Sinclair – A Center of Excellence for Dermal Research

Sinclair Research Center has put together a team of toxicologists, veterinarians, and technicians with background in dermal efficacy and toxicology to form a Center of Excellence for Dermal Research. This team works together to provide a wide range of dermal services, to take a dermal molecule from initial efficacy work all the way into regulatory toxicology. Our group has developed dermal models, validated dermal models from elsewhere, and performed both GLP and non-GLP toxicology studies to support both 505 (b)(2) and New Chemical Entity regulatory filings. In addition, we have worked to minimize potential challenges in dermal scoring to provide consistent high quality data to our sponsors.

Dermal Efficacy

Sinclair Research Center performs a large set of dermal efficacy work, including pharmacokinetics and pharmacodynamics (link to pharmacokinetics page), a broad variety of full and partial wound healing modeling with or without co-morbidity associated diseases (link to wound healing models page), and a range of inflammatory mediated skin conditions (link to inflammatory models page) with specific complementary assays to provide a highly translational picture.

Pharmacokinetics and Pharmacodynamics

For any dermal drug administered, understanding how the drug is absorbed, distributed, metabolized, and excreted is essential for a complete picture of efficacy and potential accumulation which could lead to unwanted effects with repeated administration. To better understand these parameters, pharmacokinetic studies (measuring the amount of drug in the blood) and pharmacodynamic studies (measuring a biomarker in the blood affected by the administered drug) can be performed. The team at Sinclair Research Center offers dermal studies in multiple species, including miniature swine, mice, rats, rabbits, guinea pigs, dogs, and non-human primates and has performed pharmacokinetic and pharmacodynamic studies in each.

Wound Healing

With skin that is very similar to human, the miniature swine is the preferred model for studying wound healing. The experts at Sinclair Research Center offer multiple wound healing models in miniature swine, including full- and partial-thickness excisional wounds, ischemic wounds, and thermal wounds. In addition to providing these models in normal pigs, Sinclair Research offers a diabetic pig model that can be used with any wound type. Our veterinary staff is well trained in inducing these wounds and ensuring the best care for the animals to minimize pain and distress, while maintaining the efficacy of the model. With the capability for digital measurement and 3D photography of the wound site, the efficacy of a compound can be completely characterized.

Inflammatory

Inflammation of the skin, characterized by erythema (redness) and edema (swelling), can be induced by chemical induction, pharmacological intervention, or surgical modification. The team at Sinclair Research Center has experience with inflammatory models in multiple species, including mice (dermal edema, psoriasis, and hypersensitivity), rabbits (local skin irritation), dogs (atopic dermatitis), and non-human primates (atopic dermatitis). Understanding the irritation potential of dermal compounds early in the development process can be used to either rank efficacious molecules (based on severity of irritation) or to remove highly irritating molecules from a program early, saving time and money. Sinclair also offers a full battery of inflammatory and immunological assays to support our models.

Dermal Toxicology

When bringing a dermal drug to market, an understanding of the available regulatory pathways

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and required safety studies is essential. The Sinclair Research team has experience in dermal toxicology programs needed for either 505(b)(2) or New Chemical Entity submissions to the FDA (link to dermal sell sheet here).

505(b)(2) IND Process

If a drug has previously been approved by the FDA with a different route of administration, (i.e. from oral or intravenous to dermal) then the abbreviated 505(b)(2) IND regulatory pathway allows for faster and more cost-effective development. A recent FDA guidance from 2015 outlined this process in detail. Typically, for the 505(b)(2) IND process, a dermal drug should go through irritation, sensitization, genotoxicity, and photosafety testing.

Irritation and sensitization studies are typically performed in vivo for FDA approval, using rabbits and guinea pigs, respectively. **Genotoxicity** studies can be performed using a combination of in vitro and in vivo methods to understand the potential of the compound to induce genetic changes that may ultimately lead to a downstream cancer risk. **Photosafety** testing can initially be done by analyzing the chemical for absorption of UV radiation, followed by in vitro testing. If these are equivocal or positive, then in vivo testing should be performed (phototoxicity and photoallergy).

Once the 505(b)(2)IND has been approved and clinical trials have started, then a **9-month dermal** minipig study is typically performed to examine the potential long-term effects of the compound. Several lineages of minipig (Hanford, Yucatan, Sinclair, and Gottingen) are available for these studies that are acceptable to the regulatory agencies, including the Hanford lineage that is currently bred at Sinclair Research.

Regardless of the lineage of minipig used for the 9-month dermal study, if there is a lack of pre-neoplastic lesions observed, then the FDA permits a carcinogenicity waiver to be filed, per the FDA guidance, which would allow for approval without an additional dermal carcinogenicity study being performed (saving 3-4 years of development time and millions of dollars).

New Chemical Entity – IND Approval

A novel dermal drug (one not previously approved by the FDA) would require a much more intense preclinical program. These programs are more typical of ones done with any traditional new chemical entity (NCE) regardless of the route of administration (including rodent and large animal toxicology, safety pharmacology, reproductive toxicity, and many others).

The FDA usually requires additional studies for a dermal drug IND program above and beyond those done for the oral or intravenous route. This is because of the potential for inadvertent exposure via other routes (ocular and ingestion) to a compound applied to the skin. Therefore, in addition to running the studies outlined above for the 505(b)(2) route, it is usually also required to examine ocular toxicity and oral toxicity of the test article prior to receiving IND approval.

Dermal Scoring Challenges

Regardless of the pathway needed to get approval of the dermal drug, it is essential to consider the method by which dermal scoring will be performed in the test animals. Unlike systemic drugs, which mostly exhibit adverse events during a study through clinical observations and clinical pathology, dermal drugs can modify the skin through either redness (erythema) or swelling (edema), which can be scored. These scores are extremely subjective and can vary based on the individuals performing the observation.

Two ways to decrease that variability during a

study (or between studies) would be to either have the same individuals score every animal on the study or to take photographs corresponding to the observation. Photography, however, has its own pitfalls, as the distance from the test site, the exposure time, and even the individual taking the photo can modify the potential observation. While there are no perfect ways to ensure this consistency, having a dedicated group of individuals tasked to score and/or photograph a study will help reduce the potential variability.

Conclusion

The interest in dermal products has increased tremendously in recent years. Understanding the options available and the benefits and pitfalls of each pathway can dramatically increase the speed and decrease the cost of your efficacy program and/or gaining regulatory approval to enter the clinic. Sinclair Research Center has the ability to help with your dermal efficacy and/or dermal toxicology program. The Sinclair Research Center of Excellence in Dermal Research experts are more than happy to discuss your potential program and see how we can work together to advance your compound as quickly as possible.