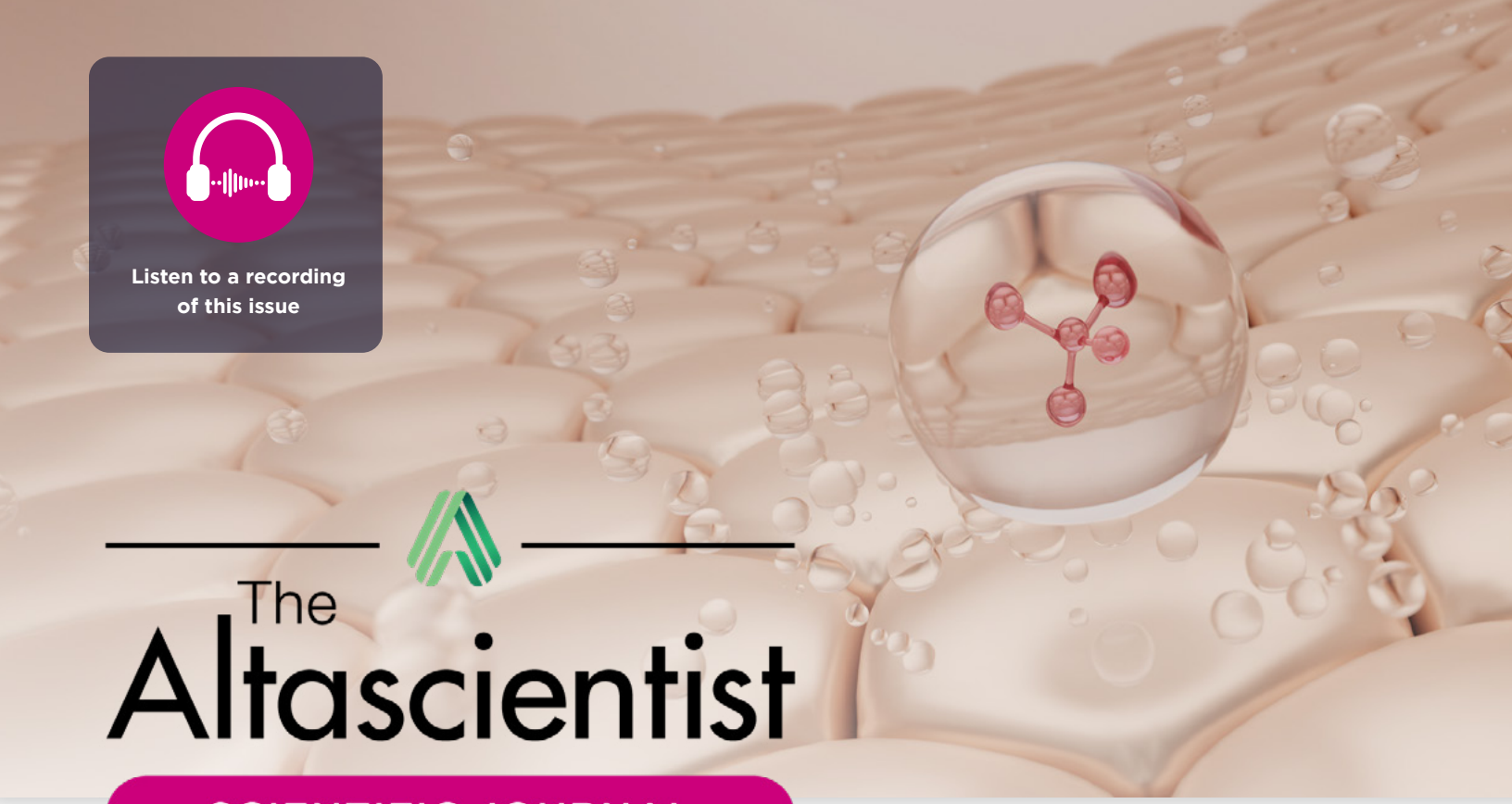

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The Altascientist

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CONSIDERATIONS FOR NONCLINICAL DERMAL STUDIES–ADVANCING TO PHASE I

Dermal drug delivery approaches are on the rise in a variety of therapeutic areas, including the reformulation of existing medications. In many instances, the improvements in the delivery system can lead to a successful 505(b)(2) application, extending the patent life of a drug for its sponsor, or creating a marketing opportunity for a company developing dermal delivery of an already marketed drug. New medications are being specially designed for dermal delivery, and advancements in the field continue as innovative approaches are being tested for the market.

Dermal studies require specific expertise and utilize minipigs due to the physiological similarities between their skin and human skin. Altasciences has decades of experience in the field and boasts access to one of the largest herds of miniature swine in North America, including the most popular breeds of minipigs for your dermal studies.

IN THIS ISSUE

We will review the specific nonclinical requirements to move a dermal program forward to Phase I clinical trials, and discuss approaches and considerations that minimize inherent challenges. We will also touch on formulation considerations for dermal programs.

CURRENT TRENDS IN DERMAL DELIVERY SYSTEMS

From a patient perspective, dermal and transdermal drug delivery systems (TDDS), also known as patches, offer greater patient compliance, ease of administration, as well as convenience and persistence, especially for conditions requiring chronic use.

Preference surveys consistently demonstrate that patients prefer a dermal route of administration for their medications.[1,2,3] Marketed medications that are currently administered by oral or parenteral routes and are well suited for dermal delivery are being reformulated to take advantage of these benefits.

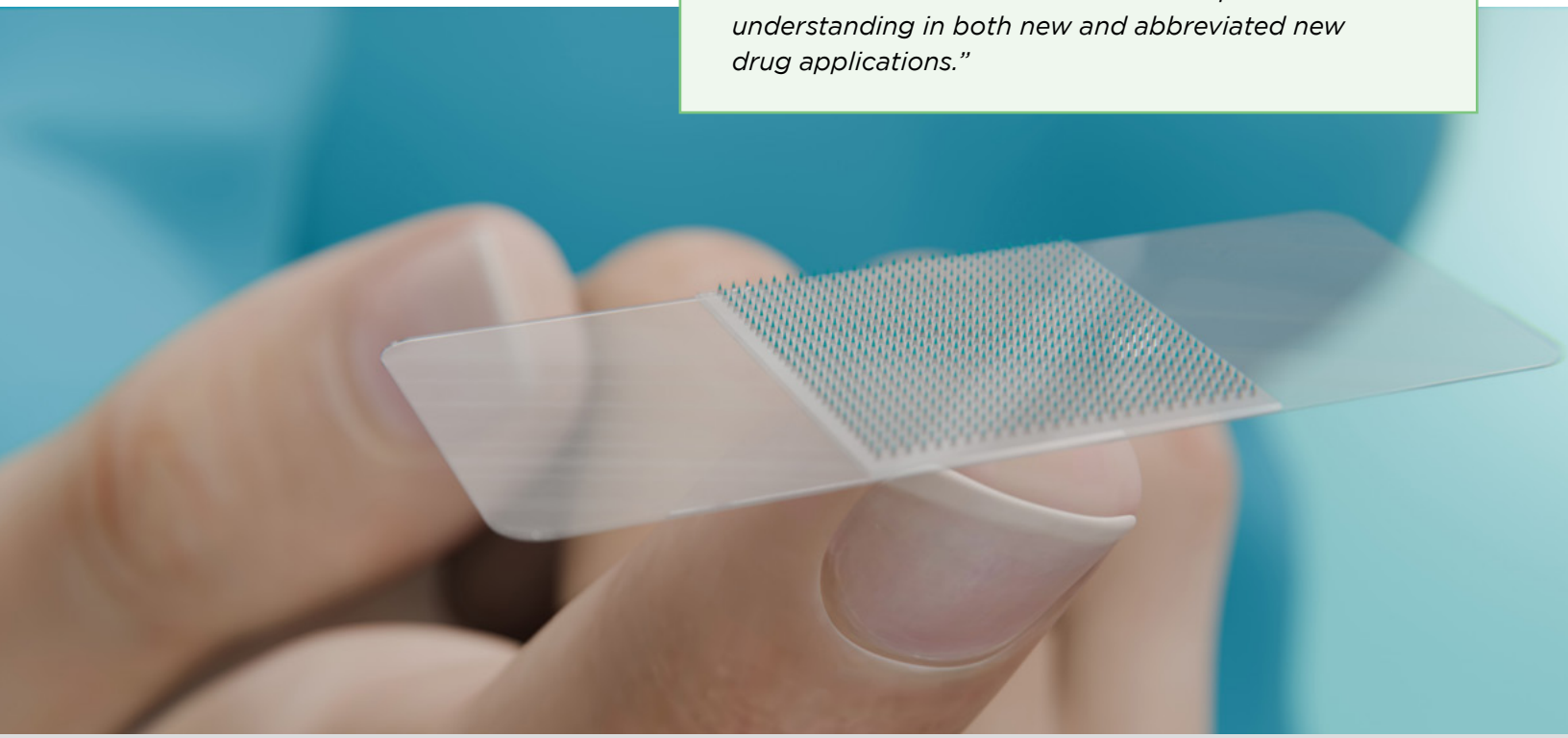
Ideal Candidates for TDDS

- Medications that cause unpleasant side effects (e.g., oral drugs that impact the gastrointestinal tract).
- Medications intended primarily to treat patients with CNS conditions.
- Therapies that require parenteral administration.
- Medications that are impacted by first-pass metabolism.
- Long-term treatment regimens where patient compliance is low.

FDA Guidance—Transdermal and Topical Delivery Systems

"Transdermal delivery systems are designed to deliver an active ingredient (drug substance) across the skin and into systemic circulation, while topical delivery systems are designed to deliver the active ingredient to local tissue. Both delivery systems present similar manufacturing and quality control concerns and similar risks to patients. TDS can be broadly divided into matrix type and liquid or gel reservoir type delivery systems.

Because of the uniqueness of the TDS dosage form, specialized developmental studies and evaluations are recommended to demonstrate full product understanding in both new and abbreviated new drug applications."



MANAGING CHALLENGES IN DERMAL DRUG DEVELOPMENT

The physicochemical properties of the skin raise multiple challenges in topical delivery of a therapeutic. The skin is our largest organ and has a multi-layered structure that can be divided into the **epidermis**, which has the protective function, and the **dermis**, where blood vessels are located and skin cells are produced. Each layer has elements that need to be addressed for dermal drug development programs.

The skin protects the body by blocking environmental hazards, such as chemicals, heat, and toxins, which would similarly impede drug delivery. When designing a nonclinical strategy for dermal programs, it is necessary to identify the target of the active molecule. For certain indications, such as vitiligo or psoriasis, the drug must be localized to the epidermis to keep systemic exposure as low as possible. In other applications, such as for CNS-active medications, the goal is a systemic circulation of the drug, and the target is the blood vessels in the dermis.

To be successful, a development program for a topical drug product must deliver the active molecule to the key targets. An appropriate dosage is determined based on the target and a suitable formulation (e.g., ointment, paste, cream, gel, lotion) is designed. Excipients are screened for key characteristics, such as amount of drug compatibility, dissolved drug, drug particle size and morphology, topical permeation and penetration, texture, viscosity, pH, and globule size.

Once a program strategy is established, the usual battery of nonclinical studies, as well as specialized safety assessment studies, are conducted, as per below. For this article, we discuss the most common studies. However, **each program is unique, and the attributes of your program dictate the studies that will be required**.

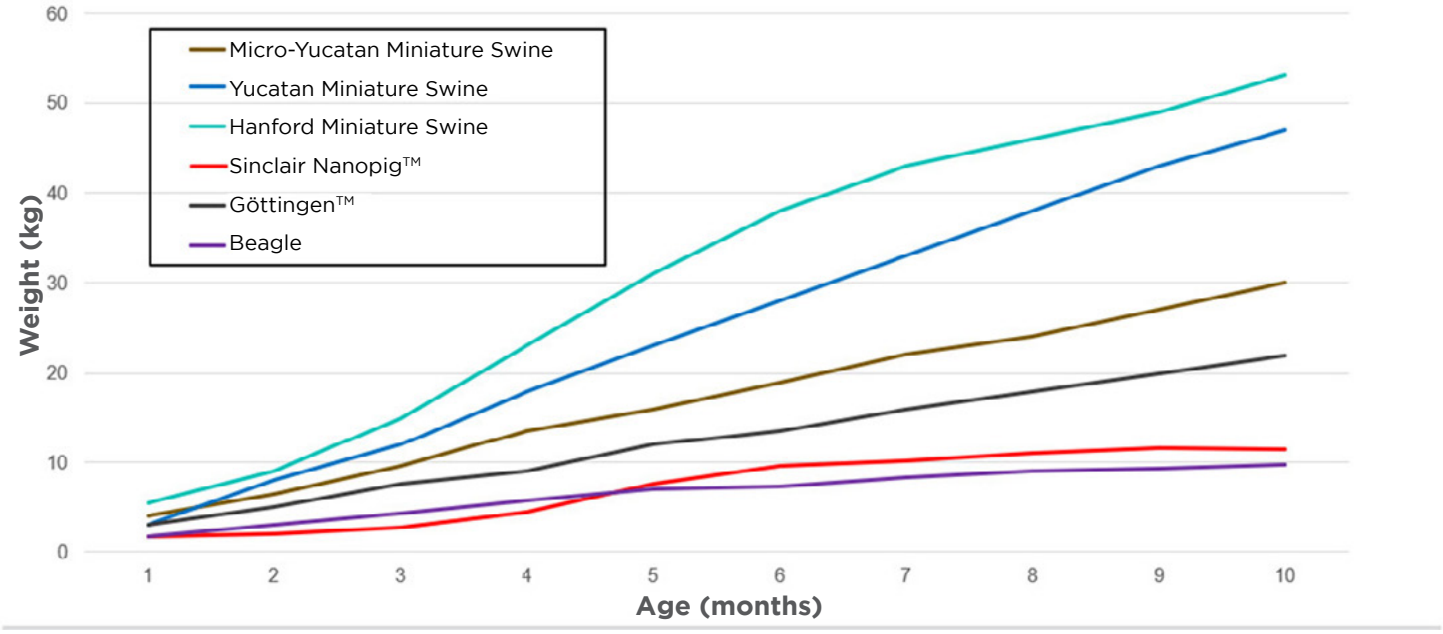
SPECIES SELECTION FOR DERMAL STUDIES

Skin researchers require efficient animal models that are predictive of human responses. Swine have been used extensively in dermal research because of the similarities of the integument to humans. Miniature swine, in particular, offer many distinct advantages for dermal research. Pig skin is anatomically, physiologically, biochemically, and immunologically similar to human skin and is fixed skin like that of humans. It also mirrors human skin with its sparse haircoat, a relatively thick epidermis, similar epidermal turnover kinetics, lipid composition and carbohydrate biochemistry, lipid biophysical properties, and a similar arrangement of dermal collagen and elastic fibers.

Porcine and miniature swine models offer significant advantages with a record of predicting treatment modalities in humans better than other alternatives. Included uses are models for malignant melanoma, wound healing (including delayed diabetic model), phototoxicity, dermal toxicology, dermal pharmacokinetics/toxicokinetics (PK/TK), iontophoresis, dermal irritation, thermal injury, contact allergic dermatitis, depigmentation, and chemical vesication. Miniature swine models provide useful safety and efficacy data for novel cutaneous therapy product development and offer researchers unique tools in dermal research.

There are several breeds of miniature swine used in nonclinical studies and, in late 2022, the downsized Sinclair Nanopig™, an even smaller breed that can decrease test article usage was first available. The Nanopig™ is the smallest of all available breeds of miniature swine, and is very similar in size to a beagle dog throughout its growth cycle.

Miniature Swine Growth Curves



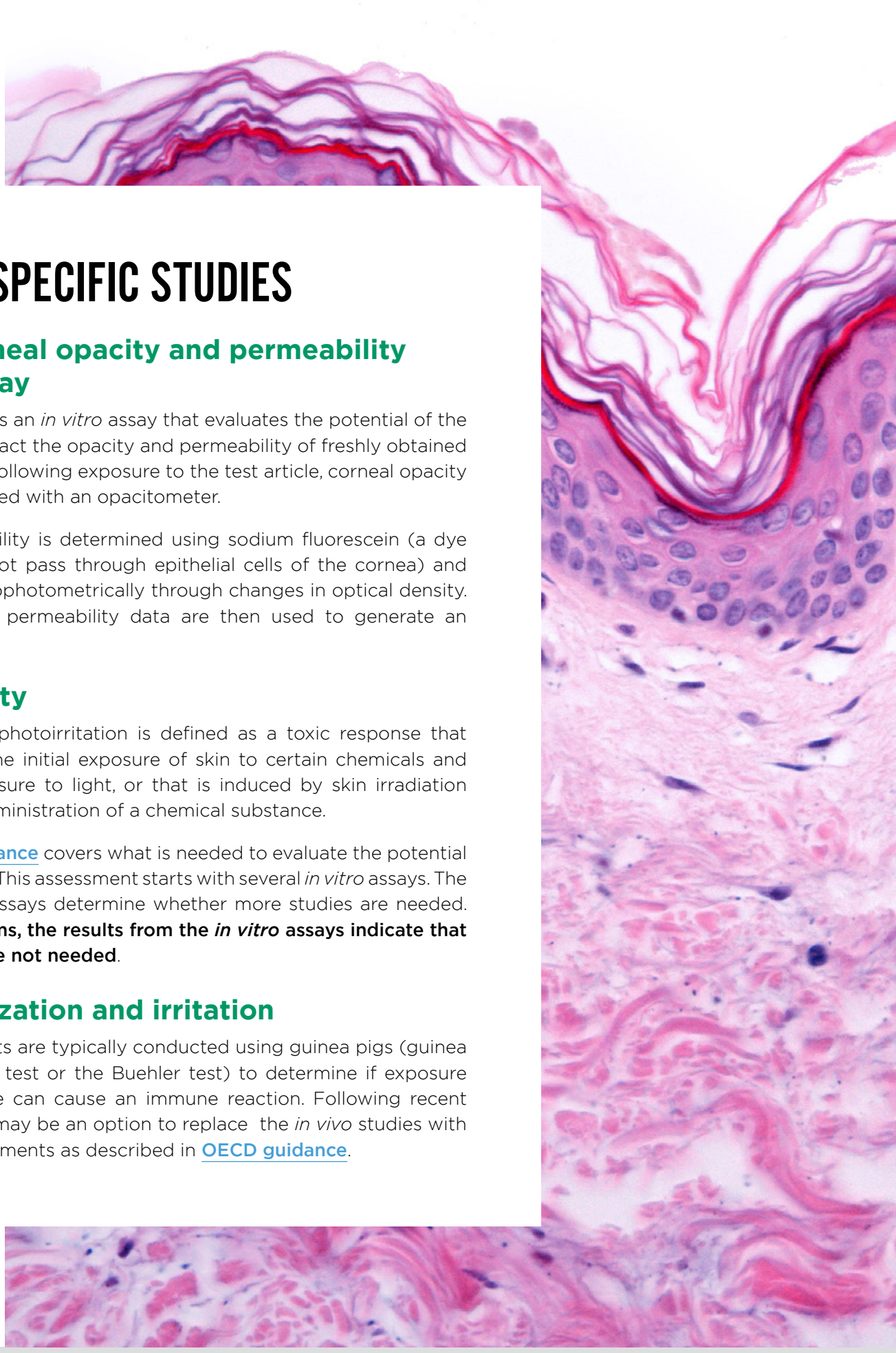
COMMONLY REQUIRED NONCLINICAL STUDIES

The required studies include the standard battery of safety tests for any dermal medication seeking to move to Phase I clinical trials in healthy normal volunteers.

Typical IND Program for a Dermal Indication

	Type of Study	Standard Species
Toxicology Studies	Standard non-GLP and GLP studies	Rat (systemic exposure) and minipig (dermal exposure)
Safety Pharmacology Studies	Standard battery (CNS, CV, and respiratory)	Rat (CNS) and minipig (cardiopulmonary)
Genetic Toxicology Studies	Standard battery (point mutations, chromosomal aberrations, and micronucleus formation)	Rat for the micronucleus formation, the others are *in vitro*

Additionally, there are studies specific to dermal/topical applications that are not typically conducted for oral or injectable drugs, including but not limited to the studies listed on Page 6.



DERMAL-SPECIFIC STUDIES

Bovine corneal opacity and permeability (BCOP) assay

The BCOP assay is an *in vitro* assay that evaluates the potential of the test article to impact the opacity and permeability of freshly obtained bovine corneas. Following exposure to the test article, corneal opacity is directly measured with an opacitometer.

Corneal permeability is determined using sodium fluorescein (a dye that usually cannot pass through epithelial cells of the cornea) and measured spectrophotometrically through changes in optical density. The opacity and permeability data are then used to generate an irritation score.

Phototoxicity

Phototoxicity or photoirritation is defined as a toxic response that is elicited after the initial exposure of skin to certain chemicals and subsequent exposure to light, or that is induced by skin irradiation after systemic administration of a chemical substance.

The ICH S10 guidance covers what is needed to evaluate the potential for phototoxicity. This assessment starts with several *in vitro* assays. The results of these assays determine whether more studies are needed. **For most programs, the results from the *in vitro* assays indicate that *in vivo* studies are not needed**.

Skin sensitization and irritation

These assessments are typically conducted using guinea pigs (guinea pig maximization test or the Buehler test) to determine if exposure to the test article can cause an immune reaction. Following recent legislation, there may be an option to replace the *in vivo* studies with the *in vitro* assessments as described in OECD guidance.

CASE STUDY

Antifungal Small Molecule Aerosol Application

Study Overview

Altasciences was contracted to conduct a safety study in minipigs involving a unique dermal dosing route of administration—an aerosol spray. For dermal studies, the regulatory expectation is to have the test article applied to 10% of the minipigs' body surface area. This is typically accomplished by applying the test article directly to the animal as a cream or ointment. With the test article being delivered by aerosol, our experts had to determine the precise amount of spray time needed to achieve the required dose. It was also necessary to ensure that the application of the test article did not result in material running off the animal.

Study Details

- **Drug Development Phase:** pre-IND
- **Class of Drug:** small molecule
- **Therapeutic Area:** antifungal
- **Animal Model:** minipig
- **# of Animals:** 18 per sex
- **Dose Route:** dermal by aerosol
- **Dose Regimen:** once daily for eight days
- **Study Design:**
  - clinical observations
  - food consumption
  - body weights
  - Draize scoring
  - clinical pathology
  - toxicokinetics
  - anatomic pathology

Study Purpose

To evaluate local and systemic toxicity and toxicokinetic characteristics of an antifungal test article and potential reversibility of any findings.

Methods

Miniature swine were dosed on the skin using an aerosol canister provided by the client. All animals were dosed once daily for eight consecutive days.

Standard safety observations and measurements were performed over the course of the study, including detailed clinical observations, body weights, food consumption, clinical pathology, and anatomic pathology.

Blood samples were collected periodically following dosing on Days 1 and 8 to determine systemic exposure.

Animals were euthanized on Day 9. Complete necropsies were conducted, and standard organ weights recorded. A full set of tissues was collected from all animals, processed to slide, stained with hematoxylin and eosin (H&E), and evaluated by Altasciences' board-certified veterinary pathologist.

Group	Test Material	Dose Level (mg/kg)	Concentration (mg/g)	Dose Weight of Formulation (g/kg)	Terminal		Recovery	
					M	F	M	F
1	Untreated Control	NA	NA	NA	4	4	2	2
2	Vehicle	0	0	0	4	4	2	2
3	Test Article	40	20	2	4	4	2	2

Results

The sponsor provided an estimated time to deliver the desired dose level using their aerosol canisters. A test run was conducted to assess the accuracy of the sponsor-provided estimate so that we could properly plan for accurate dosing during the study.

We weighed each canister before dosing, sprayed for five seconds, then weighed the canister again. If this did not deliver the desired quantity of test material, the technician would spray for another few seconds, repeating the process until the desired weight differential was obtained. In addition, the ideal distance between the canister and the animal needed to be determined to ensure even application and avoid any runoff of the test material.

Once our experts had determined the appropriate spray duration and distance, that is what was used to dose the animals on study. To achieve consistency, the same technician who performed the trial runs conducted all the dosing events during the study.

All dosing events were documented using a form that included the animal number, the canister's start weight, start time of the spray, end time of the spray, the canister's end weight, and the animal-specific spray canister IDs.

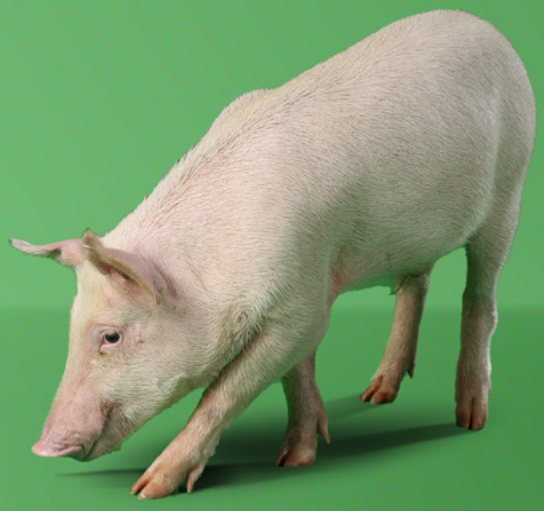
How Altasciences' Expertise Drove Results

Dermal studies typically involve a cream or ointment that can be weighed and applied to a specific area on the animal with a high degree of consistency. Since this study involved the test article being administered with an aerosol spray, the standard approach would not work. To achieve dosing that would be consistent and accurate, we worked out the duration of the aerosol application and from what distance.

As described above, miniature swine are the species of choice for a nonclinical program when the dose route is dermal.

Over the last 10 to 12 years, Altasciences' has selected the Nanopig™ for the following criteria:

- **their white color—70 to 80% of the Sinclair population has white hair coat and skin;**
- **the behavioral enhancement system (BES) developed by Sinclair and actively utilized; and**
- **their slow rate of body weight gain (similar to a beagle dog).**



Our preclinical facility in Columbia, Missouri, has access to one of the largest miniature swine populations in the United States. Our scientists, technicians, and veterinary staff are well versed in the planning, conduct, and interpretation of minipig studies and have conducted close to 200 dermal studies to date. With 80 custom-designed animal rooms and experience with both small and large molecules, our team can get your dermal safety study started in six to eight weeks following contract signing.

ALTASCIENCES' RESOURCES

Webinar

Downsized Miniature Swine, a New Take on the Oldest Model

Video

Selecting Miniature Swine for Your Toxicology Study

Posters

- Dermal Toxicology Application Area Changes as Compared to a Theoretical Total Surface Area of Hanford Miniature Swine Over 18 Weeks
- Acute Dermal Irritation Response in White Sinclair and Hanford Miniature Swine
- Miniature Swine Model of Atopic Dermatitis—Assessment of *In Vivo* and *In Vitro* Activity of Recombinant Porcine Interleukin-4 and Interleukin-13
- Why Use Miniature Swine in Dermal Research?

Webpage

Miniature Swine Models

Fact Sheet

Miniature Swine

Blog

Miniature Swine—Changing the Bias for Nonclinical Studies on Small Molecules and Biologics

ADDITIONAL RESOURCES

FDA Guidance Search

All OECD Guidances

REFERENCES:

1 https://link.springer.com/article/10.1007/s11657-022-01075-z
2 https://academic.oup.com/bjaed/article/7/5/171/535087
3 https://www.nature.com/articles/s41573-023-00670-0#Sec7

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.