

# Topical Dermatological Formulation Development

*"Things You Should Know"*



Put your molecule in good hands.



**Dow Pharmaceutical Sciences, Inc.**

The D in Topicals R&D

*Since 1977*

## Things You Should Know

Formulation Development of Topicals is Different	Pg 1
Developing a Target Product Profile is Important	Pg 2
How to Select the Topical Dosage Form	Pg 3
Definition of a “Successful” Formulation	Pg 4
The Need for Multiple Excipients	Pg 5
The Formulation Development Process	Pgs 6-7
Challenging Analytical Method Development	Pg 8
Prototype Screening Using <i>In Vitro</i> Skin Penetration Studies	Pg 9
Selection of The Lead Formulation	Pg 10
Clinical Manufacturing, Tech Transfer & Scale Up	Pg 11
About Dow	Pgs 12-13
Dermatological Product Development Flowchart	Back Cover

## Formulation Development of Topicals is Different

---

There are important issues to consider as you contemplate development of a topical dermatological product. You may already have experience with oral or parenteral products, but there are challenges and issues which are unique to development of topical formulations. A topical formulation must be aesthetically pleasing, in addition to being both physically and chemically stable, and this may require numerous excipients. The formulation must allow for optimal penetration of the drug into the skin, a complex tissue. Skin pH is approximately 5.5; thus the pH of the formulation may change following application to the skin. This brochure is based on our experience and exclusive focus at Dow Pharmaceutical Sciences in developing topical dermatological formulations since 1977.

## Developing a Target Product Profile is Important

---

- Intended Therapeutic Indication
- Preferred Dosage Form
- Anticipated Product Strength
- Desired Release Profile and Skin Penetration Goals
- Cosmetic/Aesthetic Properties
- Target Shelf Life

The first step in a successful topical formulation program is to develop a Target Product Profile, describing the key desired product attributes. The profile will include the intended therapeutic indication, the preferred dosage form (cream, gel, ointment, spray, e.g.), the anticipated product strength (% active pharmaceutical ingredient or API), the desired release profile and skin penetration goals, packaging, target shelf life, and the desired cosmetic/aesthetic properties. While not true for orals and parenterals, the cosmetic elegance of a topical formulation (i.e., feel, color, scent, spreadability, absorbability, etc.) is of great importance in topical dermatologic products and is often key to the success of the product. The ease and/or speed with which a topical product can be rubbed in, or avoidance of a greasy or sticky feel, for example, can be key. Managing these factors is one of the arts of topical formulation development.

## How to Select the Topical Dosage Form

---



Flexibility regarding dosage forms enhances the chance of success for development of a stable and elegant formulation. During early development, the target product profile is often refined based on solubility, stability and/or compatibility data, as these data may determine the dosage form. If the API is amenable to different dosage forms from a solubility and stability standpoint, the dosage form may be selected based on API release data or skin penetration data; i.e., which formulation allows for optimal penetration of the API to the target tissue (stratum corneum, epidermis, or dermis) as required for the therapeutic indication. If all dosage forms developed are similar in their stability and skin penetration characteristics, the dosage form may be selected based on compatibility with the disease state, cosmetic properties, consumer testing and marketing considerations.

## Definition of a “Successful” Formulation

---



A successful topical dermatological formulation can be considered to be one that satisfies the target product profile and is 1) physically and chemically stable (adequate shelf life), 2) releases API from the formulation and delivers it into the skin as required for the target indication, 3) is cosmetically elegant and acceptable to patients, 4) contains only excipients that are necessary, FDA-approved or acceptable from a regulatory perspective, and acceptable for the disease state, 5) is easy to apply and compatible with the desired packaging, and 6) can be manufactured with a process that is scalable to commercial levels. There are challenges during almost every development program. It is important to be able to anticipate problems, prevent them where possible, and to understand how to correct those that do occur.

## The Need for Multiple Excipients

---

Unlike oral and parenteral dosage forms, topical dermatological formulations often require many excipients. Each excipient should be justified by function and need. Those that may have activity for the disease state or that could influence the vehicle effect (thereby reducing chances of clinical success) should be avoided. A novel excipient should not be used if an older, well-characterized, inactive ingredient which is listed on the FDA Inactive Ingredients Database would work just as well. If a novel excipient is used, it is probable that FDA will require additional safety data, which will increase the nonclinical study burden (time and cost). Solvents, preservatives, antioxidants, surfactants and other agents are used to overcome solubility, stability, or skin penetration challenges and are selected based on the physiochemical properties of the API. Cosmetic elegance necessary for patient acceptance and compliance may require additional excipients. With so many excipients, interactions may occur with each other or with the API, ultimately resulting in odor, discoloration, loss of viscosity, or loss of potency. In addition, it is also important to select well-characterized excipients whenever possible, in order to avoid future issues with variability.

## The Formulation Development Process

---

Dow Pharmaceutical Sciences has developed a formulation development process which has proved to be very successful for our clients. A team from our Formulations, Analytical Sciences, Drug Delivery, and Project Management groups (with consultation from Nonclinical Toxicology, and Regulatory & Clinical Affairs) work together to custom design formulations based on the physio-chemical properties of the API, with one eye on the desired cosmetic attributes required for the clinical indication and the other on potential regulatory considerations.

Pre-formulation studies are conducted initially and form the basis for rational formulation design. The solubility of the API in different solvents (water, water miscible solvents, and lipophilic solvents) is assessed, and API stability may be assessed at this early stage. pH profiles (solubility and stability of the API in different pH ranges of aqueous systems) are conducted, and compatibility studies with solvent combinations and excipients are carried out.



---

Based on this data, multiple different prototype formulations based on different solvent and excipient systems are developed. This is done in order to minimize the need for additional formulation development at a later stage. Each topical dosage form has its special challenges. For example, emulsions (creams and lotions) can be thermodynamically unstable and prone to separation. A variety of techniques can be used to stabilize emulsions, but surfactants may also decrease the efficacy of the preservative. With improper gel formulation, loss of viscosity may occur or structures may collapse over time.

The prototypes are placed on accelerated stability, sometimes in multiple packaging components to evaluate packaging compatibility early on. The prototypes undergo freeze-thaw and warm-cold cycling as well as being stored under a wide range of temperature conditions. While chemical instability can be anticipated based on data from accelerated temperature studies, real-time physical stability data are very important. Development of a robust formulation insures that the formulation will not be adversely affected if minor adjustments to composition or process are made later during scale-up.



## Challenging Analytical Method Development

---



Topical formulations often contain multiple excipients and preservatives, as well as potentially low levels of API, sometimes making the development of stability-indicating and impurity-tracking methods challenging. The semisolid environment can accelerate degradation or other reactions. Rates of degradation can vary significantly based on the formulation matrix. Extractions can also present challenges during topical formulation development. An API method must often be modified in order to be appropriate for assay of a topical formulation containing the API. R&D methods can be developed, qualified for GLP nonclinical studies, and then validated as appropriate for GMP supplies for Proof of Concept (POC) clinical studies in a step-wise fashion, as needed for the particular stage of development. Full validation can then be completed at Phase III.

## Prototype Screening Using *In Vitro* Skin Penetration Studies

---



*In vitro* penetration studies are used to screen prototypes to ensure that the API is released from the formulation and penetrates the target tissue as required for your clinical indication. A formulation optimized for drug penetration is more efficient and requires lower concentrations of API, thus reducing cost of goods. This can also result in a product of lower irritation potential, and maximum opportunity for clinical efficacy. At Dow, human abdominal skin from elective surgery from a single donor is used for these studies. This provides test results superior to cadaver skin and avoids donor-to-donor variation. Multiple prototypes can be compared in one study using Diffusion Cell Systems (Franz Static or Bronaugh Flow-Thru, depending on desired study design).

## Selection of the Lead Formulation

---



A lead formulation is selected based on the chemical and physical stability data from accelerated stability studies, on *in vitro* skin penetration data, on the assessment of cosmetic elegance and aesthetic properties, and on results of animal efficacy testing that may be conducted (dependent on availability of predictive animal models).

In topical dermatological product development programs, it is preferable that the lead formulation selected for non-clinical and clinical studies be very close to the final commercial formulation. Significant formulation changes made later in development will likely trigger the need for bridging studies or an FDA request to repeat potentially expensive and time consuming non-clinical studies. Therefore, if optimization of the formulation (beyond minor changes) is considered necessary, it should be conducted at this stage, prior to entering into potentially costly GLP nonclinical studies.

## Clinical Manufacturing, Tech Transfer & Scale Up

---



During formulation development a process should be developed which will later allow the formulation to be scaled up to large batch sizes at a commercial manufacturing site. With topical formulations, the manufacturing process can influence both stability and product performance. When a formulation is transferred to a commercial manufacturer, depending on the type, size and mixing capacity of the equipment, process changes in mixing speed, temperature control, and order of ingredient addition may be needed. Anticipating the effect of manufacturing changes and minimizing process changes at scale-up reduces the likelihood of issues in later stage development. At Dow, the formulation and process development team leaders oversee manufacturing and filling of phase I-II clinical supplies, help select a commercial manufacturer, transfer the technology, and assist in scale-up. Management of the entire process at one location, from prototype development to commercial scale-up, ensures project continuity and can save you considerable time and money.

## *About Dow*

### Topical Dermatological Formulation Experience

---

Since 1977, Dow has focused exclusively on topicals and has developed more Rx topical formulations than any other company in the world. Most projects are for NCEs which can be difficult to formulate. From this focused experience we understand the issues and challenges and we know how to lead you through the process. By working with Dow, you gain access to all our experience and this provides your best chance for success. While other companies may provide dermatological formulation development services, most do not have the same focus on topicals, wealth of experience and history of success.

### Experience With Many Indications and Dosage Forms

---

Dow has developed topical formulations for psoriasis, acne, atopic dermatitis, actinic keratosis, rosacea, wrinkles, fungal infections, women's health, topical pain, wound healing, warts and other dermatological conditions. A range of disease-compatible dosage forms are developed as part of our formulation process, so we have considerable experience developing aqueous and non-aqueous gels, ointments, creams, lotions, foams, sprays, shampoos, solutions, and suspensions.

## Experience Working With a Broad Range of Clients

---

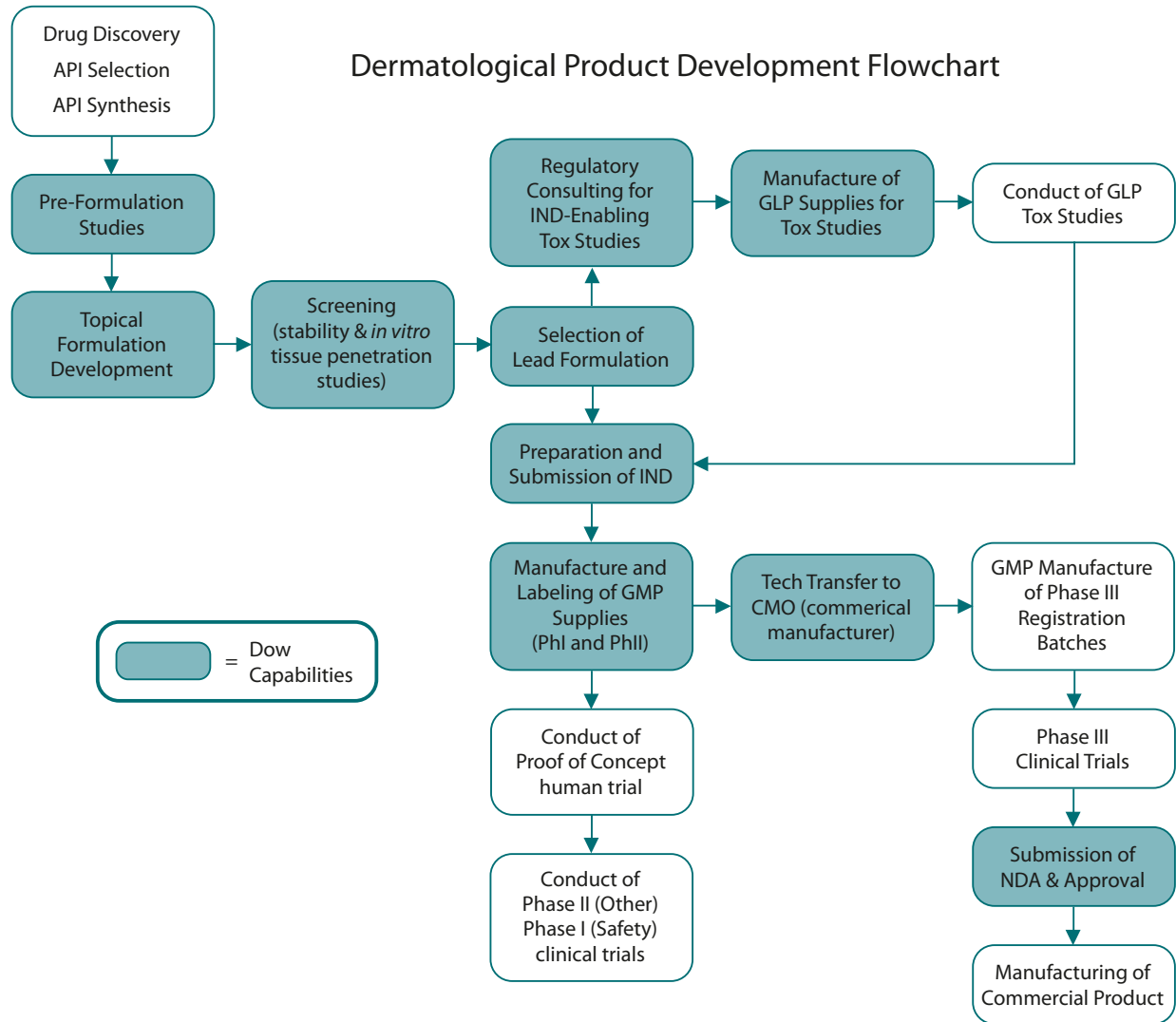
Each year we develop formulations for 20-25 new clients, including many start-ups. We understand the needs of small and large companies. Dow clients come from the USA, Europe, Australia, Canada, China, Israel, Japan, and Taiwan. Several clients are now selling products formulated at Dow including Clindagel™, Clobex Spray™, Cutivate Lotion™, Desonate Gel™, MetroGel 1%™, Ziana™ and Acanya™ to name a few.

## Everything You Need in One Location

---

All services needed to progress your topical formulation through development, testing, manufacturing, labeling and delivery to clinical sites are available at our facility in Petaluma, California. Coordinated by a Dow project manager, in one location you have a full team of specialists to provide formulation development and optimization, *in vitro* skin penetration studies, analytical method development and validation, scale-up and process development, stability, manufacturing of toxicology and clinical supplies, labeling and distribution to your clinical sites, and regulatory support. Our goal is to save you time and to provide your best chance for success.

## Dermatological Product Development Flowchart



**Dow Pharmaceutical Sciences, Inc.**

1330 Redwood Way

Petaluma, CA 94954-1169

Tel: 707.793.2600

[www.dowpharmsci.com](http://www.dowpharmsci.com)