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.

- **Cytotoxicity using a direct contact method (ISO 10993-5:2009)**
  - MTT Elimination 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-NR Flurourase test method (Karadema-S; LuDuen; - 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)**
  - 10 k Neutral Red Uptake (NRU) Assay supporting the identification of substances not requiring classification for acute oral toxicity (starting doses)

VALIDATION PROGRAM - OUTLINE

<table>
<thead>
<tr>
<th>Human vaginal epithelium</th>
<th>Stratified squamous epithelium (5-12 layers of squamous cells and columnar basal cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit vaginal epithelium</td>
<td>Two-thirds of the rabbit vagina lined by a single layer of squamous epithelium of uniform thickness (selectively derived from the stratified squamous epithelium of the human vagina)</td>
</tr>
</tbody>
</table>

**RVI - Experimental setup**

- 3-4 animals are exposed to the test article daily for 10 days.
- Organs are obtained daily, for signs of allergy, edema, edema as well as a result of the exposure to the test article.
- All of the exposed animals, parts of the mucous membranes, vaginal epithelium, and uterine tissue are collected and examined for histological changes.
- Emotional, rectal, anal, and rectal sphincter damage, damage to the vulva, urogenital area, and perianal area.
- EpiSkin Vaginal Test:
  - Negative control
  - 100% positive control
  - Up to 24 h

**US FDA**

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

**PROPOSED TESTING STRATEGY**

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

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

**Test materials:**

- **Group 1 (Hypothesis Generating Group):** final formulations with historical animal data (RVI) and mostly new in vitro data tested un-blinded.
- **Group 2 (Conformity Group):** products will be tested with historical RVI and in vitro data conducted in a blinded manner by IVIS. 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.

**REFERENCES**


https://www.fda.gov/downloads/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentTools/MDDT/.

PROGRESS REPORT, FUTURE PLANS

**MAJOR ACTIVITIES**

- **Medical Device Development Tool (MDDT): MDDT029**
  - Submission to US FDA Center for Devices and Radiological Health (CDRH)
  - Admission into the Pilot Program in the Incubator Phase

- **Pre-Qualification Package (PQP): Q170887**
  - Pre-submission, informational meeting request

- **Validation Program**
  - In vitro testing
  - Data review

**MILESTONES**

- **US FDA**
  - Submission to US FDA Center for Devices and Radiological Health (CDRH)
  - Admission into the Pilot Program in the Incubator Phase

- **Pre-Qualification Package (PQP): Q170887**
  - Pre-submission, informational meeting request

- **Validation Program**
  - In vitro testing

**COMPLETION**

- **US FDA**
  - 5 December 2016

- **Pre-Qualification Package (PQP): Q170887**
  - 13 January 2017

- **Validation Program**
  - 150 (1), Abstract # 3070, 485 (2016)

**REFERENCES**


https://www.fda.gov/downloads/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentTools/MDDT/.

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