Validation of a non-animal vaginal irritation method admitted as nonclinical assessment model (NAM) in the Incubator Phase of the United States Food and Drug Administration (US FDA) Medical Devices Development Tool (MDDT)

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ABSTRACT

Personal lubricants are considered Class II medical devices in the United States and therefore must receive pre-market clearance from the Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH). The agency-recommended biocompatibility testing battery includes: guinea pig maximization sensitization test or local lymph node assay (LLNA), acute systemic toxicity, and the rabbit vaginal irritation (RVI) test, which are all currently conducted using animals, and cytotoxicity which is assessed using *in vitro* assay(s). FDA's recently launched Predictive Toxicology Roadmap calls for the optimization of non-animal methods for the safety evaluation of drugs, consumer products and medical devices. We have created an Industry Consortium comprised of manufacturers of personal lubricants/vaginal moisturizers and companies interested in the advancement of animal alternatives working collaboratively with stakeholders and the US FDA to develop an *in vitro* testing approach that could be used in place of the RVI in pre-market submissions. Our validation program will focus on personal lubricants and vaginal moisturizers with diverse chemical and physical properties (*e.g.*, formulation, viscosity, pH, osmolality) in their final, undiluted, form. Paired *in vivo-in vitro* data for vaginal irritation generated using commercially available human reconstructed vaginal tissue models will be analyzed against existing *in vivo* RVI data to develop a Prediction Model for the safety assessment of these products. The proposal has been accepted as a Nonclinical Assessment Model (NAM) in the Incubator Phase of the US FDA CDRH Medical Devices Development Tool (MDDT) Program and is currently under review for consideration to advance to the Pre-Qualification stage. The proposed NAM aligns with the Predictive Toxicology Roadmap's goals to integrate predictive toxicology methods into safety and risk assessment with the potential to replace or reduce the use of animal testing.

INTRODUCTION

As part of a pre-market registration package, the US FDA requires a battery of biocompatibility tests be conducted for personal lubricants. The most frequently used tests are listed below.

Battery of biocompatibility tests currently conducted
Rabbit Vaginal Irritation Test (RVI) (ISO 10993-10:2010) *(in vivo)*
Guinea Pig Maximization Sensitization Test (ISO 10993-10:2010) *(in vivo)*
Acute Systemic Toxicity (ISO 10993-11:2017) *(in vivo)*
Cytotoxicity Using a Direct Contact Method (ISO 10993-5:2009): MEM Elution or Agar Overlay Assays *(in vitro)*

RVI - Experimental Setup

- Minimum 3 mature rabbits are exposed to the test article daily, for at least 5 days.
- Appearance of the external genital area is observed daily for signs of erythema, oedema, and discharge as a reaction to the exposure to the test article.
- At the end of the experiment, parts of the cervico-vagina, mid-vagina and uro-vagina are fixed, paraffin-embedded and H&E (Hematoxylin & Eosin) stained and are scored for epithelial ulceration, leukocyte infiltration, vascular congestion and oedema.

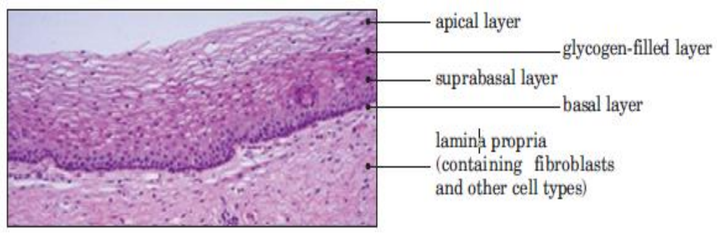
RVI - Scoring

Parameters:
epithelial ulceration, leukocyte infiltration, vascular congestion and oedema

Scoring (individual scoring)
0 = no irritation
1 = minimal irritation
2 = mild irritation
3 = moderate irritation
4 = intense irritation

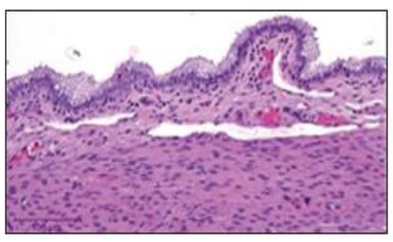
There are significant structural differences between the rabbit and human vaginal tissues: two-thirds of the rabbit vagina is lined by columnar epithelium which is distinct from the stratified squamous epithelium (8-12 cells thick) of the human vagina. These dissimilarities could contribute to different responses of the rabbit and human tissues upon exposure to personal lubricants which have been reported. This shortcoming could be addressed by an *in vitro* test system based on cells of human origin (reconstructed tissue models).

Human vaginal epithelium



Stratified squamous epithelium

Rabbit vaginal epithelium



Single layer of columnar epithelial cells

VALIDATION PLAN OVERVIEW

Goal of the program: To validate an *in vitro* method as alternative to the RVI Test which is the most frequently submitted test to meet the US FDA requirement for biocompatibility testing of medical devices (lubricants).

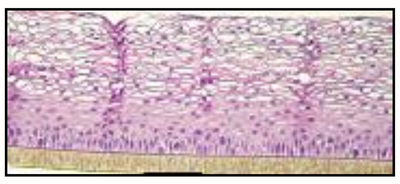
Context of use: The non-animal vaginal irritation Medical Devices Development Tool (MDDT) is accepted as a Nonclinical Assessment Model (NAM) in the Incubator Phase. When qualified, this tool will use an *in vitro* testing approach to substitute for the RVI test when biocompatibility testing for vaginal irritation is required to support:

- a clinical trial (IDE – Investigational Device Exemption)
- marketing application submissions (510k, PMA - Premarket Approval)
- *de novo* application for personal lubricants and vaginal moisturizers in their final, undiluted, formulations that are regulated as medical devices by CDRH.

The applicability domain will be limited to use with personal lubricants or vaginal moisturizers with chemical and physical properties within the boundaries of products included in the qualification package (*e.g.*, formulation, viscosity, pH, osmolality).

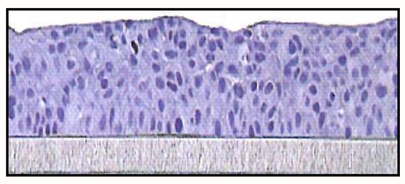
PROPOSED TESTING STRATEGY

Test system: human reconstructed tissue models such as EpiVaginal™ from MatTek Corporation and/or Human Vaginal Epithelium (HVE) from EpiSkin.



Reconstructed human vaginal mucosa (EpiVaginal™) from MatTek Corporation

Normal vaginal ecto-cervical epithelial cells



Reconstructed human vaginal epithelium (SkinEthic™ HVE) from EpiSkin

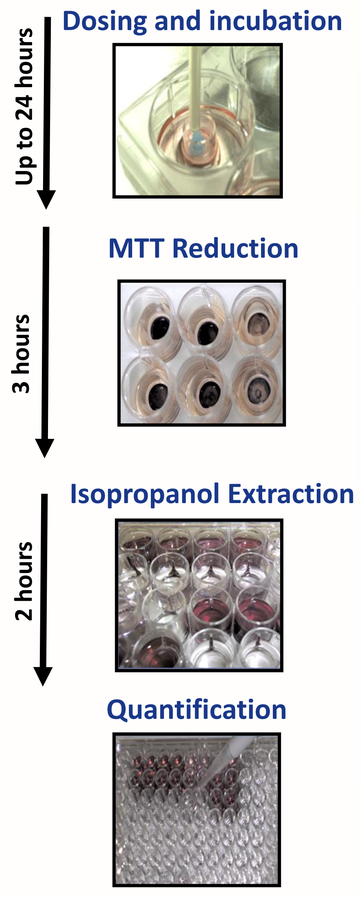
A431 cells, derived from human vulva epidermoid carcinoma

Test materials: will be selected to address a variety of chemical and physical properties (*e.g.*, formulation, viscosity, pH, osmolality, etc.).

Group 1 (Hypothesis Generating Group): 10-15 final formulations with historical animal data (RVI) and mostly new *in vitro* data tested un-blinded. After a 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* data conducted in a blinded manner by IIVS. The data will be decoded after the data analysis is performed to determine if the Prediction Model correctly categorized products in Group 2 within acceptable limits.

Testing protocol: endpoints of interest are tissue viability; histology and possibly others.

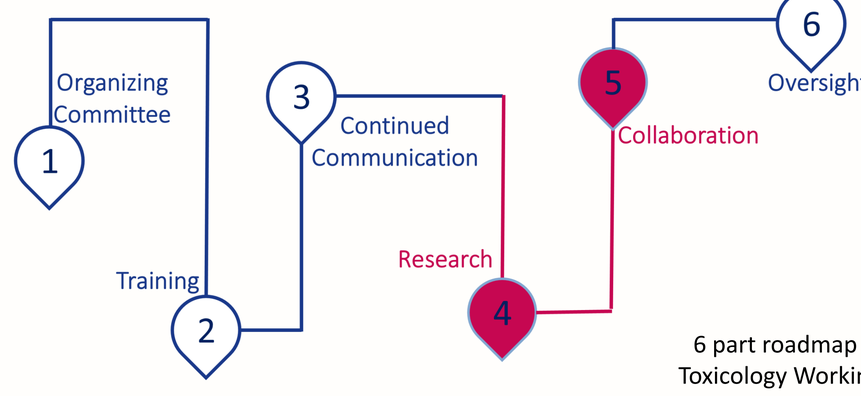


PROGRESS REPORT, FUTURE PLANS

	DEC 2016	JAN 2017	MAY 2017	JUNE 2017	AUG 2017	JULY 2018	ONGOING 2018	TBD
MEDICAL DEVICES DEVELOPMENT TOOL MDDT029 (NAM)	IIVS: NAM Submission to US FDA Center for Devices and Radiological Health (CDRH)							
		US FDA: Feed-back provided on the received NAM NAM admission into the Pilot Program in the Incubator Phase						
PRE-QUALIFICATION PACKAGE (PQP): Q170887		IIVS: Response to FDA's feed-back on NAM submitted						
			US FDA: Review of pre-submission and of informational meeting request					
				US FDA and IIVS: Initial discussion of research plan for the validation program				
							IIVS: Supplement 001 to PQP Q170887 regarding animal data interpretation and *in vitro* strategy submitted	
								IIVS: Introduction of NAM to other Industry members and assessment of their interest in participation Pending finalization of the testing plan and submission to US FDA for input
VALIDATION PROGRAM								*In Vitro* Testing
								Data Review
NAM QUALIFICATION								Final submission validation data and prediction model

ALIGNMENT WITH THE US FDA ROADMAP

Through research and collaboration with stakeholders, the proposed NAM aligns with the US FDA's Predictive Toxicology Roadmap goals to integrate predictive toxicology methods into safety and risk assessment with the potential to replace or reduce the use of animal testing.



6 part roadmap recommended by the Toxicology Working Group of the US FDA

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