Qualification of In Vitro Alternatives for Biocompatibility Assessment of Medical Devices: Use of Medical Device Development Tools (MDDTs)

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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 tool that is scientifically validated and qualified for a specific ***context of use*** (COU) for use in device development and to support regulatory decision-making

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

Context of Use (COU)

- Key aspect of Qualification
- Describes the way MDDT should be used, purpose, and conditions under which MDDT is qualified
- Complete COU should include:
  - Tool or product area in which MDDT is proposed to be qualified
  - Specific output/measure from MDDT
  - Role of MDDT in regulatory evaluation
  - Phase(s) of medical device development in which tool measurements can be used (i.e. design evaluation, animal testing, clinical studies)

MDDT: Biocompatibility Considerations

Alternatives to Biocompatibility Tests

Considerations for qualification:

- What specific biocompatibility test is being proposed for replacement? (e.g., several types of irritation tests are available depending on indication for use)
- How do the mechanisms of action evaluated in the tests compare?
  - Proposed NAM
  - Currently used biocompatibility test
- How does screening with the proposed NAM address relevant outcomes from the currently used test?

Alternatives to Biocompatibility Tests (cont.)

Considerations for qualification (cont.):

- For what types of devices can the proposed NAM be used?
  - e.g., durable/absorbable devices that include polymers, ceramics, metals, biologics, hydrogels, liquids
- What qualification data already exist for the proposed NAM, and what data gaps still need to be filled?
  - Chemical domain space relevant to medical device materials
  - Comparative data: NAM/current biocompatibility test/human outcomes

Alternatives to Biocompatibility Tests (cont.)

Considerations for qualification (cont.):

- How can positive controls be selected to confirm that the NAM can distinguish between positive and negative responses?
  - For example can the NAM:
    - Distinguish between week/moderate toxicants (e.g., for chemical-based toxicity endpoints)
    - Distinguish between positive and negative responses if there are changes in design that could impact the biological response (e.g., for endpoints like thrombogenicity where geometry and blood flow could impact thrombogenicity potential)

Alternatives to Biocompatibility Tests (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
  - Test system suitability with polar and nonpolar device extracts, if applicable
  - Optimization of treatment period to increase test sensitivity
- Are there any chemicals or device designs incompatible with the test system?

Possible NAM Developer Questions

When dialoguing with CDRH, the following may be important topics of conversation:

- How does CDRH interpret the results from animal testing for a specific biocompatibility assessment? What are the key outcomes?
- Will a single NAM likely be sufficient to address an endpoint of interest for biocompatibility, or might a battery of in vitro tests be needed?

Possible NAM Developer Questions (cont.)

When dialoguing with CDRH, the following may be important topics of conversation (cont.):

- How important is it to understand the mechanism(s) of action evaluated by a NAM, as mechanisms of action may not always be fully understood from animal studies or human outcomes?
- Can CDRH use information from NAMs if not MDDT-qualified? (e.g., through weight of evidence approaches, or as supportive evidence)

Resources

- FR notice announcing the MDDT Program (8/10/2017): https://www.govinfo.gov/content/pkg/FR-2017-08-10/pdf/2017-16827.pdf

- MDDT Guidance Document: https://www.fda.gov/media/87134/download

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

- Inquiries for information: MDDT@fda.hhs.gov

- Q-Submission Guidance Document: https://www.fda.gov/media/114034/download

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Questions?

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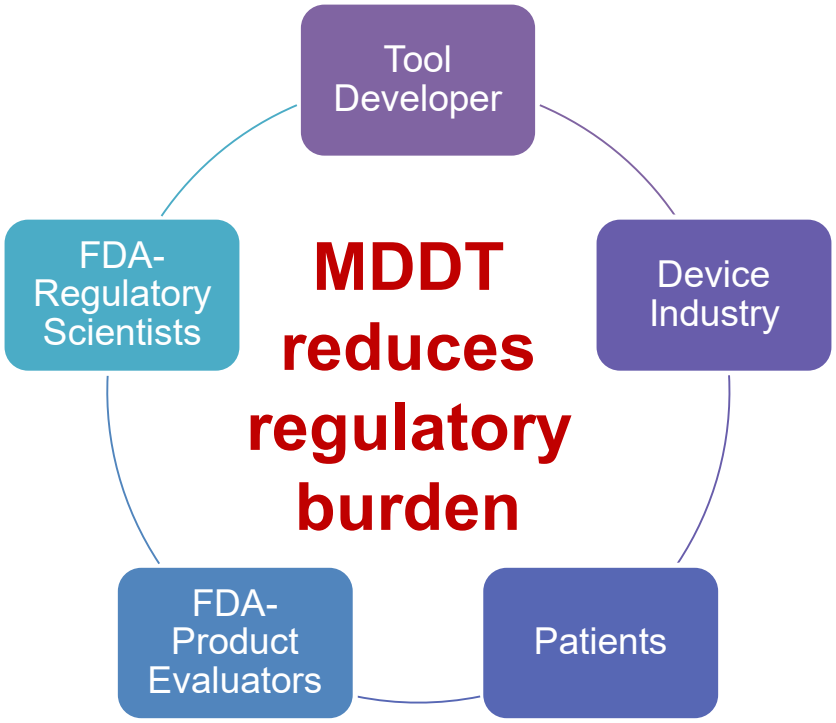
MDDT Qualification Process

Medical Device Development Tools (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

Vision for Potential Utility

- Voluntary Program for Tool Developers
- Tool submitters can be: person, group, consortium, or organization (including FDA)
- To expedite medical device innovation, development and regulatory approval/clearance through qualifying and making MDDTs publically available and by collaborating with tool developers, device industry and other stakeholders

What is MDDT Qualification?

- Qualification is a conclusion, based on FDA review, that **within the context of use (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

- CDRH encourages tool developers to make their qualified MDDTs publicly available

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