Volume 8
Issue 1

MDCPSS WINTER/SPRING NEWSLETTER

President's Message

Dear Members,

Hello and welcome to the Medical Device and Combination Product Specialty Section's (MDCPSS) spring newsletter.

This past year has been busy and productive. Our Vice President Barb Henry has served on virtually every committee and kept us moving forward, our website liaison, Vice President-Elect Taylor Builee, has done a great job of ensuring that our website is up to date and populated with useful information, Secretary/Treasurer Shawn Deng has skillfully coordinated our webinar program, Councilor Sherry Parker has been the expert editor of the specialty section's newsletter, which is our main communication vehicle, while Councilor Whitney Christian has provided key support for the webinar program and contributed timely articles to the newsletter, plus our Graduate Student Representative Daniel Lou and Postdoctoral Representative Monica Pombo have served as able ambassadors to their organizations.

Webinars: So far this year we've sponsored three noteworthy webinars that were all thought provoking and well received. Additional details are provided in this newsletter. If you missed them recordings are available on the MDCPSS website.

On April 10th our last webinar of the year will be co-sponsored by the *In Vitro* and Alternative Methods (IVAM) Specialty Section and feature two presentations:

- "ISO 10993-1 Biological Evaluation – the Risk Management of Unstudied Extractables and Leachables (E&L) Impurities in Medical Devices and Combination Products" presented by Kim Li, Amgen, Inc.
- "Animal-Specific Modeling for the 3Rs in Pre-clinical Assessment: A Bone Drugs Example" presented by Marco Viceconti, University of Sheffield.

Mark your calendars so you don't miss it!

SOT Meeting Events: This newsletter also provides a list of the MDCPSS's SOT Annual Meeting events.

Membership: In December our headcount reached 170 members, which is a record. This specialty section began in 2010 with 51 members, and we've grown steadily ever since. For those of you that haven't done so please renew your SOT membership soon and don't forget to rejoin the MDCPSS!

Executive Committee: During the recent election there were two openings on the MDCPSS Executive Committee. To fill those positions I would like to welcome our newly elected officers Sherry Parker (Vice President-Elect) and Megan Hahn (Councilor).

I also wish to thank the following individuals whose terms end in April: Alan Hood (Past President), Sherry Parker (Councilor), and Monica Pombo (Postdoctoral Representative). We're very grateful for the terrific job they all did! Please continue to check the MDCPSS website for additional information and updates on our activities. Also, don't hesitate to contact me or any other Executive Committee members with ideas, feedback, and suggestions.

We hope to see you at the MDCPSS Reception and Poster session during the SOT Annual Meeting.

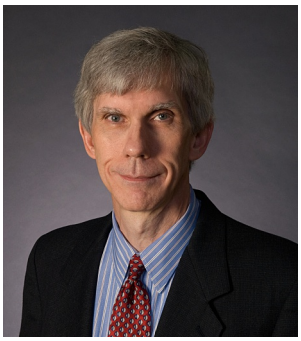
It's been an honor to serve as your 2016-17 MDCPSS President.

Sincerely,

Kelly Coleman

MDCPSS President

kelly.p.coleman@medtronic.com



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MDCPSS Webinars

MDCPSS hosted a webinar entitled "Evaluation of Medical Devices for Genetic Toxicity: A Global Perspective", held on October 19, 2016. Webinar speaker was Robert Przygoda, Johnson & Johnson.

Abstract: Genotoxicity is a key safety evaluation endpoint of healthcare products including pharmaceuticals and medical devices. It is also an ever evolving area in terms of the advancement of science and regulation. The ISO 10993-3 standard governing genotoxocity testing for medical devices was recently updated in 2014. Furthermore, quite a few national regulatory agencies have issued their own guidance to use the ISO 10993-3 standard, such as the recently published US FDA, Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management.
The presentation discussed the topics below:

- What is different about evaluating the genotoxicity of medical devices?
- How to determine if genetic toxicity evaluation is needed.
- ISO 10993-3 (2014)—Requirements (Risk Based Approach, Chemical Characterization, Tests, Test Sample Preparation, Reports)
- ISO TR 10993-33 (2015)—Guidance on Tests to Evaluate Genotoxicity Supplement to ISO 10993-3.
- Challenges using ISO 10993-3 Globally accepted but subject to interpretation by national regulatory agencies: US FDA guidance, Japan guidance and considerations for China submissions.

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 hosted a webinar entitled "ISO 10993-4 Biological Evaluation of Medical Devices: Selection of Tests for Interaction with Blood", held on December 14, 2016. Webinar speaker was Michael Wolf, Medtronic, Inc.

Abstract: For medical device companies with blood-contacting products, the ISO 10993-4 guidance document is important because it defines general requirements and considerations for evaluating interactions of concern between the devices and blood. The document describes: (1) classification of blood-contacting medical devices based upon intended use and duration of contact as defined in ISO 10993-1, (2) fundamental principles and scientific bases behind various methods of evaluating interactions of devices with blood, and (3) a structured selection of tests for consideration based upon intended use and blood contact duration. In short, this standard is a guide for start-up companies, established industry, and regulatory agencies to assess the apparent pre-

clinical blood compatibility of candidate cardiovascular devices and materials intended for human blood contact applications.

The foundation of ISO 10993-4 has several sources. However, since its inception in 2002, the document has received only minor revision. Over the past several years the revision of this document has involved review of hundreds of comments from around the world, with the FDIS recommended for formal approval in 2016. Concisely, the new document provides a simplified process flow diagram for high level planning decisions, a reduced and simplified table of example devices vs. testing categories for consideration, and a streamlined table of actual tests for consideration in each test category.

Importantly, the standard suggests more opportunities for meaningful in vitro testing to supplement or replace certain animal testing. More emphasis is also placed on the importance of testing blood contacting devices for impact on thrombosis.abolites in groundwater, pharmaceuticals, herbal substances and preparations and genotoxic drug impurities.

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 hosted a webinar entitled "Effects of Nanoscale Particles in the Brain", held January 23, 2017.
Webinar speaker was Allison Elder, Department of Environmental Medicine at the University of Rochester Medical Center

Abstract: It is well understood that exposure to particulate matter is causally associated with adverse cardiopulmonary health effects that are related to the generation of inflammatory mediators, autonomic nervous system activation, and the delivery of particles or their constituents to target tissues (translocation). A growing body of work has explored the ability of inhaled particles – with a focus on nanoscale particles (<100 nm in diameter) – to also have adverse effects in the central nervous system via similar mechanistic pathways. Studies with very poorly-soluble nanoscale particles demonstrated translocation to distal tissues like the brain and that smaller particles accumulate more efficiently than larger particles, albeit at a small fraction of applied dose. Exposures via other routes have also shown the accumulation in various tissues of nanoscale particles. The consequences of particle accumulation in the brain, such as inflammation or the induction or exacerbation of neurodegenerative processes, are also being explored in animal models. Using poorly-soluble nanoscale Mn oxide particles, for example, we found that markers of oxidative stress and inflammatory cell activation were elevated in the same regions of the brain where Mn accumulated following whole-body inhalation exposure in rats. Using a mouse model of Alzheimer's disease (AD), it was also demonstrated that exposure led to persistent microglial and astrocyte activation, elevations in amyloid β-42 protein, and decreases in synaptophysin staining. Similar findings have been reported in studies of the effects of other particle types like diesel exhaust. Taken collectively, the findings from these studies suggest that inhaled particles can be transported to the central nervous system and that they can elicit tissue responses that could contribute to the progression of pathology in those regions where accumulation occurs.
This webinar is available on the MDCPSS website:
http://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp

Medical Device Standards

Updates to Medical Device Standards

The technical committee for ISO 10993 Biological Evaluation of Medical Devices, TC 194, met in Annapolis, Maryland, September 18-23, 2016. Many of the standards are in a significant state of revision, including ISO 10993-1 (Evaluation and testing within a risk management process), ISO 10993-17 (Establishment of allowable limits for leachable substances), and ISO 10993-18 (Chemical characterization of materials). Because these standards are critical for risk assessment of medical devices, a requirement of the risk management process according to ISO 14971 (Medical devices — Application of risk management to medical devices), the working groups are working hard to align these documents. Soon to be finalized ISO 10993 standards that are in final draft international standard (FDIS) stage include ISO 10993-4 (Selection of tests for interactions with blood), and ISO 10993-16 (Toxicokinetic study design for degradation products and leachables). Coming updates to ISO 10993-4 were presented in a webinar in December by Mike Wolfe, from Medtronic.

At the end of 2016, a new version of ISO 10993-6 (Tests for local effects after implantation) was published. This version replaces ISO 10993-6:2007, and provides recommendations for brain implantation (in Annex D), more guidance throughout on implantation of absorbable materials, more detailed examples of histopathological scoring, and long term implantation timepoint of 12 weeks was changed to 13 weeks to be more consistent with the subchronic (90-day) timepoint indicated in ISO 10993-11 (Tests for systemic toxicity).

Other ongoing ISO 10993 projects include technical documents for threshold of toxicological concern (TTC), and nanomaterials.

International Organization for Standardization

New Final Draft International Standards for biological evaluation of gas pathway devices

This year, four new standards for biological evaluation of gas path devices will be finalized:

- ISO 18562-1: Biocompatibility evaluation of breathing gas pathways in healthcare applications -- Part 1: Evaluation and testing within a risk management process
- ISO 18562-2: Part 2: Tests for emissions of particulate matter
- ISO 18562-3: Part 3: Tests for emissions of volatile organic compounds (VOCs)
- ISO 18562-4: Part 4: Tests for leachables in condensate

Examples of breathing gas pathway devices include breathing systems and accessories, tracheostomy tubes, ventilators, nebulizers, CPAP devices including masks. These standards were developed to address the risk of potentially hazardous substances being conveyed to the patient by the gas stream. They provide an overall strategy for evaluation of these devices (ISO 18562-1), including risk assessment, and specific testing considerations for particulates analysis (ISO 18562-2), analysis of volatile organic chemicals from the dry gas pathway (ISO 18562-3), and analysis of leachable chemicals in condensate (ISO 18562-4). The standard provides recommendations for biological testing, and TTC levels for limited, prolonged and permanent gas pathway devices, that are appropriate for risk assessment.

The coming update to ISO 10993-1 will include a reference to ISO 18562 for biological evaluation of gas pathway devices. More information on available ISO 10993 and ISO 18562 standards can be found at ISO.org

2017 SOT Annual Meeting

Monday, March 13, 2017, 2:00-4:45 pm. Workshop, Modernizing Toxicological Risk Assessment for Compounds Released from Pharmaceutical, Consumer, Medical Device and Combination Products: Alternative Tools and Methods (CC Room 321; see below for details).
Monday, March 13, 2017, 5:00-6:00 pm. Hilton Baltimore Key Ballroom 5. Coffee Q&A Mentoring Event.
Monday, March 13, 2017, 6:00- 6:15 pm. Hilton Baltimore Key Ballroom 5. Subcommittee members meet and greet.
Monday, March 13, 2017, 6:00-7:30 pm. Hilton Baltimore Key Ballroom 5. Medical Device and Combination Product Specialty Section Meeting/Reception.
Tuesday, March 14, 2017, 1:15-4:30 pm. Poster Session, Medical Devices (P401-P425).
Tuesday, March 14, 2017, 1:00-2:00 pm, Poster session tour mentoring event (P401-P425).

Modernizing Toxicological Risk Assessment for Compounds Released from Pharmaceutical, Consumer, Medical Device and Combination Products: Alternative Tools and Methods

Monday, March 13, 2:00 PM to 4:45 PM

Chairperson(s): Richard Hutchinson, Johnson & Johnson, Somerville, NJ; and Alan Hood, US FDA, Silver Spring, MD. Endorser(s): In Vitro and Alternative Methods Specialty Section Medical Device and Combination Product Specialty Section Regulatory and Safety Evaluation Specialty Section

The potential toxicological effects of compounds released from medical devices and combination products are a patient safety concern for both device manufacturers and regulatory stakeholders. This session will address the need to advance methods for the toxicological risk assessment of compounds released from medical devices and combination products, and will explore opportunities for modernizing the risk assessment approaches for these compounds. This session is intended to generate a dialogue for recent advancements from a variety of industry and non-industry initiates in the development, acceptance, and application of alternative tools that complement or replace in vivo testing. The session focuses on two areas of toxicological risk assessment: hazard assessment, and risk characterization. The session begins with modernizing hazard assessment through systematic review using objective, reproducible methods that transparently document scientific judgments and the scientific basis of hazard identification conclusions. Then, recent insights on assigning Cramer classification to compounds that can be used as guidance and improvement of in silico tools will be

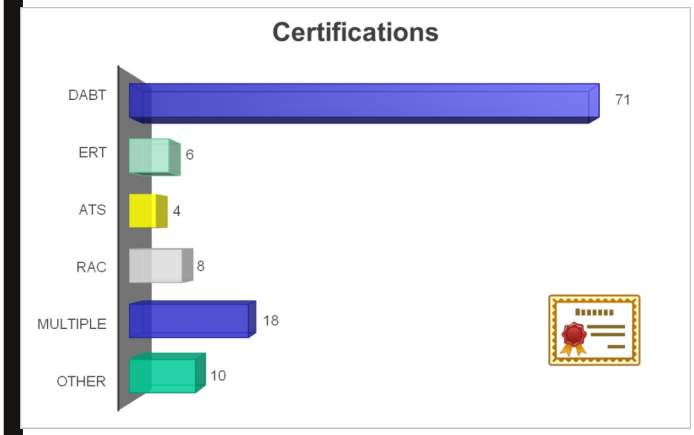
2017 SOT Annual Meeting (cont.)

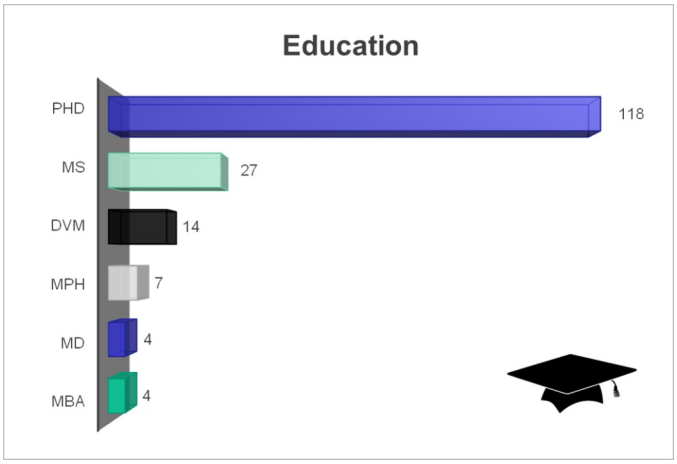
presented. Computational tools, such as QSAR models and Read-Across, to predict the toxicity of compounds lacking experimentally-derived toxicity data and the use of these predicted toxicity values will be discussed. The final topic is a semi-quantitative risk evaluation matrix to determine the amount and rigor of component testing that may be necessary and appropriate to establish that the component is suitable for its intended use. Academic/industry/consulting toxicological risk assessors and regulatory affairs representatives who have an interest in recent advancements in toxicological risk assessment in medical devices, combination, and consumer products should consider attending this workshop. Introduction. Alan Hood, US FDA, Silver Spring, MD. Evaluation of the Potential Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) with a Systematic Review Framework. Andrew Rooney, NIEHS-NTP, Research Triangle Park, NC. A Practical Guidance for Cramer Class Determination. Jie Shen, Eli Lilly and Company, Indianapolis, IN. Modernizing Toxicological Risk Assessment for Medical Devices Using ISO 10993 Standards. Ron Brown, US FDA, Silver Spring, MD. Development and Justification of a Risk Evaluation Matrix to Guide Chemical Testing Necessary to Select and Qualify Plastic Components Used in Production Systems for Medical Device and Combination Products. Dennis Jenke, Baxter International, Deerfield, IL.
See more at: http://www.toxicology.org/events/am/AM2017/program.asp#SSMonday

Membership Update

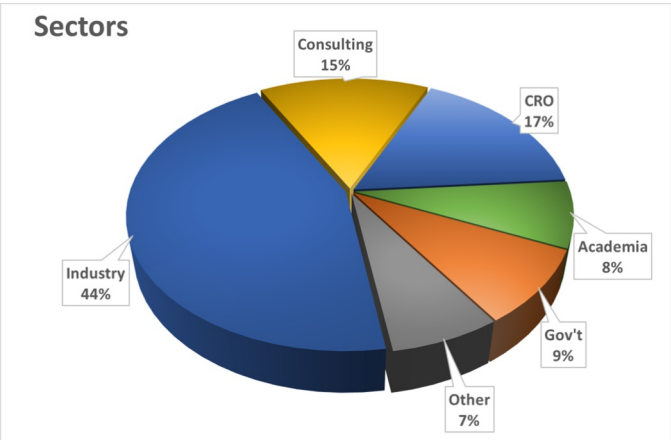
Contributed by Daniel Luo:
The MDCPSS was formed in 2009 with 51 founding members. Since then we've grown steadily and now have 170 members.

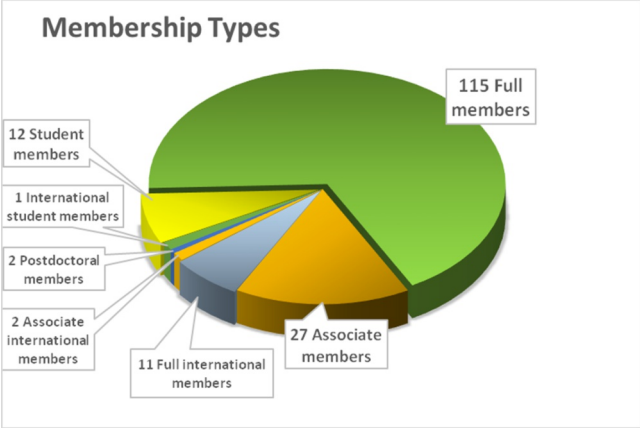
Our members come from industry, government, consulting and academia. From those who have indicated their sectors, ~44% are in industry positions, ~15% are in consulting, ~10% are in academia, and ~10% are in government related positions. Educational backgrounds range from BS degrees to those with MBAs, MPHs, PhDs, DVMs, and MDs.





Membership Updates (Cont.)





Treasury Update

2016 Net Assets

Dec	2016	$24,532
Nov	2016	$24,532
Oct	2016	$24,432
Sept	2016	$24,432
Aug	2016	$24,432
July	2016	$23,932

2016 MDCPSS Sponsors

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

2017 MDCPSS Sponsors (so far)

Medtronic
Edwards Lifesciences

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 2017 activities possible. Please consider making a tax deductible donation of any amount to support MDCPSS.

MDCPSS accepts donations by check or credit card. Checks may mailed to the following address: Medical Device and Combination Product Specialty Section, Society of Toxicology, 1821 Michael Faraday Drive, Suite 300, Reston, VA 20190. Credit card donations may be completed by contacting Raul A. Suarez (raul@toxicology.org) at SOT Headquarters (703- 438-3115 x1461). All donations should include the following: donor's name, contact information, donation amount, and payment information.

EU/MDR Updates

The European Union Medical Devices Regulation: A Brief Overview

By Whitney V. Christian

On February 22, 2017, the final version of the European Union (EU) Medical Devices Regulation (MDR)1 was published. This legislation replaces the European Active Implantable Medical Devices Directive (AIMDD)2 and the EU Medical Devices Directive (MDD)3, which were established in 1990 and 1993, respectively. The EU MDR is a more restrictive regulatory framework that must be met to obtain a Conformité Européenne (CE) Mark for medical device conformity and, in turn, approval for sale in the European Economic Area. Under prior regulatory directives, the EU device market has long been an appealing first market destination due to a less restrictive regulatory environment, which resulted in shorter market authorization timelines for medical devices. The EU therefore served as an ideal place to test innovative medtech products in patients and develop a portfolio of clinical data supporting safety, which could be used to obtain FDA approval later. With the implementation of the EU MDR, it is anticipated that the EU will become a less attractive market because of the increased cost and prolonged time-to-market associated with device registration, but for a good reason.

The full article which is available through a link on the MDCPSS website (see below) explains the implications of the MDR, and provides some of the chapter highlights and major regulatory changes in the EU MDR with specific examples. Major chaptors include the following:

Chapter I - Scope and definitions: Specific products without an intended medical purpose but with a risk profile like medical devices (e.g., products for aesthetic purposes, such as contact lens, cosmetic augmentation implants, liposuction equipment, and cosmetic lasers) are now regulated under the EU MDR (see Annex XVI).The definitions of a medical device and an accessory have been expanded in the EU MDR, resulting in products previously outside the scope of the EU MDD becoming accessories and products previously considered accessories under the EU MDD becoming medical devices (see Article 2).

Chapter II - Making available on the market and putting into service of devices, obligations of economic operators, reprocessing, CE marking, free movement: The EU MDR states that a device must meet the general safety and performance requirements set out in Annex I. Per Annex I, devices, parts thereof, or materials therein that contain more than 0.1% (w/w) substances which are carcinogenic, mutagenic, or toxic to reproduction (CMRs) or substances having endocrine disrupting properties (identified in REACH) must be labelled on the device itself and/or on the packaging with the list of such substances, and justification for their presence must be provided. Per Article 17, reprocessing of single-use devices is permitted in Member States that allow it (i.e., local law may prohibit reprocessing). The reprocessor is considered the manufacturer of the reprocessed device and assumes the obligations required of manufacturers, including product liability.

Chapter III - Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, European database on medical devices: All medical devices will require a unique device identification (UDI) code, which contains a device identifier (DI) and a production identifier (PI), for the purposes of traceability (see Article 27).

Chapter IV - Notified bodies:Under the EU MDR, NBs function as the regulatory enforcement arm of the Member States rather than an industry partner, as viewed under the EU MDD. However, under the required criteria, a conformity assessment body must meet to become designated and notified to the European Commission, thereby becoming a “notified” body (i.e., accredited), is considerably more rigorous and detailed than under the EU MDD (see Article 36 and Annex VII).

Chapter V - Classification and conformity assessment:Classification of certain devices has changed (see Chapter III of Annex VIII – 22 rules), and this may lead to recertification of a device at a higher risk class. A fairly complex set of procedures for conformity assessment appear in the EU MDR. The extent of the conformity

assessment is based on the device classification with high-risk devices receiving more in depth assessments based on quality management system assurance and assessment of the technical documentation than lower-risk devices (see Article 52 and Annexes IX, X, and XI). New general safety and performance requirements (including expanded device information on labels and websites) as well as specific structure and content (including post-market surveillance) requirements for technical files/documentation are provided (see Annexes I, II, and III). Overall, the data and format requirements are much more extensive than those of the EU MDD, which could cost manufacturers more time and money in preparing dossiers that are clear, organized, and readily searchable for the stringent review they will receive from NBs.

Chapter VI - Clinical evaluation and clinical investigations: In a clinical evaluation (per Article 61 and part A of Annex XIV), the manufacturer must provide clinical evidence to demonstrate compliance with the relevant safety and performance requirements appropriate to the characteristics of the device and its intended purpose (i.e., establish and verify clinical performance, benefit, and safety) for new devices and devices currently on the market, as there is no grandfathering (see Article 120).

Chapter VII - Post-market surveillance, vigilance and market surveillance:Per the life cycle approach of the EU MDR, several forms of post-market surveillance will be implemented that manufacturers are required to continuously carry out, including a post-market surveillance reports. Of note, the PMCF report and the summary of safety and clinical performance (see Article 32) for Class III and implantable devices is required to be updated at least annually and submitted by the manufacturer to a NB for validation; after validation, the NB will then upload the summary to EUDAMED. Reports of serious incidents and field safety corrective actions (see Article 87) as well as statistically significant trends (see Article 88) are also required.

Chapter VIII - Cooperation between Member States, Medical Device Coordination Group, expert laboratories, expert panels and device registers: Considerable effort is made in the EU MDR to ensure that the new regulations are uniformly applied across all Member States through various means of cooperation

Chapter IX - Confidentiality, data protection, funding and penalties: All parties involved in the application of the EU MDR are mandated to respect the confidentiality of information and data that is collected and shared (see Article 109), including personal data (see Article 110) as well as commercially confidential information, trade secrets, and intellectual property (unless disclosure is in the public interests). However, Article 1(16) supports freedom of information for the press and freedom of expression in the media, which potentially conflicts with the intention of protecting confidentiality and presents possible scenarios for misuse.

Chapter X - Final provisions: Per Article 120, CE Mark certificates issued by NBs under the AIMDD/EU MDD prior to the date of entry into force for the EU MDR (i.e., the date the EU MDR is published in the Official Journal of the European Union, which is projected for May 2017) will remain valid until the end of the period indicated on the certificate, with some exceptions.

References

1.Council of the European Union, Regulation of the European Parliament and of the Council 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, 22 February 2017.

2.Council of the European Communities, Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, 20 June 1990.

3.Council of the European Communities, Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, 14 June 1993.

Please see the link to the complete article at
http://toxchange.toxicology.org/p/fo/st/thread=26086

Upcoming Events

Joint webinar with IVAM:

April 10, 2017. 11am EST.

PRESENTER 1: Kim Li, PhD, DABT, MPH, Amgen Inc. Thousand Oaks, CA

Title: ISO 10993-1 Biological Evaluation – the Risk Management of Unstudied Extractables and Leachables (E&L) Impurities in Medical Devices and Combination Products

PRESENTER 2: Marco Viceconti, Executive Director, Insigneo Institute for in silico Medicine, The University of Sheffield and Sheffield Teaching Hospital NHS Foundation Trust

Title: Animal-specific modelling for the 3Rs in pre-clinical assessment: a bone drugs example

See this link to register:
https://aim-hq.webex.com/aim-hq/onstage/g.php?MTID=e037d459dcbf20aac3c525f46243d7e16

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