ABSTRACT

The vaginal mucus provides an effective barrier against numerous pathogens as one of the body’s host defense and surveillance components. However, some feminine-care and cosmetic products may induce irritation of the vaginal epithelium, consequently making the tissues more susceptible to infections. Therefore, it is important that the compatibility of newly developed commercial or personal care products with the human mucosa is assessed before the product is marketed. The most frequently used test system to screen for an adverse vaginal mucosal response is the in vitro cytokine/vaginal irritation model. However, the results of this model cannot be used as a surrogacy for in vivo results in this context. Several exposure times are tested relevant to product use. We have introduced a novel method to replace the use of animals in testing programs. To that end, a clear understanding of the current status, applicability, and limitations of available alternative tests for vaginal irritation assessment is critical when companies are designing testing strategies. We present an overview of the available alternative approaches and in vitro testing strategies. The safety testing of personal care, cosmetic, and pharmaceutical products has traditionally been performed in animals. Due to ethical and scientific concerns, non-animal human cell-based in vitro methods for eye and skin irritation have been proposed and validated. However, the current preclinical test for the assessment of vaginal irritation required by the U.S. Food and Drug Administration (FDA) for the regulation of spermicides and microbicides (regulated as drugs) and menstrual tampons and pads (regulated as devices) is the in vivo rabbit vaginal irritation (RVI) model. There are, however, other product types for intimate use (baby diapers, incontinence products, feminine deodorants and moisturizers, moist toilet tissues, personal lubricants, bath and bathwashes) for which the RVI is not specifically required but, is often used. The use of alternative, in vitro methods, which reduce, refine, and replace the use of animals, and model the human responses is of particular interest to personal care and cosmetic industries that are becoming legally and ethically restrained in their use of animals for safety testing. Currently there is no alternative test method validated and/or accepted by U.S. or European regulatory agencies for vaginal irritation assessment. However, several promising methods are being investigated. Here we provide an overview of the existing alternative in vitro pre-clinical methods with the goal of introducing the need for validation of pre-clinical in vitro methods that can predict the effects of personal care, cosmetic, and pharmaceutical products for vaginal use on humans to the representatives of the regulatory community and industries organizing supportive alternative methods.

INTRODUCTION

Preclinical safety testing of Cytokines (IL-6, IL-8, TNF-α) and Chemokines (MCP-1, Rantes, IL-8) is performed using monolayer cultures of human vaginal epithelial cells. The results of this model are not validated and are not accepted by the U.S. Food and Drug Administration (FDA) for the regulation of spermicides and microbicides. (regulated as drugs) and menstrual tampons and pads (regulated as devices) is the in vivo rabbit vaginal irritation (RVI) model. There are, however, other product types for intimate use (baby diapers, incontinence products, feminine deodorants and moisturizers, moist toilet tissues, personal lubricants, bath and bathwashes) for which the RVI is not specifically required but, is often used. The use of alternative, in vitro methods, which reduce, refine, and replace the use of animals, and model the human responses is of particular interest to personal care and cosmetic industries that are becoming legally and ethically restrained in their use of animals for safety testing. Currently there is no alternative test method validated and/or accepted by U.S. or European regulatory agencies for vaginal irritation assessment. However, several promising methods are being investigated. Here we provide an overview of the existing alternative in vitro pre-clinical methods with the goal of introducing the need for validation of pre-clinical in vitro methods that can predict the effects of personal care, cosmetic, and pharmaceutical products for vaginal use on humans to the representatives of the regulatory community and industries organizing supportive alternative methods.

FUTURE DIRECTIONS/FINAL REMARKS

Possible testing strategy

Cell-based models

- Are useful as first-line screening tests to eliminate candidates that are significantly cytotoxic or cause the release of known biomarkers of inflammation.

- Expansils or 3D reconstructed tissue models

- Could provide the next screening (and in some cases, definitive) step, critical for assessment of preliminary candidates evaluation.

Animal-based models

- Until in vitro methods become accepted by regulatory agencies, animal models are required for assessing full-length formulations and would have to be used to provide information on whole-organ response.

Clinical studies

- Clinical studies are performed for the formulations that advance through the pre-clinical tests.

Gaps

- Validation of existing models and biomarkers
- Identification of new biomarkers and models of microbial/personal care (cosmetic) induced mucosal alteration that correlate with relevant in vivo responses.
- Need to organize and share data on markers and models to assess their relative merits and limitations.

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