stakeholders who are interested in identifying mutual goals to replace animal use.

For more information on the MDDT program, CDRH has made available a [recording and transcript](#) of a webinar introducing the program.

To assess interest in MDDT, consider participating in the brief poll, available till January 31st, 2018. <http://toxchange.toxicology.org/p/su/rd/survey=884fd621-be79-11e7-9f91-bc764e101892>

Hazardous Substances Regulations

Update: Regulations on Hazardous Substances in Medical Devices

by Whitney Christian

Here are some upcoming deadlines that the Medical Device Industry has their eye on regarding the use of hazardous substances in medical devices.

PROPOSITION 65 – August 30, 2018

On August 30, 2016, the Office of Administrative Law approved the adoption of [amendments to Article 6, Clear and Reasonable Warnings, of the California Code of Regulations \(Title 27\)](#). The amendments provide new product specific warning requirements, effective August 30, 2018, for compliance with the Safe Drinking Water and Toxic Enforcement Act of 1986, also known as Proposition 65. Although Proposition 65 does not explicitly prohibit, or require reformulation or elimination of, any hazardous substances, businesses selling medical devices in California that contain one or more hazardous substances on the [Proposition 65 chemical list](#) are required to provide warnings that:

- Say that the product “can expose” users to a chemical(s).
- List the name of the chemical(s) that prompted the warning.
- Provide the link to California’s Proposition 65 website, which includes additional information on the health effects of listed chemicals and ways to reduce or eliminate exposure to them.
- Include a triangular yellow and black warning symbol (can be white and black).



WARNING: This product can expose you to chemicals including [name of one or more chemicals], which is [are] known to the State of California to cause cancer and birth defects or other reproductive harm. For more information go to www.P65Warnings.ca.gov.

Hazardous Substances Regulations (cont.)

Businesses can obtain a [warning label exemption](#) if exposures from the product are so low as to create no significant risk of cancer or are significantly below levels observed to cause birth defects or other reproductive harm. That is, showing that the product does not release a hazardous amount of a Proposition 65 chemical(s) although it contains a chemical(s) above safe harbor levels can justify warning label exemption.

EUROPEAN UNION MEDICAL DEVICES REGULATION – May 26, 2020

The [European Union Medical Devices Regulation 2017/745](#) (EU MDR) was published May 5, 2017 in the Official Journal of the European Union. Entry into force occurred on May 26, 2017 and, in turn, the date of application is May 26, 2020. Among the many changes in the EU MDR, section 10.4.1 of Annex I declares that devices, parts thereof, or materials therein that contain more than 0.1% (w/w) of substances which are carcinogenic, mutagenic, or toxic to reproduction (CMRs) or substances having endocrine disrupting properties (as defined in points (a) and (b) of section 10.4.1 per [Regulation \(EC\) No 1272/2008](#), [Regulation \(EC\) No 1907/2006](#), and [Regulation \(EU\) No 528/2012](#)) must be labelled on the device itself and/or on the packaging with the list of such substances. In addition, justification for the presence of these substances in the medical device must be provided (per section 10.4.2). Although the Medical Device Industry anxiously awaits further clarification of these regulations [e.g., guidelines on justification to support not using alternative non-hazardous substances (section 10.4.2), guidelines on phthalates (section 10.4.3), and guidelines on CMRs/endocrine disruptors (section 10.4.4)], the MDR has clearly initiated a major effort to understand and restrict the presence of hazardous substances in medical devices in support of patient safety in the EU.

RESTRICTION OF HAZARDOUS SUBSTANCES 3 – July 22, 2021

On June 4, 2015, the EU Commission published [Directive 2015/863/EU](#), which amended Annex II of the Restriction of Hazardous Substances (RoHS) 2 ([Directive 2011/65/EU](#), which replaced RoHS 1 [Directive 2002/95/EC](#)). Although an amendment to RoHS 2, Directive 2015/863/EU is being called RoHS 3 and adds four phthalates (max allowable concentration: 0.1% w/w) to the list of RoHS restricted substances (now totaling ten):

- Bis(2-Ethylhexyl) phthalate (DEHP)
- Benzyl butyl phthalate (BBP)
- Dibutyl phthalate (DBP)
- Diisobutyl phthalate (DIBP)



For medical devices (category 8), the RoHS 3 deadline for compliance is July 22, 2021. Interestingly, it appears like the EU is imposing a major phase out of phthalates from medical devices, which seemed like an underlying implication of the EU MDR (see sections 10.4.2 and 10.4.3 of Annex I). Therefore, if design/material changes are apparent, they should begin sooner rather than later since heavy phthalate restrictions are evident.

Upcoming Events

IMPORTANT DATES FOR MDCPSS

December 22, 2017

- Nominations for MDCPSS Executive Committee



January 6, 2018

- Submission for Best Published Paper Award at 2018 SOT Meeting
- Submission for Best Overall Abstract Award at 2018 SOT Meeting

January 25, 2018

- Submission for Student Travel Awards (2) for 2018 SOT Meeting

February 17, 2018

- Submission for Best Poster Award at 2018 SOT Meeting



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SOT 2018 San Antonio
★ March 11-15 ★

MDCPSS Mission

The mission of the Medical Device and Combination Product Specialty Section is 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.

Don't forget to visit the MDCPSS Website for regular updates:

<https://www.toxicology.org/groups/ss/MDCPSS/index.asp>