Non-animal testing approach to address biocompatibility testing of medical devices required by the United States Food and Drug Administration (US FDA)

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ABSTRACT

Starting in December 2015, personal lubricants must receive pre-market approval from the US FDA Center for Devices and Radiological Health (CDRH) in order to be sold in the US. Part of the testing battery for biocompatibility includes the *in vivo* Rabbit Vaginal Irritation (RVI) test. We have created an Industry Consortium comprised of personal lubricants manufacturers and are working collaboratively with stakeholders and the US FDA to develop an *in vitro* testing approach to substitute for the RVI. Our Validation Program will analyze paired *in vivo-in vitro* data for vaginal irritation utilizing commercially available human reconstructed vaginal tissue models. A Prediction Model will be proposed that can be used for the safety assessment of personal lubricants. Our Validation Program proposal has been accepted in the Incubator Phase of the US FDA Medical Device Development Tool (MDDT) Pilot Program and is currently ongoing.

INTRODUCTION

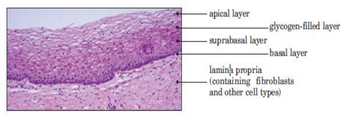
To support clearance of personal lubricants, the US FDA requires a battery of biocompatibility tests be conducted. The most frequently used *in vivo* tests are listed below alongside available *in vitro* methods for each endpoint.

***In vivo* biocompatibility tests currently conducted**	**Available *in vitro* methods**
Cytotoxicity using a direct contact method (ISO 10993-5:2009)	MEM Elution Assay (FDA approved) Agar Overlay Assay (FDA approved)
Guinea Pig Maximization Sensitization Test (ISO 10993-10:2010)	Direct Peptide Reactivity Assay (DPRA) - OECD TG 442C ARE-Nrf2 luciferase test method (KeratinoSens; LuSens) - OECD TG 442D Human Cell Line Activation Test (hCLAT) - OECD TG 442E
Rabbit Vaginal Irritation Test (RVI) (ISO 10993-10:2010)	Use of a reconstructed tissue model (MatTek Corporation or EpiSkin)
Acute systemic toxicity (ISO 10993-11:2006)	3T3 Neutral Red Uptake (NRU) Assay supporting the identification of substances not requiring classification for acute oral toxicity (starting doses)

VALIDATION PROGRAM - OUTLINE

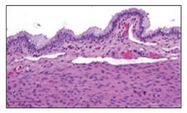
Human vaginal epithelium

Stratified squamous epithelium (8-12 layers of squamous cells and columnar basal cells)



Rabbit vaginal epithelium

Two thirds of the rabbit vagina lined by a single layer of columnar epithelial cells of uniform height (structurally distinct from the stratified squamous epithelium of the human vagina)



RVI - Experimental setup

- 3-4 mature rabbits are exposed to the test article daily, for 10 days.
- Organs are observed daily for signs of erythema, edema, 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 stained and are scored for epithelial ulceration, leukocyte infiltration, edema and vascular congestion.
- Endpoints: histopathology, epithelial damage, colposcopy, leukocyte number and phenotype, cytokines and soluble markers, apoptosis, microflora.

RVI - Scoring

Parameters:
epithelial ulceration, leukocyte infiltration, edema, and vascular congestion
Scoring (individual scoring)
0 = no irritation
1 = minimal irritation
2 = mild irritation
3 = moderate irritation
4 = intense irritation

Goal of the program: The goal of this program is 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).

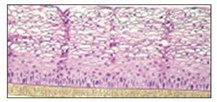
Context of use: The non-animal vaginal irritation Medical Device Development Tool (MDDT) is proposed as a Nonclinical Assessment Model (NAM). When qualified, this tool will use an *in vitro* testing approach to substitute for the RVI test when biocompatibility testing for vaginal irritation is required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

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

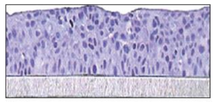
The applicability domain will be limited to use with personal lubricants or vaginal moisturizers with chemical and physical properties within the boundaries of products included in the qualification package (*e.g.*, formulation, viscosity, pH, osmolality).

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 from MatTek
normal vaginal-ectocervical epithelial cells

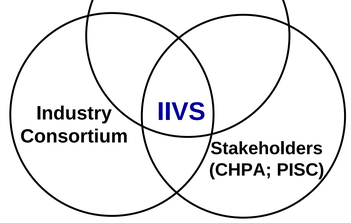


Reconstructed human vaginal epithelium (HVE) from SkinEthic
A431 cells, derived from human vulva epidermoid carcinoma

Test materials:

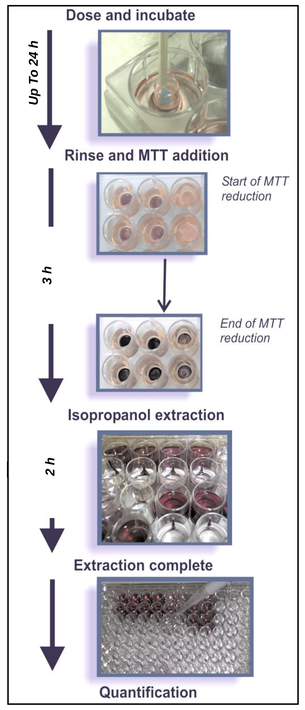
Group 1 (Hypothesis Generating Group): final formulations with historical animal data (RVI) and mostly new *in vitro* data tested un-blinded. Based on a data correlation analysis to be performed with Group 1, a provisional Prediction Model will be generated to the best alignment of the *in vivo* and *in vitro* data sets.

Group 2 (Confirmatory Group): 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.



- PETA International Science Consortium Ltd. (PISC)
- Consumer Healthcare Products Association (CHPA)

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



PROGRESS REPORT, FUTURE PLANS

MAJOR ACTIVITIES	MILESTONES	COMPLETION
Medical Device Development Tool (MDDT): MDDT029	Submission to US FDA-Center for Devices and Radiological Health (CDRH)	**5 December 2016**
	Admission into the Pilot Program in the Incubator Phase:	**13 January 2017**
Pre-Qualification Package (PQP): Q170887	Receipt of written feed-back from the US FDA	**13 January 2017**
	Response submitted by IIVS	**12 May 2017**
	Review of request for pre-submission, informational meeting request	**6 June 2017**
	Initial discussion of the research plan for the validation program	**16 August 2017**
Validation Program	*In vitro* testing	**TBD**
	Data review	
Qualification Package	Final Submission including validation data and proposed prediction model	TBD

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