



# MDCPSS SPRING NEWSLETTER

Volume 13 / Issue 1

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## PRESIDENT'S MESSAGE

The countdown to the 2022 in-person SOT Annual Meeting in San Diego has begun! I'd like to update you on our progress, alert you to Medical Device and Combination Product Specialty Section's (MDCPSS) offerings at the meeting and highlight some excellent opportunities for networking with your medical device colleagues. Since the last SOT meeting, we've sponsored 4 thought-provoking and well-received webinars including "Evolving Use of In Vitro Hemocompatibility for the Biological Evaluation of Blood Contacting Medical Devices", "Biostability and Product Life-Cycle Evaluation of Medical Devices", "Practical Application of Computational Models to Predict Release Kinetics and Toxicity of Compounds Released from Medical Devices", and "Nitrosamines: Evolving Regulatory Landscape and Its Potential Impact on Medical Devices and Combination Products". If you missed any of them, the recordings are available on the MDCPSS website.

At the Annual Meeting, we look forward to an excellent Medical Devices poster session, when over 20 medical device-related posters are slated to be presented on March 28. Finally, the program and awards committee has selected deserving recipients for the awards that are given by the Specialty Section each year, and the Executive Committee has already begun planning for additional webinars for 2022. We hope to see you at the MDCPSS poster session and reception.

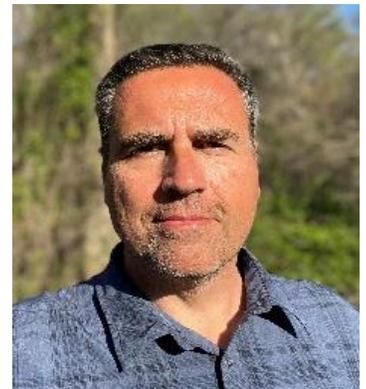
I'll close by thanking the Executive Committee for their ongoing and diligent support of the MDCPSS. It's been an honor to serve as your 2021-2022 MDCPSS President.

Sincerely,

Jan Oberdoerster, PhD, DABT

MDCPSS President

[joberd@wlgore.com](mailto:joberd@wlgore.com)



# MDCPSS Webinars



## **Webinar—Nitrosamines: Evolving Regulatory Landscape and Its Potential Impact on Medical Devices and Combination Products**

**Date and Time:** Tuesday, January 25, 2022, from 12:00pm to 1:00pm ET

**Chairs:** Mansi Krishan, MDCPSS Vice President-Elect and Jan Oberdoerster, MDCPSS President

Nitrosamine compounds are potent genotoxic agents in several animal species, and some are classified as probable (2A) or possible human carcinogens (2B) by IARC. They are referred to as “cohort of concern” compounds in the ICH M7 (R1) guidance for industry on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. Recent unexpected finding of nitrosamines impurities in some types of drug products due to the use of vulnerable processes and materials that may produce nitrosamine impurities led the US FDA and other international regulatory agencies to conduct a detailed analysis of these impurities in affected APIs and drug products and triggered the need for a risk assessment strategy for potential nitrosamines in any pharmaceutical product. In 2020, several regulatory guidance documents were published on nitrosamines including the US Food and Drug Administration (US FDA) guidance on “Control of Nitrosamine Impurities in Human Drugs”, European Medicines Agency (EMA) published assessment report “Procedure under Article 5(3) of Regulation EC (No) 726/2004, Nitrosamine impurities in human medicinal products”, and US Pharmacopeia (USP) draft “General Chapter <1469> Nitrosamine Impurities”. This webinar will provide an overview of (i) 2020 US FDA Guidance on Nitrosamine Impurities; and (ii) Opportunities and challenges: perspective from medical devices and combination product industry.

### ***Overview of US FDA guidance on “Control of Nitrosamine Impurities in Human Drugs***

**Speaker:** Owen McMaster, US FDA

**Abstract:** Since the 2018 discovery of nitrosamines impurities in valsartan and products, regulatory agencies around the world including the FDA have worked hand-in-hand with industry to document, interpret and mitigate the impact of these nitrosamine impurities. In September 2020, FDA published a Guidance for Industry entitled ‘Control of Nitrosamine Impurities in Human Drugs’, a document which has been recently updated. This talk will discuss the information contained in this guidance regarding potential sources of contamination in active pharmaceutical ingredients (API’s) and drug products. There will also be a discussion of recommendations to drug manufacturers for mitigating the presence of these nitrosamines and avoiding drug shortages.

### ***Opportunities and Challenges: Perspective from Medical Devices and Combination Product Industry on Recent Regulatory Guidance for Nitrosamines***

**Speaker:** Daniel Nazarenko, PhD, Becton, Dickinson, and Company (BD)

**Abstract:** Opportunities and Challenges: Perspective from Medical Devices and Combination Product Industry on Recent Regulatory Guidance for Nitrosamines. The term nitrosamine describes a class of compounds having

the chemical structure of a nitroso group bonded to an amine (R1N(-R2)-N=O). These compounds can form by a nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions). These compounds are known for their potent carcinogenicity, and widespread occurrence in the environment, from air and water to our diets and drugs. N-Nitrosamines are considered cohort-of concern compounds per ICH M7 (R1) guidance as some members of this class are highly potent carcinogens in experimental animals. Voluntary recall of a drug in 2018 due to the presence of a nitrosamine followed by other recalls due to presence of nitrosamine impurities in other drugs led to increased surveillance by regulatory bodies across the globe and publication of guidance documents on control of nitrosamine impurities in human drugs by US FDA, EMA, and USP in 2020. Even though US FDA guidance and EMA assessment focus on nitrosamines in APIs only, their impact has been observed in combination products and medical devices. This presentation will provide an overview of (i) potential sources of nitrosamines in combination products and medical devices; (ii) challenges with identification and quantification of nitrosamines non-API matrices; and (iii) risk assessment approaches.

This webinar is available on the MDCPSS website:

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

## 2022 SOT Annual Meeting



**Sunday, March 27**

**Continuing Education Courses**

**AM04:** How Advances in Exposure Science and Toxicology Are Changing Assessments of the Effects of Chemical Mixtures on Human Health

**PM12:** Principles and Applications of Read-Across in Human Health Risk Assessment

**Monday, March 28, 2022, 9:00 am - 10:45 am**

**Poster Presentation | Medical Devices**

**21 Posters**

**Monday, March 28, 2022, 5:00 to 6:00 pm**

**Medical Device and Combination Product Mentoring Event**

This in-person event is intended to provide students, postdocs, and early-career scientists the opportunity to learn about toxicology career paths from mentors in diverse job sectors. This is planned to be held in the same location as the MDCPSS reception that follows.

**Monday, March 28, 2022, 6:00 to 7:30 pm**

**Medical Device and Combination Product Specialty Section Reception**

**Tuesday, March 29, 2022, 11:00 am - 12:20 pm**

**Roundtable Session**

Harmonization of Approaches for the Biological Safety Assessment of Medical Devices and Pharmaceutical Packaging: Implications for Drug-Device Combination Products

**Chair:**

Ronald Brown, Risk Science Consortium LLC

**Co-Chair:**

Cheryl Stults, C&M Technical Consulting LLC

**Primary Endorser: Medical Device and Combination Product Specialty Section**

**Registration deadline:**

- **Early bird by January 28**
- **Standard January 29 to February 25**
- **Final after February 25**

**2022 Awards and Application Deadlines**

Best Poster Award – **February 22, 2022**

For more information on awards, see our [website](#).

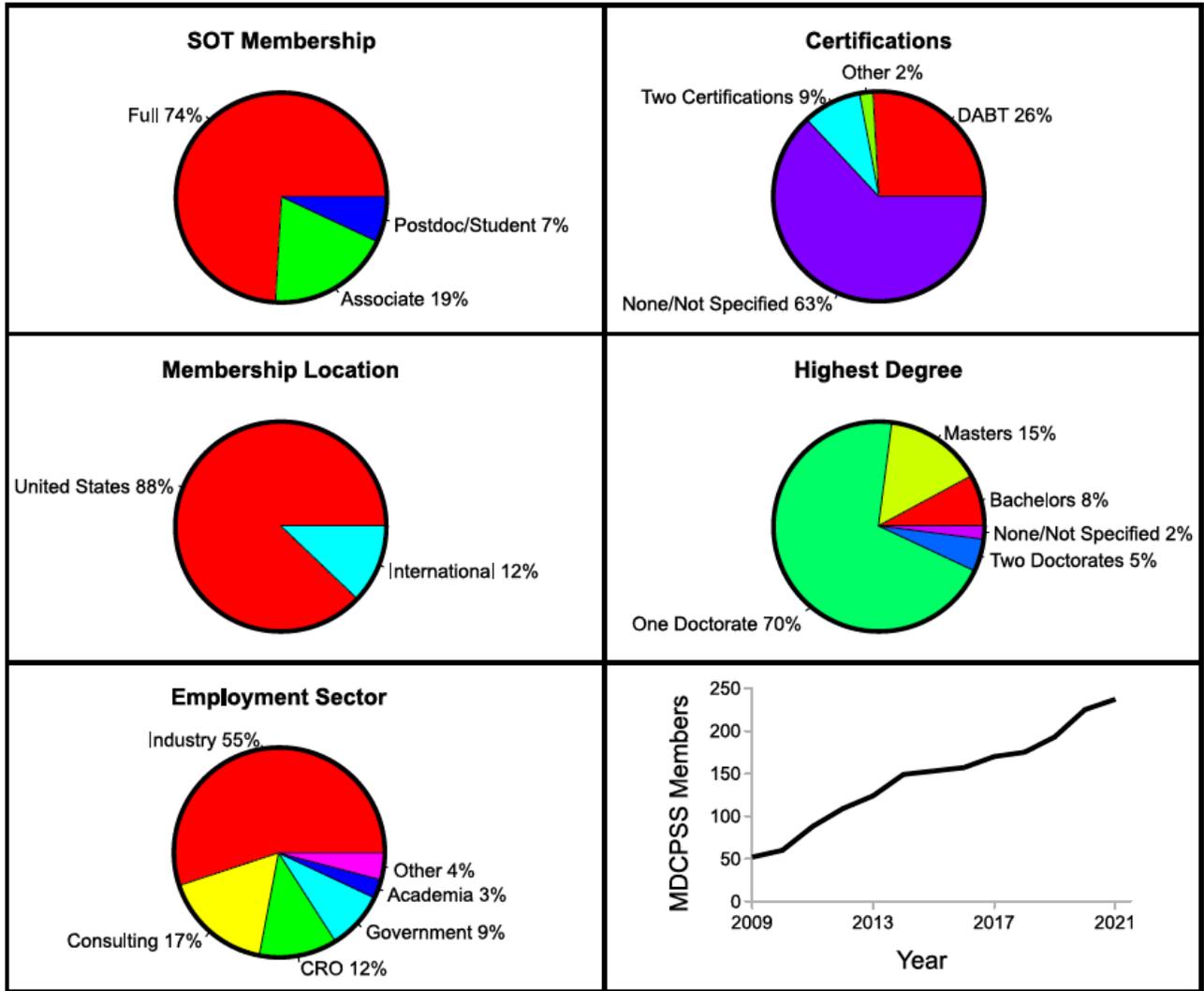


## Membership Update

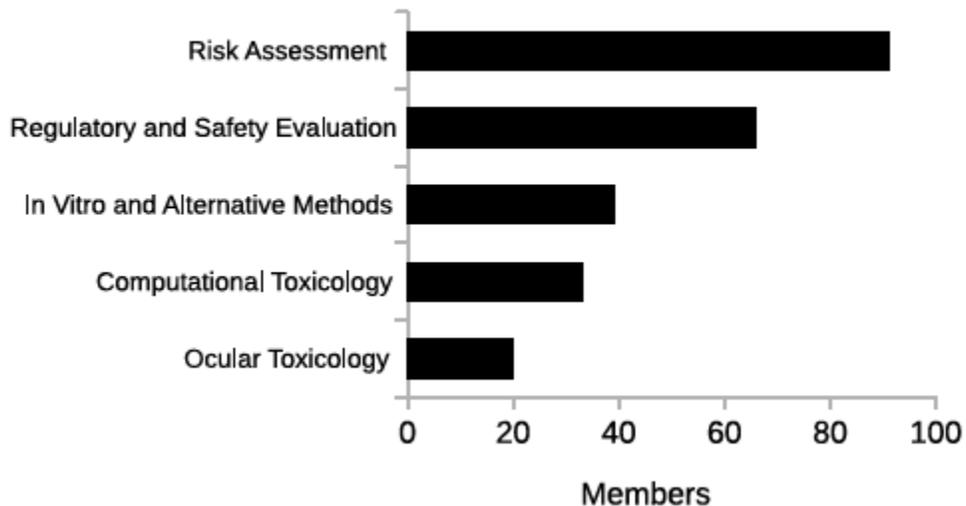
The MDCPSS was formed in 2009 with 51 founding members. Since then we've grown steadily and now have 237 members by Nov 2021, a 5% increase in the past year.

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.

At the time of writing this newsletter, membership renewals are still being processed. Therefore, the membership breakdown shown below is from 2021.



70% of MDCPSS members are also members of one or more other Specialty Sections. Here are the top 5:



# Treasury Update

The MDCPSS Executive Committee would like to thank our sponsors for helping to make MDCPSS 2020-2021 activities possible. MDCPSS had a successful year in member registrations and net assets, with modest expenses.

## 2021 Net Assets

July	\$25,832
August	\$25,832
September	\$25,831
October	\$25,831
November	\$25,831

## 2020-2021 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](mailto:mhahn@namsa.com)), or Belinda "Bo" Inscho ([belinda@toxicology.org](mailto:belinda@toxicology.org)) at SOT Headquarters.

## Medical Device standard and regulation updates in China

**By Chenghu Liu, Director of Biological Evaluation Department, NMPA-Shandong Quality Inspection Center for Medical Devices**

In recent years, the China National Medical Products Administration (NMPA) has released a series of important regulations on the biological safety evaluation of medical devices.

- Regarding the updates in these regulations, the "Regulations on the Supervision and Administration of Medical Devices" came into effect on June 1, 2021. This regulation requires that the biological evaluation tests and reports for the regulatory submissions can either come from a certified or accredited Contract Research Organization (CRO) or from the manufacturer itself through self-inspections. Subsequently, the NMPA issued the "Regulations on the Management of Self-inspection of Medical Device Registration", which regulates the main body, content, and format of the self-inspection report from the manufacturer.
- In terms of regulations on the animal tests of medical devices, the NMPA recently issued the "Guiding Principles for Medical Device Animal Experiment Research Technical Review Part One: Decision Principles" and "Medical Device Animal Experiment Research Technical Review Guidelines Part Two: Test Design, Implementation Quality Assurance". These regulations provide the framework on the reduction of animal experiments and avoiding unnecessary animal experiments on medical devices from the scientific perspective.

In China, the biological evaluation standards for medical devices are authored and released by the National Standardization Technical Committee for Biological Evaluation of Medical Devices. The secretariat of this technical committee resides in the Shandong Institute of Medical Devices and Drug

Packaging Inspection (formerly Shandong Medical Device Product Quality Inspection Center). The designated biological evaluation standards include national standards and industry standards.

- National standards (GB or GB/T means mandatory or voluntary) are approved and released by Standardization administration of the People's Republic of China (SAC); industry standards (YY or YY/T) are approved and issued by NMPA.
- In the past three years, China has updated 7 GB/T16886 standards. This series of standards are equivalent to the ISO 10993 series of standards in order to achieve simultaneously harmonized ISO 10993 standards. At the same time, China has also published 20 new YY standards, especially YY/T 0870 series of genetic toxicity standards, the YY/T 1292 series of reproductive and developmental toxicity standards, and the YY/T1465 series of immunogenicity standards. These standards have further systemically improved and enhanced the biological evaluation standards for medical devices in China.

## Medical Device standard and regulation updates in Japan

By Chikako Kitayama, PhD, Senior Biological Safety Scientist, NAMSA

The biological safety evaluation of medical devices in Japan is performed in accordance to the following guidelines:

- Ministry of Health, Labour and Welfare (MHLW)/Pharmaceutical Safety and Environmental Health Bureau (PSEHB)/Medical Device Evaluation Division (MDED) Notification No. 0106-1 issued on January 6, 2020: Revision of Basic Principles of Biological Safety Evaluation Required for Application for Approval to Market Medical Devices
- JIS T 0993-1 (2020): Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process (Japanese translation of ISO 10993-1 (2018))
- MHLW/PSEHB/MDED Notification No. 0531-5 issued on May 31, 2021: Revision of Basic Principles of Biological Safety Evaluation for Medical Devices Used in Dentistry
- JIS T 6001 (2021): Dentistry – Evaluation of biocompatibility of medical devices used in dentistry (Japanese translation of ISO 7405 (2018))

The MHLW Notifications are the announcements from the MHLW to medical device manufacturers and testing labs in Japan and describe the principles and thoughts of MHLW for the biological safety evaluation required for medical device submissions.

Japanese biological safety evaluation is harmonized with the ISO standards, as MHLW No. 0106-1 states in Section 3 of “*Basic Principles for the Biological Safety Evaluation of Medical Devices*”: “*In principle, biological safety evaluation of medical devices shall be performed in compliance with JIS T 0993-1 "Biological evaluation of medical devices-Part 1: Evaluation and testing within a risk management process" or the latest version of international standards of ISO 10993 series.*”

The test methods described in the latest ISO 10993 standards are generally acceptable, as MHLW No. 0106-1 states: “*The official standards have been continuously revised according to the development of science and technology. Accordingly, an appropriate test method must be selected, referring the most current standards at the time when testing is conducted.*” However, slight differences may be found in specific test methodology (e.g., sensitization, see below).

**Cytotoxicity:** Quantitative assays are preferable for Japanese submissions, as outlined in ISO 10993-5 (2009). In addition, MHLW No. 0106-1 mentions “*Guidance Document on Using In Vitro Data to Estimate In Vivo Starting Doses for Acute Toxicity, 2001. NIH Publication No. 01-4500*”, which is referenced in ISO

10993-5 (2009). The MHLW notification states quantitative methods described in this guidance, such as MTT, XTT, and MTS assays, are acceptable.

**Irritation:** There was a slight difference in methodology in the irritation test method described in the previous version of the MHLW notification. However, the irritation test method described in MHLW No. 0106-1 is now fully harmonized with ISO 10993-23 (2021). In addition, the *in vitro* skin irritation method is presented in MHLW No. 0106-1 and is ready to be accepted by Japanese regulatory bodies.

**Pyrogenicity:** Regarding material mediated pyrogenicity, MHLW No. 0106-1 states: “*In the ISO 10993 series of standards, the pyrogen test is included in Part 11: Systemic toxicity, which recommends the pyrogen tests found in the USP [United States Pharmacopeia], EP [European Pharmacopeia], and JP [Japanese Pharmacopeia]. The sensitivity of these testing methods is considered to be practically equivalent to that of the method in the guidance given here. Accordingly, it is not necessary to repeat this test if a result is available from another test that was conducted in accordance with ISO 10993-11 or national pharmacopoeias.*”

**Hemocompatibility:** Details regarding hemocompatibility testing were not well described in the previous version of the MHLW notification; however, MHLW No. 0106-1 contains ample information that is harmonized with ISO 10993-4 (2017).

**Sensitization:** MHLW No. 0106-1 requires the extraction method using organic solvents for medical devices made of polymer materials, which is an optional method described in Annex B of ISO 10993-10 (2021). Although this organic solvent extraction method is the first choice for devices made of polymers, evaluation using other extraction methods, such as the normative extraction method (described in Annex A) using saline and vegetable oil, are acceptable for devices made of non-novel materials that are either (1) single use with limited contact, or (2) less invasive and the risk is easily managed (e.g., Class I or Class II devices).

**Chemical Characterization:** Omitting biological testing using the chemical characterization data is not a common approach in Japan, as of now. MHLW No. 0106-1 states, “*For the omission of biological testing based on the result of chemical characterization testing, PMDA Consultation meeting (Medical device evaluation consulting (safety)) is highly recommended prior to the submission.*”

## 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>