Modernizing Biocompatibility Testing: Replacing Animal Tests through the FDA CDRH Medical Device Development Tools (MDDT) Program

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Introduction

The FDA CDRH Medical Device Development Tools Program

In 2018, the U.S. Food and Drug Administration (FDA) announced in its Predictive Toxicology Roadmap that the agency is upgrading its toxicology toolbox. In part, this upgrade emphasizes the agency's interest in bringing safer medical products to market by replacing the use of outdated animal tests with new methods that reflect recent breakthroughs in the toxicological sciences.[1]

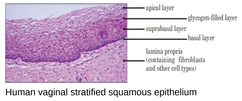
To achieve this goal, FDA Center for Devices and Radiological Health (CDRH) introduced the MDDT Program to establish a clear pathway for the medical device industry to qualify new test methods for use in place of animal-based tests that are routinely requested or required in regulatory risk assessments.[2] Projects accepted into the program are developed with agency input. Tools that are successfully qualified by the FDA through this program are subsequently fit for use with any device within the defined context of use. We describe the process of developing two MDDT projects as a template for those interested in using non-animal test methods in medical device regulatory submissions.

MDDT Project Development

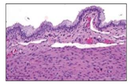
MDDT 1: Replacing the Rabbit Vaginal Irritation Test (RVI)

In the U.S., personal lubricants are classified as Class II medical devices that require premarket clearance from CDRH. As a part of a personal lubricant pre-market registration package, the agency routinely recommends that sponsors conduct a battery of biocompatibility tests that includes the rabbit vaginal irritation test (RVI).[3]

Nevertheless, there are significant structural differences between rabbit and human vaginal tissues (***Fig. 1***).[4] These dissimilarities could contribute to reports of different responses of rabbit and human tissues exposed to personal lubricants. This shortcoming can be addressed using an *in vitro* test system based on reconstructed human tissue models in place of the RVI.[5]



Human vaginal stratified squamous epithelium



Rabbit single layer columnar vaginal epithelial cells

Figure 1: *A comparison between Hematoxylin and Eosin (H&E)-stained human and rabbit vaginal epithelium*[4]

Organizing the MDDT Project

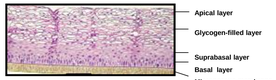
- The PETA International Science Consortium and the Institute for In Vitro Sciences (IIVS) recruited personal lubricant manufacturers, industry associations, and manufacturers of reconstructed human tissue models to form an industry consortium.
- Participants developed a proposal describing the tool (*in vitro* reconstructed human tissue models), the proposed context of use (a range of personal lubricant formulations), the public health impact (improved, human-relevant biocompatibility assessment), an assessment of the advantages and disadvantages of the tool (replacement of *in vivo* animal testing, long term cost reductions), and a proposed evidence collection plan to support the use of this tool as a nonclinical assessment method (NAM).
- The FDA evaluated the proposal and accepted the project into the Incubator Phase of the MDDT Program (coded MDDT029).[6]

MDDT 1 (Continued): Replacing the RVI, Project Overview and Progress

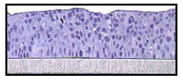
Project goal: To validate an *in vitro* method to replace the RVI in medical device biocompatibility testing for personal lubricants. When qualified, this tool will use a reconstructed human vaginal tissue model when biocompatibility testing for vaginal irritation is required to support 510(k) and PMA marketing application submissions.

Context of use: Limited to use with personal lubricants and vaginal moisturizers with chemical and physical properties within the boundaries of products included in the qualification package.

Test systems: Human reconstructed tissue models, EpiVaginal™ (MatTek Corporation), SkinEthic™Human Vaginal Epithelium (EpiSkin). Endpoints of interest are tissue viability, histology, and possibly others (***Fig. 2***).



EpiVaginal™, derived from normal vaginalecto-cervical epithelial cells



SkinEthic™, derived from human vulva epidermoid carcinoma A431 cells

Figure 2: *A comparison between H&E-stained vaginal epithelium of reconstructed human vaginal mucosa from MatTek Corporation and EpiSkin. Images provided by the manufacturers.*

Test materials: Selected to address a variety of chemical and physical properties, e.g. formulation characteristics, viscosity, pH, and osmolality.

- *Group 1, Hypothesis generating group*: 10-15 final formulations with historical RVI data and mostly new *in vitro* data tested un-blinded by IIVS. After data correlation analysis, a provisional prediction model will be generated to the best alignment of the *in vivo* and *in vitro* data sets.
- *Group 2, Confirmatory group*: 20-30 products with historical RVI and *in vitro* testing conducted in a blinded manner by IIVS. Data decoded after analysis to determine if the prediction model correctly categorized Group 2 products within acceptable limits.

Progress: After admission into the MDDT Program, participants continue to refine the project's evidence plan in collaboration with CDRH and industry partners. To increase the number and diversity of products covered by the tool's context of use, the consortium continues to recruit additional industry partners interested in participating in the project before new testing begins.

Major Tasks	Milestones	Completion
MDDT Project Proposal	Submission to CDRH	December 2016
	Admission into the MDDT Program Incubator Phase	January 2017
MDDT Project Refinement	Receipt of written feedback from CDRH	January 2017
	Response to CDRH feedback submitted	May 2017
	Review of request for pre-submission, informational meeting request	June 2017
	Initial discussion of the research plan for the validation program with CDRH	August 2017
	Supplement 001 to PQP: Q170887 regarding testing strategy	17 May 2018
	Recruitment of additional industry participants	*Ongoing*
Validation Program	*In vitro* testing	*To be determined*
	Data review	
Qualification Package	Final submission including validation data and proposed prediction model	*To be determined*

MDDT 2: Replacing Animal-Based Pyrogen Tests

Pyrogens are a diverse group of substances that produce fever when introduced to the body and are generally evaluated as part of medical device biocompatibility testing. Medical devices that come in contact with the cardiovascular system, cerebrospinal fluid, have ophthalmic contact or are implanted or injected, and any devices labeled "non-pyrogenic" must meet CDRH pyrogen limit specifications before they can be marketed.[7] Two animal-based pyrogen tests are typically used for evaluation of pyrogenicity: the rabbit pyrogen test (RPT) and the limulus amoebocyte lysate test (LAL), which are performed using rabbits or hemolymph derived from horseshoe crabs, respectively.[8] However, non-animal replacements are available, including human monocyte activation tests (MAT) (***Fig. 3***).[9]

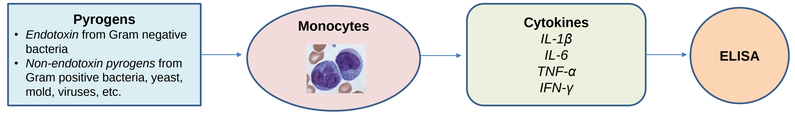


Figure 3: *Summary of MAT, a device or extract is incubated with human monocytes, which detect pyrogens via surface toll-like receptors and subsequently release cytokines that are detected via ELISA.*

Considering the breadth of devices subject to pyrogen testing requirements and the choice of multiple MAT test protocols, identifying an appropriate evidence collection plan and context of use for an MDDT project requires broad input from interested parties. In September 2018, the PETA International Science Consortium and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) convened a workshop to explore industry interest in developing the MAT as a replacement for the RPT and LAL.[10] Workshop participants—including medical device manufacturers, MAT experts, and regulators—agreed on the value of preparing an MAT MDDT project proposal, which is currently underway.

Conclusions

Under the MDDT Program, organizing collaborative partnerships between industry, regulators and other organizations that support non-animal test methods is an ideal solution for facilitating use of modern predictive toxicology tools that can support regulatory decision-making while minimizing uncertainty about the acceptability of these new methods in regulatory submissions. The MDDT program is flexible and adaptable, and tool developers are encouraged to engage with CDRH throughout the tool development process.

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