The FDA MDDT Program and Considerations for MAT Testing of Medical Devices

Chandramallika (Molly) Ghosh, Ph.D., DABT
Toxicologist
FDA/CDRH, Office of Device Evaluation, Division of Neurological and Physical Medicine Devices

NICEATM/PETA Workshop: Using the MAT as a Standalone Release Test for Medical Devices

September 18-19, 2018

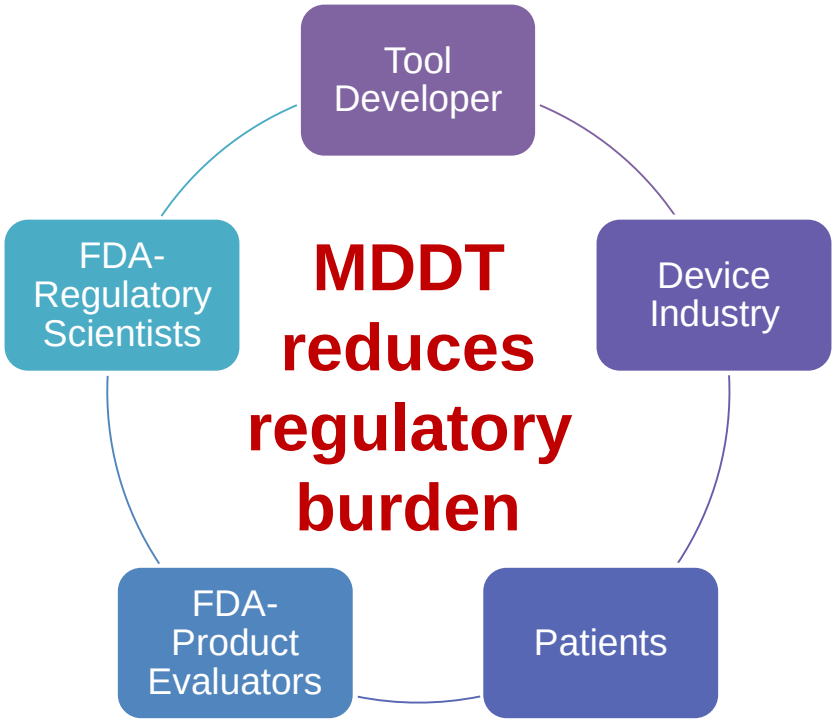
Bethesda, MD

Outline

- FDA's MDDT Program
- FDA's Predictive Toxicology Roadmap
- Pyrogenicity Assessment for Medical Devices
- Considerations for Qualification of *In Vitro* Alternatives for Pyrogenicity Assessment of Medical Devices
- MDDT Submission Logistics

Medical Device Development Tool (MDDT) Program: Benefit of Qualifying Tools

Promotes Efficient Medical Device Development



- Fosters innovation
- Encourages collaboration
- Reduces resource expenditure
- Qualified MDDT applied in multiple device submissions
- Efficiency in CDRH regulatory review resources
- Minimizes uncertainty in regulatory review process

What Is An MDDT?

- **Medical Device Development Tool (MDDT)** is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device
  - A MDDT is scientifically validated and qualified for a specific ***Context Of Use*** (COU)
  - COU describes the way the MDDT should be used, purpose in device evaluation and/or regulatory submission, and specific output/measure from the tool
  - Qualification is a FDA conclusion that within the COU a MDDT can be relied upon to have a specific interpretation and application in medical device development and regulatory review
  - CDRH reviewers should accept the MDDT outcomes within the qualified context of use (COU)) without the need to reconfirm the suitability and utility of the MDDT when used in a regulatory submission

MDDT Types

COA

- Patient selection for clinical studies
- Clinical study outcomes
  - Objective and subjective

BT

- Objective measure of biologic process or response to an intervention
- Patient selection
- Predict or identify outcomes

NAM

- Models (computational and animal) to measure/predict a parameter of interest
- Reduce / Replace animal testing
- Reduce test duration or sample size

Clinical Outcome Assessments

Biomarker Tests

Nonclinical Assessment Models

MDDT Exciting Growth Opportunities

- The MDDT program is seeking new MDDT submissions in the following key areas:
  - Surrogate outcomes for clinical trials
  - Biomarker Tests for physiological safety (e.g., electrical hazard, light/EM radiation hazard, biocompatibility, toxicology)
  - Bench Testing Evaluation Methodologies
  - Computational Modeling and Simulation tools
  - Phantom Tools
  - Image Databases with Ground Truth Annotation
  - Patient Preference Tools

MDDT: Resources for More Information

Inquiries for additional information email: MDDT@fda.hhs.gov

- FR notice announcing the MDDT Program (8/10/2017): https://www.federalregister.gov/documents/2017/08/10/2017-16827/qualification-of-medical-device-development-tools-guidance-for-industry-tool-developers-and-food-and

- MDDT Guidance Document: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm374432.pdf

- MDDT Public Webpage: http://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/default.htm

- Q-Submission Guidance Document: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm311176.pdf

U.S. FOOD & DRUG ADMINISTRATION

Alternative(s) to Animal Testing: Pyrogenicity Assessment for Medical Devices

FDA's Predictive Toxicology Roadmap

- Released online: December 2017 https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM587831.pdf
- Report p.8: Toxicology Areas That Could Benefit from Improved Predictivity
  - "Optimizing in vitro alternative methods for use with low dose mixtures extracted from medical devices or with aqueous and non-aqueous lubricants used as medical devices or accessories"
- FDA Public Hearing: September 12, 2018 https://www.fda.gov/ScienceResearch/AboutScienceResearchatFDA/ucm601090.htm
  - Sought comments on how to foster the development and evaluation of emerging toxicological methods and new technologies and incorporate them into regulatory review, as applicable.

Pyrogenicity Assessment for Medical Devices

- **Pyrogen is any substance that induces fever**
- **Pyrogenicity Assessment**
  - Implants
  - Sterile devices having direct or indirect contact with cardiovascular system, lymphatic system, or cerebrospinal fluid regardless of duration of contact
  - Devices labeled as “non-pyrogenic”
- **Why pyrogenicity assessment?**
  - To protect patients from the risk of febrile reaction

Potential Sources of Pyrogen in Medical Devices

- **Bacterial Endotoxins**
  - Assessed as part of the sterility assessment
  - Limulus Amoebocyte Lysate (LAL) Test (also known as Bacterial Endotoxin Test)
- **Potential pyrogenic chemicals including manufacturing residuals that may leach out from devices (material-mediated pyrogenicity) during clinical use**
  - Assessed as part of the biocompatibility assessment
  - Rabbit Pyrogen Test (RPT) per USP <151>
    - Detects both endotoxin and non-endotoxin mediated pyrogenic response
    - Gives a yes (pyrogenic) / no (not-pyrogenic) answer
    - Not a lot-release test
    - Requires a large number of test samples

Alternative Test(s) for Pyrogenicity Assessment for Medical Devices

Considerations for qualification:

- **Is the proposed test going to replace both Bacterial Endotoxin and Rabbit Pyrogen Tests?**
  - If so, is test qualified for detection of both endotoxin and non-endotoxin pyrogens?
  - Non-endotoxin pyrogens:
    - Chemical agents (material-mediated pyrogenicity)
    - Microbial components other than LPS
- **How does the endpoint measured in the test relate to the fever response in human which is a complex process?**
  - Rabbit pyrogen test detects whole body fever response
  - Relationship between single/multiple cytokine levels (e.g. IL-1 and/or IL-6) produced in cultures of monocytes vs. fever response in human

Alternative Test(s) for Pyrogenicity Assessment for Medical Devices (cont.)

Considerations for qualification (cont.):

- **Is the proposed endpoint the sole outcome measure for assessing the fever response irrespective of the mechanism of action of pyrogens?**
  - **For e.g.,** endotoxin vs. agents that directly affect the thermoregulatory center in the brain vs. uncoupling agents of oxidative phosphorylation

- **With what types of devices can the proposed test be used?**
  - e.g., durable/absorbable devices that include polymers, ceramics, metals, biologics, hydrogels, liquids

Alternative Test(s) for Pyrogenicity Assessment for Medical Devices (cont.)

Considerations for qualification (cont.):

- **Assay Interference Testing**
  - Testing to verify that a test article/extract does not interfere with cell system or with the cytokine-specific ELISA
- **Can this test be qualified for use with devices having different regulatory "EU/device" limits?**
  - 20 EU/device (for devices in direct or indirect contact with cardiovascular system and lymphatic system)
  - 2.15 EU/device (for devices in contact with cerebrospinal fluid)
  - ≤ 0.2 EU/device (for intraocular lenses)

Alternative Test(s) for Pyrogenicity Assessment for Medical Devices (cont.)

Considerations for qualification (cont.):

- **Are any device-specific method optimizations needed? For example:**
  - Use with large versus small surface area devices
  - Use with device extracts versus direct testing on the device itself
  - If direct testing on the device:
    - Is the test limited to detecting surface bound pyrogens only? Is this sufficient?
    - Is there any difference if the test is done under static vs. dynamic incubation conditions?
    - Can the test detect all pyrogenic extractables/leachables?
      - How comparable is the amount of pyrogenic extractable/leachable that can elute out during the exposure period in this assay vs. in the test extract prepared using ISO 10993-12 extraction condition (e.g. for saline extract prepared by extracting the device in saline at 50^{o}C for 72 hour using an extraction ratio of 3 cm^{2} surface area of the test article /ml of saline)
  - Optimization of treatment period to increase test sensitivity

Alternative Test(s) for Pyrogenicity Assessment for Medical Devices (cont.)

Considerations for qualification (cont.):

- **Are there any chemicals or device designs incompatible with the test system?**
- **How can positive controls be selected to confirm that the proposed test can distinguish between positive and negative responses for non-endotoxin pyrogens?**
- **What qualification data already exist for the proposed test, and what data gaps still need to be filled?**
  - Chemical domain space relevant to medical device materials as well as the domain space for combination products (device-drug and device-biologic)
  - Comparative data: MAT/RPT and LAL tests/human outcomes

MDDT Submission Logistics

- Before submitting: Identify likely review division:
  - Recognized consensus standards https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
  - "Standard Designation Number" search term: 10993 (for ISO biocompatibility standards)

  - At Bottom of the supplementary information sheet (e.g., 10993-11), find the division of the FDA Technical Contact:

MDDT Submission Logistics (Cont.)

- MDDT staff are incredibly helpful with logistical information:
  - Website: https://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttoolsmddt/

The proposal should be submitted as an "informational meeting" Q-submission based on the FDA guidance document "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff." The cover sheet contents should follow the enclosure: Proposal Cover Sheet. If you have any questions, please contact us at MDDT@fda.hhs.gov.

Acknowledgements

Hilda Scharen, M.Sc., CAPT, USPHS

Director, Medical Device Development Tools (MDDT)

Jennifer Goode, B.S.

Biocompatibility Program Advisor, CDRH/ODE

Beth Gonzalez, Ph.D.

Microbiologist, CDRH/ODE/DRGUD

Questions?

Molly Ghosh, Ph.D., DABT
FDA/CDRH/ODE/DNPMD
10903 New Hampshire Avenue
WO Bld 66, Room 2658
Silver Spring, MD 2093
Phone: 301–796–6496
Email: Molly.ghosh@fda.hhs.gov