MDCPSS FALL NEWSLETTER

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PRESIDENT'S MESSAGE

Dear Medical Device and Combination Product Specialty Section (MDCPSS) Members,

I hope you and your families are safe and well during these challenging times due to the COVID-19 pandemic. Although we may be navigating through uncertainty, I assure you the MDCPSS will be providing you the opposite with a year full of informative webinars and events that will be beneficial to your education and career. With that, I am honored to serve as the President of the MDCPSS alongside an incredibly talented group of Executive Committee officers: Sherry Parker (Past President), Jan Oberdoerster (Vice President), Shelby Skoog (Vice President-Elect), Megan Hahn (Secretary/Treasurer), Xiaoling (Sharlene) Dai (Councilor), James (Jim) Kleinedler (Councilor), and Ju Young (Julie) Park (Postdoctoral Representative).

As a continuous improvement initiative, this year I am focusing on three goals in the areas of membership, mentoring, and education.

- Membership: as the Executive Committee reflected on the past year, we could see that the MDCPSS had grown to its greatest membership size, 225 members! However, we realized that we are lacking international members. In order to be more globally represented, I will be focusing on boosting membership outside the US. Please join this initiative to grow and develop an international foundation by providing connections and spreading the word. Also, please remind those you come across that we continue to waive membership fees for students and postdoctoral fellows, who may be interested in joining the MDCPSS.

In addition to increasing membership enrollment, I would like to increase our members' involvement in MDCPSS committees; these are open to all members and give them the opportunity to contribute to a variety of areas, including webinar planning, mentoring events, and the newsletter. I encourage you to volunteer and participate. Your contributions will be greatly appreciated.

- Mentoring: Mentoring has been a passion of mine since joining the Executive Committee many years ago. I felt during my development as a professional toxicologist, I had little, and I want to change that for others who may be in a similar situation as I once was. In previous years, I have tried to incorporate more mentoring events at our annual SOT meetings to provide career advice in general but also to provide insight into opportunities within the field of Medical Device and Combination Product Toxicology.

These events included guided MDCPSS poster tours, mentoring Q&A sessions, mock interviews/CV reviews, and "Meet the Leaders" events, which evolved into MDCPSS social networking events. At SOT 2020, the MDCPSS was slated to co-host its first career panel, but unfortunately, we could not meet in person. This event, however, was salvaged and occurred in a virtual format on September 21st. If you missed it, a recording of the mentoring session is posted on the MDCPSS website.

This is great progress, but simply put, I want to explore taking this to the next level. The Executive Committee has discussed establishing a mentorship program and would like to gauge the interest of our members in participating in such a program as well as the level and type of mentor-mentee interaction involved. Please keep an eye out for future communications regarding a MDCPSS mentorship program.

- Education: Medical Device and Combination Product Toxicology is hot right now. The need for toxicologists in this field has never been greater, and with that, the continuing education of our members and people joining this profession is important. I have always been impressed by the quality of webinars and informative sessions that the MDCPSS has sponsored over the years. I feel that there is so much knowledge to share and discuss about developments within this dynamic field that the MDCPSS could host a webinar every week. Because of this, my goal is to double the number of MDCPSS-sponsored webinars this year, as we are planning to organize and deliver a number of informative sessions that will be of great benefit to our members.

On that note, although we are a little behind with MDCPSS-sponsored webinars due to SOT 2020 being virtual and, in turn, extended into late Spring/early Summer, I am excited that our programs committee kicked off this year's webinar series with a big, three speaker webinar entitled "Industry, CRO, and FDA Perspectives on Medical Device Chemical Characterization per ISO 10993-18:2020" on September 25th. Chemical characterization has been a topic of great interest over the recent years and continues to evolve, which is why I am sure the content of this webinar was valuable to our members. Please check out the upcoming webinars listed within the newsletter and please contact the MDCPSS with topics that you are interested in learning more about or that are impactful to your area of work. We want to bring you content that is most useful to your needs.

This newsletter would not be possible without the efforts of Megan, who thankfully has returned to the Executive Committee after being away a year, and Sharlene, who joins the team for the first time. Also joining us for the first time is Julie, who I look forward to working with to expand our international footprint and connect with SOT postdoctoral scholars. I'd like to recognize Shelby for her reliable assistance in organizing our webinars and notifying our members of events through ToXchange and MDCPSS website updates. Jan has been a great teammate bringing a fresh perspective and steadfast drive to the programs committee alongside Jim; I am really looking forward to working closely with Jan this year to improve the MDCPSS. And last but not least, I am ever so grateful for the guidance of Sherry, who has served alongside me every year since I joined the Executive Committee and keeps us on track.

Together, the 2020-2021 Executive Committee wishes to extend a huge thank you to our members for their continued support, which has made the MDCPSS a success. I look forward to your scientific contributions, participation, and feedback throughout the year, and hope you enjoy the Fall newsletter!

Sincerely,

Whitney Christian
MDCPSS President
whitney.christian@medtronic.com

MDCPSS Webinars

Industry, CRO, and FDA Perspectives on Medical Device Chemical Characterization per ISO 10993-18:2020

Date and Time: Friday, September 25, 2020, at 12:00 PM –2:00 PM (EDT)

A Systematic Testing Strategy in Performing a Successful Chemical Characterization at Medtronic — How Industry May be Performing Chemical Characterization Differently than FDA Preferences and Why

Speaker: Dr. Jianwei Li, Medtronic

Abstract: This presentation will provide a general strategy overview in performing a successful chemical characterization to support biocompatibility evaluation of medical devices. A major focus is to examine critical issues in a chemical characterization to meet scientific and regulatory requirements. The topics of discussions include extraction solvent requirements and polarity scale, correlation of polarity scale with material swelling, fundamental principles in selecting multiple solvents for exhaustive and exaggerated extractions, difference between semipolar and nonpolar solvents for extraction, impact of material swelling on kinetics/thermodynamics of extractables release, and finally the technical considerations of NVR (nonvolatile residue) test and its relation to chromatographic measurement results. Medtronic general practices are outlined at the end.

Mitigating Response Variation and the need for Uncertainty Factors (UFs) in Extractables and Leachables Analysis

Speaker: Dr. Mark Jordi, Jordi Labs

Abstract: Chemical characterization of extractables and leachables from medical devices and combination products has become an important component of biocompatibility testing. Extractables and Leachables are those substances which leach out of a product under either the use condition or an exaggerated laboratory condition. The recently released ISO 10993-18: 2020 guidance has clarified many important aspects of how this testing should be conducted. This includes additional information on establishing an analytical evaluation threshold (AET) which aids in determining which chemicals are at a concentration which present a potential toxicological concern. A major problem in the application of the AET is quantitative error caused by response factor (RF) variation. This error occurs because most extractables do not give a consistent response using mass spectroscopy detectors. This problem is further exacerbated by the fact that many extractables and leachables cannot be readily obtained as commercial standards (oligomers, degradation products, catalyst residues, etc.) and are therefore quantitated using surrogate standards. Recent publications have highlighted the risks posed by RF variation for both LCMS (Jordi et al. Journal of Pharmaceutical and Biomedical Analysis 150 (2018) 368–376) and GCMS (Jenke and Odufu, Journal of Chromatographic Science 2012;50:206–212). The importance of this issue has been recognized by the FDA resulting in the addition of an uncertainty factor (UF) in the calculation of the analytical evaluation threshold (AET) designed to account for response variation. While this aids in mitigating

the risks of under reporting of extractables, the resulting revised AET creates significant analytical challenges often exceeding the limit of detection (LOD) of current mass spectrometry instrumentation and requiring sample concentration. Degradation or loss of extractables during concentration can undo the perceived benefit gained by using the uncertainty factor. Response variation also creates questions as to the validity of risk assessments based on relative quantitation values and is one of the key issues at the root of poor reproducibility in recent high profile interlaboratory studies. It is therefore strongly desirable to define improved methods for quantitation with more universal RFs which mitigate the need for UFs. In this presentation, an alternative strategy for quantitation will be shown using triple detection liquid chromatography mass spectroscopy (LCMS) with ultraviolet (UV) and charged aerosol detection (CAD) as well as duel detection Gas Chromatography Mass Spectroscopy (GCMS) with simultaneous Flame Ionization Detection (FID). The response factor distributions for UV, LCMS, GCMS, FID and CAD will be described as obtained by analyzing a broadly constituted database of extractables. A method will be presented for reducing response variation through application of optimized detectors thus reducing the associated need for UFs and increasing confidence in the resulting risk assessments.

Chemical Analysis for Medical Devices: Strategies for Reducing Scientific Questions

Speaker: Dr. Berk Oktem, US FDA

Abstract: Medical devices are unique in the diversity of materials of construction, extent/types of tissue contact, and duration of contact. When evaluating the safety of medical device extractables, it is these unique attributes that necessitate medical device specific analytical/toxicological considerations that will be discussed. Following the publication of ISO 10993-18:2020 and the CDRH partial recognition in July 2020, some scientific questions emerged in the field of chemical analysis of medical devices. Considerations of unique non-targeted analytical methods that generate data adequate for toxicological risk assessment will be discussed, including, but not limited to: extraction method design, analytical instrument/tool selection, system suitability, identification/semi-qualification, and data reporting. The selection and application of the analytical evaluation threshold (AET) will also be discussed.

This webinar is available on the MDCPSS website:
http://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp

OTSS/MDCPSS Virtual Career Panel – SOT Mentoring Event

Date and Time: Monday, September 21, 2020, at 12:00 PM–1:00 PM (EDT)

Abstract: The Ocular Toxicology Specialty Section (OTSS) and the Medical Device and Combination Product Specialty Section (MDCPSS) are holding a virtual career panel as a mentoring event for SOT members interested in career development within the ocular and medical device toxicology fields. The panel will consist of professionals at early, middle, and late stages of their career from Academia, Government, Industry, and Consulting. The panelists will introduce themselves, provide a brief overview of how they arrived at their current position, and address questions from the event moderators. Then the Q&A session will be opened to the audience to engage the panel on career advice, strategy, and goal setting. Please join MDCPSS for our upcoming virtual career panel.

Panelists:

Academia	Government	Industry	Consulting
Mindy Reynolds Washington College	Ron Brown Risk Science Consortium	Hiromi Hosako Alcon	Joel Cohen Gradient Corp.
Neera Tewari-Singh Michigan State Univ.	Alan Hood US FDA	James Kleinedler Boston Scientific	Andrea Rodrigues Tox Strategies
—	Elissa Wong US FDA	Bob Przygoda* Johnson & Johnson	William Wustenberg Mycroft Medical LLC
—	—	Ed Reverdy Johnson & Johnson	—

*Retired

This webinar is available on the MDCPSS website:
http://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp

Impact of 2017/745 EU Medical Device Regulation (MDR) on Biological Evaluation of Medical Device

Date and Time: Thursday, January 16, 2020, at 11:00 AM–12:00 PM (EST)

Speakers: Jeremy Tinkler, Director of Regulatory Consultancy and Quality Assurance, MedPass International SAS;
Varun Sukumaran, Senior Strategic Consultant, MedPass International SAS

Abstract: This webinar will focus on the impact of the 2017/745 EU Medical Device Regulation (MDR) on biological evaluation of medical devices. The webinar will compare relevant MDR General Safety and Performance Requirements (GSPR) with the Medical Devices Directive (MDD) Essential Requirements; compare MDR GSPR with ISO 10993 and ISO 14971; and discuss the impact of changes in ISO 10993-1:2018 and other ISO standards. A generous Q&A session is planned to accommodate conversation with the speaker—Chairman of ISO/TC 194 Biological Evaluation and Director of Regulatory Consultancy and Quality Assurance at an EU Authorized Representative, regulatory consultancy, and CRO.

This webinar is available on the MDCPSS website:
http://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp

SOT Annual Meetings

Unfortunately, we missed each other at the 59th Annual Meeting and ToxExpo! However, the Virtual 2020 Meeting still allowed us to hold our sponsored Workshop:

Known Unknowns: Challenges and Approaches for Handling Chemical, Hazard, and Regulatory Uncertainty in Medical Device Safety Assessements

Date and Time: Thursday, April 16, 2020, at 1:00 PM–2:45 PM (EST)
Co-Chairs: Tom Lewandowski, Gradient; and Alan Hood, US FDA/CDRH

Introduction
Tom Lewandowski, Gradient, Seattle, WA

Chemical Characterization Strategies for Medical Device Biocompatibility Assessment
Adam Kozak, Cambridge Polymer Group Inc., Boston, MA

Predictive Toxicology Approaches for Medical Device Biocompatibility Assessment
Joel Cohen, Gradient, Cambridge, MA

CDRH Scientific Perspective on Material Characterization and Toxicological Risk Assessment of Nontargeted Medical Device Extractables
Berk Oktem, US FDA/CDRH, Silver Spring, MD

Extractables and Leachables Analysis of Medical Devices in a Changing Global Regulatory Environment
Whitney Christian, Medtronic, Jacksonville, FL

Abstract: The regulatory landscape for the safety evaluation, clinical testing, and commercial development of medical devices is undergoing considerable changes, including new requirements for material characterization and chemical risk assessment early on in the development process. In this dynamic environment, extractables/leachables (E/L) analysis is becoming a key tool in biocompatibility assessments to ensure patient safety and establish regulatory compliance. The first speaker will begin the discussion on medical device chemical characterization strategies, a necessary step for understanding potential chemical exposures from medical device components. The presentation will include examples of how information concerning material chemistry and the manufacturing process can reduce the cost and effort associated in resolving "unknown" extractable compounds. The next presentation will focus on predictive toxicology methods (e.g., computational toxicology programs, read-across, Threshold of Toxicological Concern) for evaluating potential risks from extractable compounds. Case studies will be presented to demonstrate the importance of expert judgment when interpreting *in silico* hazard predictions, as well as approaches for justifying a read-across approach for risk assessment of extractable compounds. The third speaker will then discuss the US Food and Drug Administration (US FDA) perspective on the issues raised in the preceding talks. Agency experience with unique nontargeted analytical methods that generate data adequate for toxicological risk assessment will be presented, which include, but are not limited to, extraction method design, analytical instrument/tool selection, selecting an analytical evaluation threshold (AET), sample manipulation, system suitability, calibration, identification/semi-qualification, and data reporting. The final speaker will present a broader overview of the global regulatory landscape for medical device safety evaluation. Notable activity includes the revision of ISO 10993-1, implementation of the European Union's revised Medical Devices Regulation, and amendments to California Proposition 65. This presentation will cover how new requirements for extractables/leachables analysis will affect the manufacturer's ability to justify the safety of hazardous substances within devices, verify warning label exemption, evaluate biological equivalence of predicate/proposed devices, and support supply chain controls and ensure efficient change management.

Congratulations to our 2020 Award Winners!!!

Best Abstract Award

Frances K. Hsia, Sherry P. Parker, Sarah L. Huebert, and Catherine D. Christensen for "A critical evaluation of the NAVI model for thrombogenicity evaluation of cardiovascular medical devices: Correlation between *in vitro* hemocompatibility test results and *in vivo* thrombus scores"

Best Published Paper Award

David M. Saylor, Vaishnavi Chandrasekar, David D. Simon, Paul Turner, Laura C. Markley, and Alan M. Hood. (2019). Strategies for Rapid Risk Assessment of Color Additives Used in Medical Devices. *Toxicological Sciences* **172**(*1*):201–212. (https://doi.org/10.1093/toxsci/kfz179)

Best Poster Award

Bradford D. Bagley, Dayna Dreher, Tim Dunbar, and JoAnne Fitch for "Risk Assessment of Extractables from Warmed and Room Temperature Dental Composite Restoratives"

Student Travel Award

Alexander Nguyen for "Cytotoxicity and Mutagenicity Assessment of Lithium Phenyl(2,4,6-trimethylbenzoyl)phosphinate (LAP) Photoinitiator with Exposure to 405 nm Light"

Other information and past activities from 2019-2020, including the Hall of Presidents over the last **10 years**, is available via the MDCPSS Annual Meeting & Reception presentation.

While SOT had hoped to be able to hold a traditional, in-person meeting in Orlando, FL, it became clear that this would not be feasible. Hence, the 2021 SOT Annual Meeting and ToxExpo will be held as a virtual event. Nearly 60 Scientific Sessions will be presented as part of the Virtual 2021 SOT Annual Meeting, alongside 14 Continuing Education courses. More details on these sessions, as well as the official schedule, will be available in the coming months.

The MDCPSS will sponsor an Informational Session on "**Safety Assessment of Devices Used in Assisted Reproduction Technology: Mouse Embryo Assay**".

The abstract submission period is currently open until **December 1, 2020**. Abstracts must be submitted through the online Abstract Submission System for consideration for the 2021 SOT Annual Meeting and ToxExpo. Please note that some SOT awards are contingent upon having an abstract submitted to and accepted

for the SOT Annual Meeting. Some of these award deadlines precede the abstract submission deadline, so plan accordingly.

Information on registration fees and other registration-related details for the all-virtual meeting will be available soon. Stay tuned!

2021 Award Deadlines

Best Overall Abstract Award – **January 6, 2021**

Best Poster Award – **February 22, 2021**

Best Published Paper Award – **January 6, 2021**

Malek Toxicology Delaware LLC Student Excellence Award – **January 6, 2021**

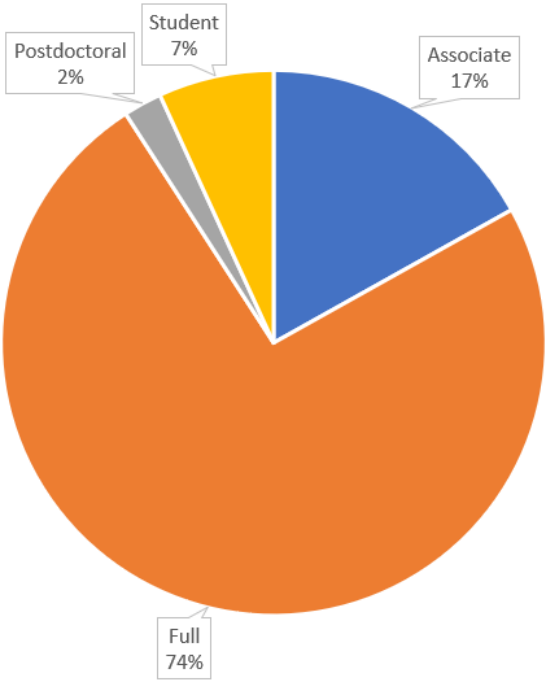
Student Achievement Award – **January 6, 2021**

For more information on awards, see our website.

Membership Update

The MDCPSS was formed in 2009 with 51 founding members. Since then we've grown steadily and now have 225 members, a 17% increase in the past year.

Our members come from 17 countries and include representatives from industry, government, consulting, and academia. Our membership includes Full SOT Members, followed by Associate, Student, and Postdoctoral Members (see Figure below). Educational backgrounds range from BS degrees to those with MBAs, MPHs, PhDs, DVMs, and MDs.



Postdoc Member Highlight

Dr. Ju Young (Julie) Park is an ORISE fellow at the US Food and Drug Administration, where she is evaluating *in silico* quantitative risk assessment methodologies that could be applied to assess potential reproductive and developmental toxicity of chemicals present in, or released from, a medical device. She received her doctorate in Toxicology in 2017 from the University of Washington in Seattle, where she also completed risk assessment emphasis courses in conjunction with her PhD degree. Dr. Park worked as a postdoctoral fellow at the same University until she joined the US FDA in November 2019. While at the University of Washington, she had served as a president and secretary in many student organizations, including the Korean Graduate Student Association and the Department's Student Advisory Committee. She is author/co-author of five peer-reviewed publications with many more to come. She has been an active member of many specialty sections of the SOT and am happy to join the Medical Device and Combination Product Specialty Section (MDCPSS) as a postdoctoral representative. Julie looks forward to meeting and working with all of you in the near future.

MDCPSS Member Achievements

The MDCPSS Executive Committee would like to congratulate our members on their professional accomplishments. Congratulations to all!

Awards, Promotions, Certifications:

Kazi Tasneem won the Best Trainee Abstract Award, from the Biological Modeling Specialty Section of SOT for the research: "Toxicokinetic Model Predicts Cellular Exposure in Organ-on-Chip Microdevices"; and 2020 WE Local Guiding Star Award from Society of Women Engineers for Exceptional Collegiate Leader.

Sarah Huebert was promoted to Principal Toxicologist at Boston Scientific.

James Kleinedler was promoted to Regulatory Affairs Fellow at Boston Scientific.

Relevant Publications:

A paper co-authored by Acting NICEATM Director Nicole Kleinstreuer describes Pred-Skin, a web tool that integrates multiple quantitative structure-activity relationship models to predict whether chemicals might be skin sensitizers with the potential to cause allergic contact dermatitis. Pred-Skin was developed by NICEATM in collaboration with scientists at the University of North Carolina at Chapel Hill and the Universidade Federal de Goiás, and is available at http://predskin.labmol.com.br/.

Borba JVB , Braga RC, Alves VM, Muratov EN, Kleinstreuer N, Tropsha A, and Andrade CH. (2020). Pred-Skin: A Web Portal for Accurate Prediction of Human Skin Sensitizers. *Chemical Research in Toxicology* **Article ASAP**. DOI: https://doi.org/10.1016/j.yrtph.2020.104787

Badding MA, Vargas JR, Fortney J, Cheng QJ, and Ho C-H. (2020). Toxicological Risk Assessment of Bisphenol A Released from Dialyzers under Simulated-Use and Exaggerated Extraction Conditions. *Regulatory Toxicology and Pharmacology* **118**:104787. DOI: https://doi.org/10.1016/j.yrtph.2020.104787

Please submit your achievements for the next newsletter to Megan Hahn (mhahn@namsa.com).

Treasury Update

The MDCPSS Executive Committee would like to thank our sponsors for helping to make MDCPSS 2019-2020 activities possible. MDCPSS had a successful year in member registrations and net assets, with modest expenses.

2020 Net Assets

January	$15,332
February	$14,505
March	$15,855
April	$15,855
May	$15,855
June	$20,868

2020 MDCPSS Sponsors

Malek Toxicology Delaware, LLC
NAMSA
Kelly P. Coleman/Medtronic
WL Gore & Associates Inc.
WuXi AppTec, Inc.

To support MDCPSS activities, please consider making a tax deductible donation. If you would like to dedicate a contribution to supporting one or more activities, the EC will gladly facilitate your tax free donation and recognize your support at the annual event and in our communication. MDCPSS accepts donations by check or credit card. For additional information regarding donations to MDCPSS, please contact the MDCPSS Secretary/Treasurer, Megan Hahn (mhahn@namsa.com), or Belinda "Bo" Inscho (belinda@toxicology.org) at SOT Headquarters.

ISO 10993 Updates

By Kelly Coleman[‡]
[‡]Medtronic Physiological Research Labs, Minneapolis, MN

During 2020 several of the ISO 10993 standards for the biological evaluation of medical devices were finalized or being completed by working groups of ISO Technical Committee 194 (ISO/TC 194) [https://www.iso.org/committee/54508.html].

ISO/TC 194, which has 32 participating members, currently publishes 31 standards, and has nine others under development. Brief summaries on the status of five of these standards are presented below.

ISO/DIS 10993-10

Biological evaluation of medical devices — Part 10: Tests for skin sensitization

The Draft International Standard (DIS) version of the new Part 10 standard focuses solely on skin sensitization. It is comprised of seven clauses and eight annexes. The clauses concern the three *in vivo* sensitization tests: Local lymph node assay (LLNA), Guinea pig maximization test (GPMT) and closed-patch Buehler test. The information about these tests, which was carried forward from the existing ISO 10993-10:2010 standard, has been updated in the DIS.

In addition to the updated normative clauses, there is a new 15-page informative annex on *in vitro* sensitization assays. The Final DIS (FDIS) version of this standard will be released in the fall for voting and comments. When the ISO/FDIS 10993-10 standard is finalized and published, the existing ISO 10993-10:2010 standard will be withdrawn.

ISO/FDIS 10993-12

Biological evaluation of medical devices — Part 12: Sample preparation and reference materials

The FDIS version of the new Part 12 standard, which was approved in July, contains 11 clauses and seven informative annexes. By comparison, the existing ISO 10993-12:2012 standard contains 11 clauses and four informative annexes. Annexes A, B, C, and D in the new Part 12 have been updated. They concern Experimental Controls, Sample Selection and Preparation, Test Sample Extraction, and Exhaustive Extraction. The new ISO 10993-12 standard should be published by ISO by end of 2020.

ISO 10993-16:2017

Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables

This updated standard, which was approved by ISO/TC 194 in 2017, was adopted by AAMI in 2020. It is comprised of five clauses and one annex, which was the same as ISO 10993-16:2010. Some of text in the 2017 version has been modified and several new references have been added to the Bibliography. The Annex titled, *Circumstances in which toxicokinetic studies shall be considered*, contains some new text about nano-objects but otherwise is virtually identical to the 2010 version. The ISO 10993-16:2017 standard is available directly from ISO.

ISO/CD2 10993-17

Biological evaluation of medical devices — Part 17: Toxicological risk assessment of medical device constituents

The second Committee Draft (CD) of the updated Part 17 standard will be released during the fall of 2020 for comment and voting. This version consists of eight clauses and five annexes.

It represents a major update and expansion of the existing ISO 10993-17:2002 standard.

Key themes include obtaining toxicological information, determining exposure doses, derivation of tolerable intakes and tolerable contact levels, the threshold of toxicological concern, toxicological screening limits, and calculating margins of safety. The Part 17 writing team has until June of 2021 to complete the standard. Between now and then it is anticipated that there will be at least one DIS and an FDIS. Once finalized the new standard will be published by ISO, probably during the fall of 2021.

ISO/FDIS 10993-23:2020

Biological evaluation of medical devices — Part 23: Tests for irritation

The FDIS version of this standard, which was approved on September 1, 2020, is comprised of eight clauses and nine informative annexes. The normative text is primarily concerned with *in vitro* and *in vivo* irritation testing. The *in vitro* irritation clause is based on the results of the recent *in vitro* irritation round robin study that was

sponsored by ISO/TC 194 Working Group 8. The *in vivo* irritation clause, which concerns rabbit skin irritation testing, was carried forward from the existing ISO 10993-10:2010 standard. The general principles clause of the Part 23 standard states: "The *in vitro* irritation test shall be performed before animal testing or human patch test is considered." The annexes provide additional information about *in vitro* testing, human skin testing, and a background summary on irritation tests. The new ISO 10993-23 standard should be published by ISO by the end of 2020. Once published it will become the standard for all medical device irritation testing and supersede ISO 10993-10:2010.

US FDA Partial Recognition

US FDA Partial Recognition of ISO 10993-18:2020 – Implications for Toxicological Risk Assessment

By Joel Cohen* and Rachel Y. Chang†
*Gradient, Boston, MA
† Gradient, Seattle, WA

On July 6, 2020, the US Food and Drug Administration (US FDA) issued a partial recognition of ISO 10993-18:2020, "Chemical characterization of medical device materials within a risk management process."[1] This standard details a framework for characterizing the identities and quantities of the materials of construction of a medical device, the chemical constituents in each material of construction, the chemical substances used in the manufacturing process (*e.g.*, processing aids, mold release agents), and the potential of the device (or its materials of construction) to release chemical substances under clinical use conditions (extractables and leachables) resulting in exposures to patients under clinical use conditions. The results of analytical testing conducted according to ISO 10993-18:2020 may be reviewed by a toxicologist in their risk assessment of potential chemical exposures to patients. Below we outline sections of the guidance that US FDA does not recognize, and we summarize some implications for what will be considered acceptable chemical testing and reporting, as well as for how toxicologists should interpret the chemical characterization data.

As detailed in US FDA's Supplementary Information Sheet (SIS) issued on July 6, 2020,[2] the following sections of the ISO 10993-18:2020 standard are not recognized:

- **US FDA does not recognize clause 5.5, second and third sentences**: "The [analytical evaluation threshold] AET should preferably be derived from a safety-based threshold (such as the [threshold of toxicological concern] TTC) but if this is not practically achievable, an analytical threshold, such as the Limit of Quantification (LOQ) can be used as the reporting threshold. However, the difference between the AET and the LOQ shall be considered in the toxicological risk assessment and the difference shall be justified."

[1] International Organization for Standardization (ISO). 2020. "ISO 10993-18:2020: Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process (Second Edition)." ISO 10993-18:2020(E), 74p.
[2] US Food and Drug Administration (US FDA). 2020. "Recognized Consensus Standard database record for ISO 10993-18 Second edition 2020-01 Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process. Part B: Supplementary Information Sheet (SIS)." Center for Devices and Radiological Health (CDRH). July 6. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=41050.

Implication: Extractables should be identified when present above an AET derived based on a safety-based threshold. In cases where the LOQ is greater than the TTC, additional effort may be necessary to generate high confidence identification and quantification of extractable chemicals for subsequent toxicological risk assessment.

- **US FDA does not recognize clause 7, second paragraph**: US FDA does not recognize the phrase "assist in any toxicological risk assessment."

  Implication: This phrase comes at the end of the following statement: "As necessary and appropriate, identified substances in the test solutions could be grouped into compound classes, based on structural or functional group similarities, to assist in any toxicological risk assessment." US FDA's partial recognition suggests that unique chemical structures should be provided for each identified extractable chemical quantified above the AET for the purposes of toxicological risk assessment. Medical devices comprised of polymer systems extracted under exaggerated conditions can often release hundreds upon hundreds of structurally similar oligomers that may now require unique structural information. Here, US FDA is taking issue with chemistry reports where similarly structured extractables are grouped together using generalized chemical descriptions (*e.g.*, glycerol-related compounds, or polyethylene glycol-related compounds), ultimately reducing the number of individual chemical structures reported. In light of this partial recognition, it may now fall upon the toxicologist to justify grouping similarly structured compounds in a category assessment approach in accordance with best practices.[3,4] Additional guidance on conducting read-across assessments of medical device extractables and leachables may be forthcoming in future updates to the ISO 10993-17:2002 standard.[5]

- **US FDA does not recognize Table D.3 in clause D.5 of Annex D**

  Implication: Table D.3 summarizes potential surrogate extraction vehicles for correlating chemical testing (according to ISO 10993-18:2020) to biological testing (*e.g.*, *in vitro* cytotoxicity tests according to ISO 10993-5:2009[6]). For example, Table D.3 suggests 1/9 (v/v) ethanol/saline to be an appropriate surrogate extraction solvent to best mimic biological testing conducted with an extraction in cell culture medium without serum. US FDA indicates this table conflicts with a prior guidance document by the Center for Food Safety and Applied Nutrition (CFSAN) on testing chemical migration from food contact substances.[7] The 2007 CFSAN guidance states, "There does not appear to be one solvent that will effectively simulate a food oil for all polymers," and recommends consulting with US FDA prior to selecting a solvent exposure testing. The reference to this 2007 CFSAN guidance suggests special care

[3] Organisation for Economic Co-operation and Development (OECD), Environment Directorate, Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. 2014. "Guidance on Grouping of Chemicals, Second Edition." ENV/JM/MONO(2014)4, OECD Environment Health and Safety Publications Series on Testing and Assessment No. 194, 141p., April 14.

[4] Escher, SE; Kamp, H; Bennekou, SH; Bitsch, A; Fisher, C; Graepel, R; Hengstler, JG; Herzler, M; Knight, D; Leist, M; Norinder, U; Ouédraogo, G; Pastor, M; Stuard, S; White, A; Zdrazil, B; van de Water, B; Kroese, D. 2019. "Towards grouping concepts based on new approach methodologies in chemical hazard assessment: the read-across approach of the EU-ToxRisk project (Editorial)." *Arch. Toxicol.* 93:3643–3667. doi: 10.1007/s00204-019-02591-7.

[5] International Organization for Standardization (ISO). 2002. "ISO 10993-17: Biological Evaluation of Medical Devices - Part 17: Establishment of Allowable Limits for Leachable Substances." ISO 10993-17:2002, 32p.

[6] International Organization for Standardization (ISO). 2009. "Biological Evaluation of Medical Devices - Part 5: Tests for In Vitro Cytotoxicity (Third Edition)." ISO 10993-5:2009(E), 34p., June 1.

[7] Center for Food Safety and Applied Nutrition (CFSAN). 2007. "Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances (Chemistry Recommendations)." Accessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-preparation-premarket-submissions-food-contact-substances-chemistry.

must be taken in selecting appropriate surrogate solvents for medical device chemical extraction testing, and consulting with the agency early on is recommended.

- **US FDA does not recognize Formula E2 and paragraph preceding Formula E2 and two paragraphs following Formula E2 in clause E.2 of Annex E**

  Implication: Formula E2 defines a possible statistical approach for establishing and justifying a particular uncertainty factor (UF), which is then used to derive an appropriate AET. US FDA cites a recent publication by Jordi *et al.* (2020)[8] that suggests calculating UFs according to this formula "can result in UF values <1 in some cases, and provides unreasonably large UF values for other cases where there is only modest [response factor] variation." Jordi *et al.* instead recommend calculating UFs as follows:

  $$UF = 1 / (1\text{-}RSD)$$

  where "RSD" refers to the relative standard deviation of a response factor database. US FDA's SIS indicates the equation and corresponding text will be corrected by ISO in forthcoming publications.

- **US FDA does not recognize example C2 in clause E.4 of Annex E**

  Implication: Example C2 suggests 120 µg/day is an appropriate dose-based threshold (DBT) for establishing the AET for a permanent contact device. US FDA is requiring a more conservative DBT that is strictly based on the anticipated duration of body contact, as outlined in ISO TS 21726:2019.[9] US FDA's approach here is consistent with the agency's partial recognition of ISO 10993-17:2002,[10] whereby allowable limits for extractables of devices with exposure duration >30 days should not be extrapolated from µg/day to µg/device based on the anticipated exposure duration.

Cobalt Hazard Up-Classification

Update on CMR 1B Classification of Cobalt and the Creation of an Industry-Wide EU MDR Justification for the Use of Cobalt-Containing Alloys in Medical Devices

By Whitney V. Christian[§] and Edward E. Reverdy[¥]
[§]Medtronic PLC, Jacksonville, FL
[¥]Johnson & Johnson, Somerville, NJ

On February 18th 2020, the 14th adaptation to technical progress (ATP)[1] of the Classification, Labelling and Packaging of Substances and Mixtures Regulation (the CLP)[2] was published in the European Union's Official Journal. The ATP contained the up-classification of cobalt metal (CAS 7440-48-4) to a CMR 1B substance

[8] Jordi, MA; Rowland, K; Liu, W; Cao, X; Zong, J; Ren, Y; Liang, Z; Zhou, X; Louis, M; Lerner, K. 2020. "Reducing relative response factor variation using a multidetector approach for extractables and leachables (E&L) analysis to mitigate the need for uncertainty factors." *J. Pharm. Biomed. Anal.* 186:113334. doi: 10.1016/j.jpba.2020.113334.

[9] International Organization for Standardization (ISO). 2019. "Biological evaluation of medical devices - Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents." ISO/TS 21726:2019(E), 12p.
[10] US Food and Drug Administration (US FDA). 2016. "Recognized Consensus Standard database record for ISO 10993-17 First edition 2002-12-01, Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances. Part B: Supplementary Information Sheet (SIS)." July 26. Center for Devices and Radiological Health (CDRH). https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=36860.

(carcinogen 1B, reprotoxin 1B, mutagen 2). This classification entered into force on March 9th 2020 and, as a result, on October 1st 2021, cobalt will be in scope of the European Union Medical Devices Regulation (EU MDR)[3] Annex I, Section 10.4. This means that hazardous substance labelling and justification will be required when cobalt is present at >0.1% *w/w* in invasive device materials, such as cobalt-containing pigments and alloys.

As reported in the Fall 2019 MDCPSS newsletter, a number of medical device companies came together in collaboration with MedTech Europe and Cardno ChemRisk to prepare for the cobalt up-classification by creating a base of evidence for an industry-wide justification to continue using alloys that contain >0.1% *w/w* cobalt, like cobalt-chrome and stainless steel. This MedTech Europe working group has written five manuscripts that contain scientific, medical, and epidemiology data showing that medical devices consisting of cobalt-containing alloys do not present a hazard or risk of carcinogenicity and reproductive toxicity and are safe for use in patients. All five manuscripts are slated for publication in a special edition issue of the Journal of Regulatory Toxicology and Pharmacology in the upcoming months.

To inform European Notified Bodies of the data within these manuscripts and illustrate their use as a justification, the MedTech Europe working group had two meetings with several Notified Bodies on March 24th and June 30th of this year. The working group explained the lack of pre-clinical and epidemiology evidence for the carcinogenic and reprotoxic hazard/risk of cobalt-containing alloys in medical device applications (per Section 10.4.2.a), provided scientific evidence supporting the safety and superior functional characteristics of these alloys in comparison to alternative materials (per Section 10.4.2.b), and concluded with a benefit-risk assessment that strongly supported the continued use of cobalt-containing alloys in medical devices (per Section 10.4.2.c). All of this is contained within the five manuscripts and satisfies the justification criteria delineated within EU MDR Annex I, Section 10.4.2, parts a – c. With that, the working group proposed the use of the published manuscripts as a sufficient justification for the presence of cobalt at >0.1% *w/w* in medical device alloys, and this was not met with rejection from the Notified Bodies.

Although there may be follow-up meetings with the Notified Bodies after publication of the manuscripts, the MedTech Europe working group believes this will be an acceptable approach for the Industry to justify the continued use of cobalt-containing alloys in medical devices. Stay tuned for updates and keep an eye out for the next revision of MedTech Europe's MDR Requirements on Hazardous Substances, which may contain additional details.

References

1. Commission Delegated Regulation (EU) 2020/217 of October 4, 2019 to amend and correct Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures.
2. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.
3. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

Advanced Materials for COVID-19

Public Health Emergencies and Advanced Materials Solutions: How to Navigate in COVID Era?

By Kazi Tasneem**
**Vanderbilt University, Nashville, TN

During a global pandemic such as COVID-19, an extensive amount of research has been redirected toward using advanced materials to health emergency solution that are moving rapidly from the laboratory scale to the commercial application. Engineered nanomaterials and other advanced material technologies appear to offer promising solutions, including for use in antimicrobial and anti-fogging coatings, diagnostic tools, personal protective equipment, filtration, sensors, medical devices, and other applications. As Scientists we need to orient research that can be adopted quickly by commercial entities around the world to fight COVID-19 and humanitarian needs at a global level. With this motivation, Advanced Material Pandemic and Future Preparedness Taskforce (AMPT) was formed in April 2020 in response to the COVID-19 pandemic and continues to evolve and grow as an organization.

AMPT is an international public-interest initiative focused on using Advanced Material to help solve some of humanity's most pressing challenges. Currently with over 15 country chapters, 10 working groups and over 30 institutions, AMPT is set to establish a comprehensive roadmap, library of knowledge and map of user-centric needs to deliver a framework to devise strategies, coordinate global activities and fast track solutions to address the technological and societal needs of the post pandemic world.

As the research community continues to implement advanced technologies, it is critical to close the scientific and regulatory gaps needed in order to expedite the application of these materials, especially nanotechnology, as the next generation of solutions in health emergencies. Within AMPT, the Applied Public Health and Environmental, Health, and Safety Working Group has three primary aims: 1) to address the challenges of conducting urgent toxicological testing for nanomaterials solutions during a health emergency, 2) to analyze the existing regulatory framework and associated gaps in regulatory testing and risk assessment, and 3) to ensure that the nanomaterial solutions have intended results, receive proper vetting and comply with applicable laws, regulations, and standards. Based on the fast-track roadmap of the working group, it will be possible to identify advanced materials solutions on their own or as part of the application of medical devices that can reasonably and safely be implemented in a short period of time to mitigate public health challenges by providing an innovative public health solution.

In AMPT, an expansive international network of expertise, resources, organizations, universities, scientific labs, advanced material companies, testing facilities and information clearing partners are working together to evaluate and use Advanced Materials as a solution to current and future health crisis. To learn more, visit the AMPT Network.

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