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 recommends 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 assays). RVI'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-Disposition 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 to be conducted for personal lubricants. The most frequently used tests are listed below.

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

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 most often 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 IVS. 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.

Progress Report, Future Plans

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.

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 method will be used 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).

References

- https://www.fda.gov/medicaldeviceinfo/learn/medcdevinfo/medcdevinfo.html

Alignment with the US FDA Roadmap

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