Bringing NAMs into regulatory decision-making: replacing the use of animals in personal lubricant biocompatibility testing via the FDA MDDT Program

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References, resources, and contact

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Goal: Replace the rabbit vaginal irritation (RVI) test with a human-relevant method

FDA's Medical Device Development Tool[1] (MDDT) program presents a pathway to ensure the qualification and acceptance of non-animal test methods that can replace animal-based methods required to evaluate medical device biocompatibility. A commercially available human tissue-based test system, EpiVaginal™, is a promising replacement for the rabbit vaginal irritation test for personal lubricants.[2] With feedback from the FDA through the MDDT program, we have developed a step-wise approach that answers the principal question required for qualification:

How do we establish that the EpiVaginal™ Test System is suitable for making regulatory decisions about the potential for personal lubricant products to cause vaginal irritation?

1. Establish fit-for-purpose and human relevance[2,3]

Identify Context of Use: Water-based formulations

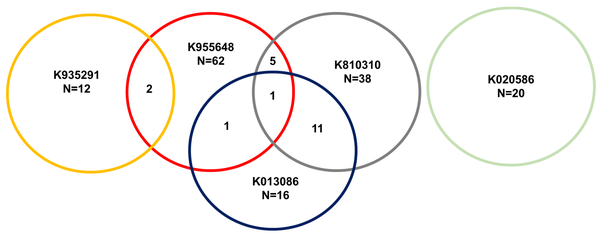


Figure 1. The NAM is being developed for use on water-based personal lubricants. When these products are registered with the FDA using a 510(k) clearance process, each product must compare itself to an existing predicate product. Specifically, products claiming a relationship to the predicate must have formulations that are "substantially equivalent" for the purposes of FDA's review process. Each Venn diagram is annotated by the number of products and the root predicate device. There are two major groupings of predicate devices. The personal lubricants we will test for qualification fall within these two major categories to ensure the NAM covers the diversity of these medical devices.

Use human-based biological response

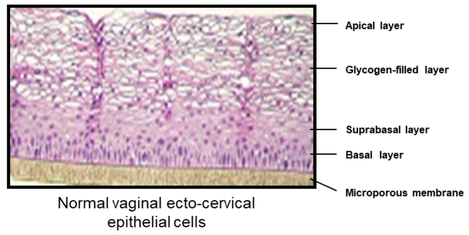
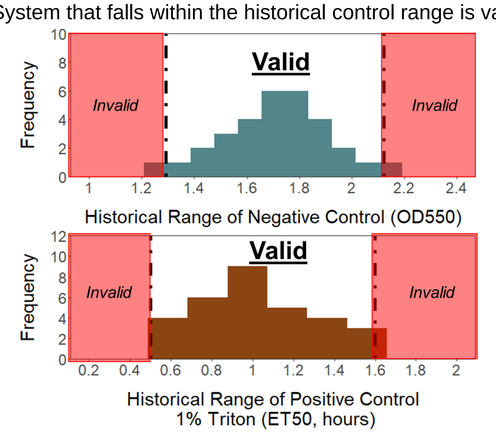


Figure 2. The EpiVaginal™ Test System is a reconstructed human tissue that mimics the structure and function of human physiology. Measured tissue viability from EpiVaginal™ is used to support an assessment that a product formulation may lead to an "acceptable" or a "not acceptable" levels of vaginal irritation.

2. Ensure measurement quality and conduct preliminary testing[3,4]

Any new measurement from the EpiVaginal™ Test System that falls within the historical control range is valid



The EpiVaginal™ Test System can rank levels of vaginal irritation based on tissue viability

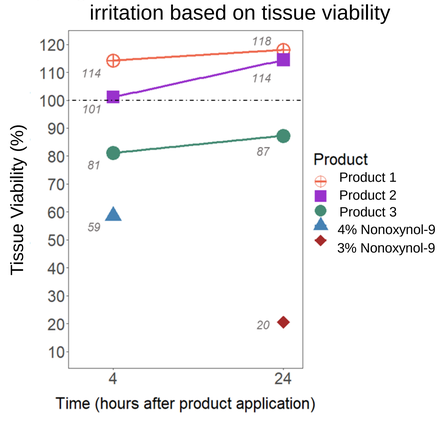
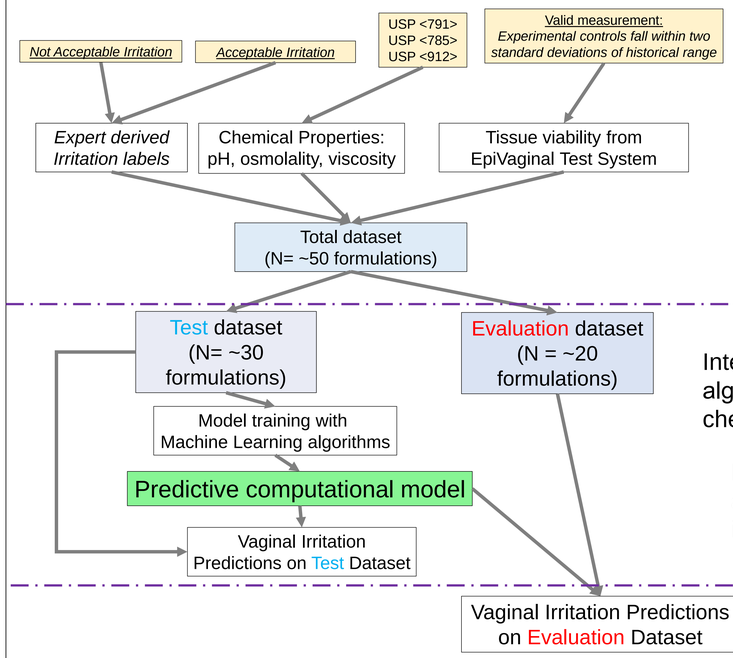


Figure 3. Historical ranges of the negative and positive controls from 31 independent trials of the EpiVaginal™ Test System serve as a reference for establishing confidence in new measurements. Any new experimental values of both controls that fall within historical ranges is valid and is suitable for use in decision-making.

Figure 4. Tissue viability of five different products were measured from the EpiVaginal™ Test System. Product 3 contains a sensate and caused lower tissue viability than products 1 and 2, which do not contain a sensate. Products with N-9 caused even lower tissue viability compared to products 1-3. Products with N-9 caused lower tissue viability over a 24 hour exposure compared to a four hour exposure.

Next steps: Map tissue viability from the EpiVaginal™ Test System into two classes of vaginal irritation

3. Qualification[3] approach in three steps



Initial: Construct a dataset annotated with vaginal irritation labels, chemical properties, and EpiVaginal™ results

How to assign labels?

- *Acceptable*: marketed products
- *Not Acceptable*: spike with known vaginal irritants based on literature

Candidate spiking ingredients

- Phenoxyethanol
- Chlorhexidine
- SDS
- Benzalkonium Chloride
- Glycol
- Nonoxynol-9
- Glycolic Acid
- Salicylic Acid
- Cetrimonium chloride
- Cinnamaldehyde

Intermediate: Construct a model using machine learning algorithms to map the EpiVaginal™ Test System and chemical properties with two classes of vaginal irritation

Key Outcome – The model outputs a prediction as either an "acceptable" or a "not acceptable" level of vaginal irritation for each personal lubricant

Final: Evaluate model performance and compare with prior expectations to support Qualification[3,5]

Table 1. Empirical performance is evaluated in a 2x2 matrix that compares model predictions with the expert-derived irritation labels. Model agreement is represented by the TP and TN. Model error is represented by the FP and FN. The confidence in the overall model, or accuracy, is calculated as the (TP+TN) / total samples. Confidence in the model output of either an "acceptable" or a "not acceptable is calculated as the predicted value.

		Expert-derived irritation labels		
	Classifications	**Not Acceptable**	**Acceptable**	**Predictive Value**
Model Predictions	**Not Acceptable**	True Positive (TP)	False Positive (FP)	TP/(TP+FP)
	Acceptable	False Negative (FP)	True Negative (TN)	TN/(TN+FP)

Table 2. **If the empirical performance of the tool meets or exceeds prior expectations, then the tool can meet Qualification.** Prior expectations were derived from the repeatability of similar irritation endpoints. Eye and skin irritation are bridgeable because the same species is use and tissue scoring is categorized for decision-making.

Prior expectations	Eye Irritation (Luechtefeld et al., 2016[6])	Skin Irritation (Rooney et al., 2021[7])
Accuracy	83%	88%
Positive Predictive Value	73%	81-85%
Negative Predictive Value	93.9%	93-95%

We provide a quantitative frame around an *in vitro* method to drive suitable use for regulatory decision-making around vaginal irritation

- Development of *in vitro* methods for evaluating personal lubricant medical devices is mentioned within FDA's Predictive Toxicology roadmap and has been supported by the MDDT program.
- We established confidence in the measurement quality and biological relevance of EpiVaginal™.
- We have a robust test plan for evaluating NAM performance and to support regulatory use when the NAM's performance meets or exceeds prior expectations. Iterative feedback with FDA has helped us refine the test plan and qualification approach.