Welcome to Vehicles Matter, Part I, the first in a two-part series that explores the important role of the vehicle on the efficacy, safety, and tolerability of a drug formulation. Starting with the process of formulation planning through the FDA approval process, this first edition of Vehicles Matter elucidates the critical considerations that go into designing a new topical therapy. In Part II (June 2010), we’ll take a closer look at specific drug formulations in order to better understand the unique ways that these various products address the challenges of formulation to ensure tolerability and efficacy.

The insights you’ll find in this supplement represent the combined knowledge of a panel of specialists, with expertise in pediatrics, allergic contact dermatitis, clinical practice, and research. This seven-member panel convened for a lively and informative dialogue in November 2009.

I am confident that this innovative and exciting supplement series to Practical Dermatology will help you make more informed therapeutic decisions and more effectively communicate those decisions with your patients, colleagues, and others involved in patient care. Be sure to visit VehiclesMatter.com on a regular basis for additional information, a glossary of important terms, updates on new formulations, and patient education resources.

I hope you find this content as informative as we did, and I thank our panelists for participating in this important initiative.

— Leon H. Kircik, MD
Program Chair

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Every time that a dermatologist prescribes a topical therapy, that decision represents the culmination of several important considerations. Often the clinician knows which active agent is most appropriate for the skin disease being treated, but he or she must determine: which dosage form is most appropriate for the anatomic site of treatment, which formulation will provide the least discomfort to the patient with the lowest risk of adverse events, and which product offers the best efficacy, among other considerations. Although clinicians make therapeutic selections based on their unique knowledge and extensive clinical experience, these decisions are frequently disregarded and therapeutic substitution occurs at the pharmacy.

The practitioner should be familiar with the drug development process that brings formulations to the market. Expanded knowledge of the formulation development and drug approval process allows the prescriber to better make treatment selections. From the initial considerations of the product formulator to the scrutiny provided by the Food and Drug Administration (FDA), significant resources of time, money, and intellect go into the development of a topical drug formulation. The following is an overview of the topical drug development and FDA’s approval process with emphasis on those aspects that have clinical relevance.

**Topical Drug Delivery**

The epidermal barrier functions to prevent entry of chemicals and noxious materials, thus the most significant challenge in topical drug delivery is designing an appropriate vehicle. For this reason formulators must understand the structure and function of the stratum corneum in order to optimize delivery of drugs to the intended site of activity within the skin. Formulation development projects begin with the identification of the active ingredient to be used to provide a desired effect. A target product profile is developed, establishing the goals of vehicle development by exploring and answering a series of key questions about the formulation to be developed. Six primary considerations guide the development of a vehicle. The vehicle must:

1. Efficiently deposit the drug on the skin with even distribution.
2. Release the drug so it can migrate freely to the site of action.
3. Deliver the drug to the target site.
4. Sustain a therapeutic drug level in the target tissue for a sufficient duration to provide a pharmacologic effect.
5. Be appropriately formulated for the anatomic site to be treated.
6. Be cosmetically acceptable to the patient.

Due to the efficiency of the epidermal barrier, the amount of topical drug that gets through the stratum corneum is generally low. Rate and extent of absorption vary depending on characteristics of the vehicle but is also influenced by the active agent itself. Topical corticosteroids are representative of many commercially available topical drug products regarding bioavailability of lipid-like drugs through skin. These agents result in systemic absorption through intact, non-inflamed skin of
Knowledge of skin barrier function has expanded in the last two decades, elucidating both the manner in which drugs penetrate and the topical formulations that efficiently deliver drugs. This advancement in skin biology has fueled the development of novel vehicles that have advanced dermatologic therapy with both new formulations of old drugs and new drug entities.

Mechanisms of Drug Absorption. There are three primary mechanisms of topical drug absorption: transcellular, intercellular, and follicular. Most drugs pass through the torturous path around corneocytes and through the lipid bilayer to viable layers of the skin. The next most common (and potentially under-recognized in the clinical setting) route of delivery is via the pilosebaceous route. Follicular delivery is typical of several commonly used drugs that are present in vehicles as fine particulate suspensions: benzoyl peroxide, azelaic acid, and dapsone.

Follicular delivery is preferred for diseases of the pilosebaceous unit, such as acne, folliculitis, and hair loss, but is also utilized to create a reservoir effect. Drug microparticles deposited into the follicle may slowly dissolve over time, creating a controlled release or reservoir effect.

In practice, drugs are absorbed through combinations or perturbations of these pathways. For example, propylene glycol, because of its solvent and humectant properties, is a common ingredient in topical formulations. At relatively high concentrations, propylene glycol has been shown to promote desquamation, thus widening the cellular pathways through which topically applied drugs may pass.

Hydration of the stratum corneum is an important tool for modifying drug delivery. As epidermal cells swell, the aqueous/lipid ratios within the skin are altered and, as a secondary effect, those cells no longer resist mechanical sheering and stress forces. Hydration also helps maintain normal desquamation, as the serine proteases that instigate dissolution of the desmosomes require water. In certain disease states, such as psoriasis, water can encourage desquamation of the corneocytes and thus enhance penetration of a drug through thick, scaly plaques.

Drug Metabolism. The epidermis is not simply a passive membrane that either blocks or permits entry of a drug. The skin, rich in enzymes, is the largest drug metabolizing tissue in the body. Research has identified 13 CYP2 genes expressed in human skin, with most expressed in the non-vascular tissue of the epidermis. Esterases and serine proteases are abundant. Biotransformation of compounds can and often does occur in the epidermis, presenting both challenges and opportunities to formulators. Epidermal biotransformation could render a drug such as a peptide ineffective before it reaches its target or, in the case of some pro-drugs, transform a biologically inactive molecule to an active form. Epidermal metabolism and inactivation of certain drugs may permit safe topical appli-
cation of a drug that possesses systemic toxicity.

Gama benzene hexachloride (GBH, Lindane, Morton Grove Pharmaceuticals), for example, is largely biotransformed as it passes through the epidermis and into the dermis, therefore the risk of systemic toxicity associated with extensive topical application (up to 30-60mL) is relatively low. By contrast, less than 15mL of Lindane ingested orally is in the range of LD50 for humans. Topical tazarotene is another drug that is rapidly skin metabolized (to tazarotenic acid and other metabolites),10 accounting for its relatively low risk of systemic exposure.

Cutaneous metabolism allows for the topical application of pro-drugs that are transformed to active drugs. Retinol is metabolized in the dermis to retinoic acid.11 However, the efficiency of biotransformation of retinol to retinoic acid is relatively low, so retinol is considered safe for use as an ingredient in topical cosmetic products without retinoid safety labeling.

Theoretically, pro-drugs could be used in topical formulations as a strategy to alter the physicochemical properties of the active ingredient to improve delivery into the skin or to minimize toxicity. Suppose a biologically activated drug is intended for delivery to the dermis but is inactivated in the epidermis. An inactive pro-drug molecule might pass through the epidermis and be metabolized to the biologically active drug at the dermal layer, where it can produce the desired effect.

**Disease Sites and Anatomic Treatment Areas.** The site of the disease within the skin—whether it be the epidermis, dermis, capillaries, or the pilosebaceous unit—must be taken into account in designing an effective vehicle for a drug. With the modern understanding of skin biology, formulators can target delivery of a particular drug molecule by the skillful selection of excipients and their concentration, proper choice of vehicle type, and careful attention to the physical state of the active ingredient (i.e., the degree of solubility in vehicle or particle size in the case of suspensions) and control of the characteristics of the secondary formulation. Similarly the anatomic location(s) of treatment and the range of body surface area guide development of a vehicle that will allow the drug to be applied uniformly and with relative ease.

Clinicians know that choice of vehicles depends on the location being treated as well as the skin disease. For example, an ointment is not cosmetically acceptable for application to the hair-dense scalp for many people. The scalp is an interesting delivery area to consider in terms of product formulation because of the variability of density and texture. Unless the topical formulation can be applied directly to the scalp skin (e.g., a foam or spray applied via a delivery tube to pass through the hair), scalp treatment involves a greatly increased skin and appendage surface area that will interface with the topical delivery system. Scalp and other very hairy areas generally require the application of more drug formulation per square centimeter than glabrous skin. Additionally, the scalp is almost always covered by a thin layer of sebum. Sebum incorporates into the formulation after application to the scalp skin, potentially altering the kinetics of intercellular transport. For this reason effective topical formulations take into consideration the in vivo environment from which the active ingredient is delivered to the site of action within the skin.

**Drug-Specific Considerations.** Specific properties of the drug to be delivered guide the development of the vehicle. Ideal vehicles are drug-specific; There are no vehicles that without customization work efficiently for a wide variety of drug molecules. The stability of the active ingredient and its bioavailability are primary considerations in creating an optimal vehicle. Based on the physicochemical properties of the drug, a rational strategy can be developed to create the vehicle. Key factors include: a) degree of solubility or insolubility in various excipients such as oils, humectants, and water, b) compatibility or incompatibility with potential excipients, and c) sensitivities to molecule degradation and instability. With this knowledge, the formulator
can create multiple vehicles for the drug with the goal that one will survive stability testing, assessment of cosmetic and functional properties, in vitro skin penetration studies, antimicrobial preservative effectiveness testing, and other screening criteria. The development process is lengthy and far from simple.

**Secondary Formulations.** Beyond the physicochemical considerations and requirements for the formulation and its physical container to provide stability and uniformity, formulators also must consider the physical changes that occur as a formulation is applied to the skin. When present in a vehicle, volatile components such as water, alcohol, and propellants, all eventually evaporate, thereby concentrating the active drug and non-volatile excipients. During the application process these residual components become mixed with the hydrolipidic film on the skin surface, creating what some call the “secondary formulation.” It is from this secondary formulation that drug is typically delivered into the skin. Consider difficult-to-solubilize dapsone that has been formulated into a gel (Aczone, Allergan). The marketed formulation contains water along with a solvent called diethylene glycol monoethyl ether (also known as DGME, Transcutol® or ethoxydiglycol). DGME solubilizes a percentage of the dapsone in the formulation; the remaining undissolved dapsone particles remain in suspension. Once the gel is applied to the skin, water—the highly volatile component—dissipates, and dapsone particles become concentrated in the residual non-volatile solvent DGME. As the gel is rubbed in, mechanical rubbing action helps to further dissolve dapsone into the solvent, while undissolved particles are deposited in the follicle, creating a reservoir of drug slowly dissolved by sebum over time. At the same time, sebum and other debris on the surface of the skin become incorporated into the secondary formulation.

Of the many topical solubilizing agents used, propylene glycol may be the most widely used and best known. At high concentrations (greater than 10%) propylene glycol can be more irritating to the skin or provoke allergic reactions, though it is generally well-tolerated at moderate and low concentrations. High concentrations of PG may be problematic for some individuals; The incidence of positive patch reactions for allergic contact dermatitis in those using up to 30% concentration of PG is about 3.5 percent.12

**Penetration Enhancers: Benefits and Challenges**

In order to promote absorption of drugs, vehicles often include penetration enhancing ingredients that temporarily disrupt the skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into skin. So-called penetration enhancers are drug substance- and vehicle-dependent and therefore are not universally effective. Propylene glycol is a multifunctional excipient in topical formulations, having humectant, solvent, and antimicrobial properties. The mechanism of permeation enhancement by propylene glycol is multiple and varies with concentration and formulation type. Propylene glycol is commonly used as an excipient in topical drug formulations and is found in a majority of formulations of corticosteroids. It is shown to diminish barrier function,13 and often functions as a penetration enhancer. Interestingly, despite its utility and safety in topical formulations, propylene glycol at high doses is toxic to humans.14

Other penetration enhancers, including detergents and emulsifiers, disrupt the barrier to encourage migration of active drug through the stratum corneum. Oleic acid can be a penetration enhancer in certain formulations and its mechanism is thought to be through fluidizing the intercellular lipids of the stratum corneum. Isopropyl myristate (IPM) is a unique penetration enhancer that is thought to provide benefit by fluidizing stratum corneum lipids and partially dissolving them.15 It is
used in clobetasol propionate 0.05% spray (Clobex Spray, Galderma) to encourage rapid penetration of corticosteroid into the treated skin.

Most penetration enhancing excipients have the potential to be irritating to the skin, depending upon concentration and the other inactive ingredients in a particular vehicle.

Only relatively recently have formulators focused on modulating the detrimental effects of penetration enhancers by reducing or ameliorating the signs and symptoms of irritation. Review of three modern formulations of benzoyl peroxide (BPO)—an inherently irritating drug—and clindamycin demonstrate how vehicles may be formulated in efforts to reduce the irritation potential.

Benzaclin (clindamycin, 1%, benzoyl peroxide, 5%, Sanofi-Aventis) contains micronized benzoyl peroxide in an aqueous gel with surfactant and no non-volatile solvent. Upon application, the micronized BPO is deposited in the sebum-rich follicle where it exerts its effects.

In Duac (clindamycin, 1%, benzoyl peroxide, 5%, Stiefel) micronized benzoyl peroxide is formulated in an aqueous gel with surfactant, glycerin, a humectant to minimize the desiccating effect of BPO, and the emollient dimethicone to help moisturize the skin.

Acanya gel (clindamycin phosphate 1.2%, benzoyl peroxide 2.5%, Coria Laboratories) contains a 2-fold lower dose of benzoyl peroxide than the other clindamycin/BPO products, yet laboratory evidence suggests delivery of a similar amount of BPO to the skin. This may be an effect of low concentration propylene glycol in the formulation that helps to solubilize the BPO microparticles and transports them into the sebum.

The use of microspheres represents another approach to minimizing BPO-induced irritation. NeoBenz Micro (Intendis) entraps micronized benzoyl peroxide within polymeric sponges, offering slow release of the drug over time. Slow release of benzoyl peroxide through microspheres is shown to reduce irritation and minimize percutaneous absorption.

Other attempts to minimize the irritancy associated with BPO while enhancing efficacy have focused on solubilizing the drug. A gel and lotion formulation (ClenziDerm, MD, Obagi Medical Products) features chemically micronized, solubilized BPO molecules to ensure even distribution in the vehicle. In clinical trials comparing solubilized BPO gel to a non-solubilized BPO/clindamycin combination formulation, the solubilized gel produced a greater reduction in non-inflammatory lesions at weeks 1 and 2 and an equivalent reduction in inflammatory lesions at week 12. Solubilized BPO is shown to produce a greater reduction of colony forming units of P. acnes compared to combination BPO/clindamycin.

Ethanolic foam vehicles that dissolve at body temperature (Olux and Luxiq, Stiefel) not only provide good spreadability and cosmetic elegance, but also enhance delivery of corticosteroids compared to other traditional formulations. The mechanism to enhance penetration is the creation of a supersaturated drug solution in the propylene glycol-rich secondary formulation remaining on the skin after evaporation of the alcohol and propellants. Supersaturation provides a driving force for drug delivery into the skin. Despite good overall tolerability with original ethanolic foams, a newer foam vehicle (Olux E, Stiefel) features emollients that counter the drying effect of the ethanolic foam, thereby hydrating the skin and providing a lubricant film to counteract sensations of stinging, burning, and dryness related to ethanol.

In the case of Metro 1 (metronidazole 1%, Galderma), metronidazole is not very soluble in water or oil, so the molecule was formulated inside a dextran ring (Betadex NF or beta cyclodextrin) to which niacinamide was added in order to keep 10mcg/g in solution. Given the physicochemical characteristics of metronidazole, optimal delivery would be predicted from a solution rather than a suspension of the active ingredient. Niacinamide is further shown to improve skin hydration and barrier function. Low concentrations of glycerin in the formulation enhance percutaneous absorp-
tion and provide humectant effects. Betadex has a polyhydric hydrophilic surface (to enhance solubility and moisturize the skin) and hydrophobic core that encapsulates the metronidazole molecule. This newer formulation enables once-daily dosing of a higher concentration of metronidazole than had previously been available, and with improved tolerability.

Topical Dosage Forms

The classification of topical dosage forms has recently been updated and codified. While some terms commonly used to describe specific vehicles are actually developed for marketing purposes, FDA recognizes eight topical dosage forms: Solution, Suspension, Lotion, Paste, Gel, Ointment, Cream, or “Other,” which includes foams, aerosols, powders, patches, etc.2 (See Table 1.)

The clinical significance of these classifications varies; however there are many situations where the vehicle matters. Clinicians may favor certain dosage forms for specific uses, and they often ascertain the benefits of various forms from clinical study data, practical experience, product package inserts, manufacturer’s materials, and peer educators. For conditions such as atopic dermatitis, psoriasis, and contact dermatitis with unique skin reactivity, the improper choice of vehicle can impact therapeutic outcomes leading to signs and symptoms of cutaneous irritation, poor patient compliance, and production of allergic contact dermatitis due to a preservative.

An occasional mismatch between the official designation of a product and its practical appearance may have a significant impact on patient

<table>
<thead>
<tr>
<th>Is it Pourable?</th>
<th>Yes</th>
<th>No</th>
</tr>
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<tbody>
<tr>
<td>Non-liquid, Non-semi-solid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Other”: Formulations that are not liquid or semisolid fall into this category, which includes aerosols, powders, etc.</td>
<td></td>
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<tr>
<td>Liquids</td>
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<tr>
<td>Solutions: Clear and homogeneous</td>
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<tr>
<td>Suspensions: Solids dispersed in liquids</td>
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<tr>
<td>Lotions: Emulsions</td>
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<tr>
<td>Semisolids</td>
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<tr>
<td>&gt;50% water and other volatiles</td>
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<tr>
<td>Gel: Solution or colloidal dispersion stiffened with a gelling agent</td>
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<tr>
<td>Ointments: More than 50% of hydrocarbons, waxes or PEG and less than 20% water and volatiles</td>
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<tr>
<td>Pastes: Contain 20-50% dispersed solids</td>
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</tr>
<tr>
<td>Cream: One or both does not apply: • More than 50% of hydrocarbons, waxes or PEG • Less than 20% water and volatiles</td>
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Table 1. Topical Dosage Forms for Dermatological Applications

Despite its dosage form designation, Diprolene Lotion 0.05% (betamethasone dipropionate, Shering Corp.) would be categorized as a solution under today’s FDA naming system, as the vehicle is in fact a clear hydroalcoholic solution intended for scalp treatment, and not a fluid emulsion of oil and water (i.e. lotion).

These dosage form classifications are particularly relevant to the development of generic challengers of innovator formulations. To apply for marketing approval from the FDA, a generic formulation must challenge a specific existing product (active drug, concentration, and dosage form). For example, if the FDA had only approved a New Drug Application (NDA) for triamcinolone acetonide 0.1% cream, and no other dosage form were yet available; a generic manufacturer could only challenge the branded product with a 0.1% cream dosage form via the inexpensive generic approval route with an Abbreviated New Drug Application (ANDA). Triamcinolone 0.1% in any other dosage form (lotion or gel) would need to go through the full NDA and review process in this hypothetical case. For this reason, and because choice of vehicle matters to dermatologists for unique and clinically important reasons specific to the individual patient, non-dermatologists, pharmacists, and insurance providers should not substitute different dosage forms or vehicles than the one prescribed by the dermatologist.

Gels and foams, both of which will be further addressed in the second installment of this series, are the dosage forms that have probably witnessed the greatest advancement in recent years. Alcohol-based gels, once considered appropriate only for oily skin, have largely been replaced by hydrogels and nonaqueous gels, changing the way that clinicians view gels and broadening their use. The term “hydrogel” is a descriptive marketing term. Although it is not an official designation recognized by the FDA, it does have a technical meaning in the industry. A hydrogel has low residue, is non-sticky when applied, has a high cosmetic acceptability, is free of acetone, alcohol and significant levels of harsh solvents, and has a very high water content. In this sense, the term describes the consistency and appearance of the hydrogel, as well as potential benefits to the patient. These formulations do not sting or burn and are associated with a lower incidence of adverse events compared to alcohol-based gels. Typically, a humectant ingredient is incorporated to provide what is called a “pillow effect.” Whereas traditional gels dry down very quickly and make the skin feel tight, the water-retention properties of the humectant in a hydrogel impart a softness to the skin.

Many of the gel formulations marketed today are hydrogels, with a few exceptions. Generic tretinoin gel 0.025% is an alcohol gel, and Xolagel (Ketoconazole 2%, Stiefel) is an anhydrous gel, different from a hydrogel.

Formulating for Special Populations

In addition to the drug to be delivered, the site of drug activity, and the anatomic site targeted, formulators must also consider any specific needs and preferences of the population to be treated. Data and experience show that factors such as difficulty of use, messiness, odors, and staining all affect patients’ preferences. Patient age is a potentially significant consideration. While the structure and function of the skin of a child may not differ significantly from that of an adult on a cellular basis, there is an important physiologic difference, due to the higher ratio of skin surface to body mass in children. This is particularly relevant to the treatment of widespread skin disease and use of topical corticosteroids (a more complete discussion of factors associated with corticosteroids begins on p. 12).

Due to regulatory requirements coupled with caution on the part of investigators, few formulations are studied in patients under age two (or over age 65; See Sidebar: Age


"Cosmetically elegant" is a subjective, descriptive term with a marketing rather than regulatory or classification function. For a cosmetic product to be considered cosmetically elegant, it must feel good, look good, and smell good (based on fragrance content). For topical drug products, the issue of a pleasing fragrance is generally not as significant; however, the formulation should feel good and not have an unpleasant appearance (such as odd color or grainy consistency). A cosmatically elegant drug formulation hopefully will at least not smell bad, although some topical agents and excipients have a scent that is unpleasant to many patients.

With few exceptions (such as DermaSmooth [fluocinolone acetonide Topical Oil, 0.01%, Hill Dermaceuticals] and Renova [tretinoin cream 0.02%]), fragrances are not added to topical drug formulations, although masking agents (typically neutralizing fragrances) can be used—leading to an "unscented" or "fragrance-free" claim. Sodium sulfacetamide and sulfur combination products for acne and rosacea usually have an unpleasant and lingering odor. Rosanil wash (sodium sulfacetamide 10% and sulfur 5%, Galderma) however, contains masking agent that eliminates the sulfurous odor.

Fragrances are the most common family of allergens to cause contact dermatitis from cosmetics. Of the roughly 2,500 fragrancing chemicals that are used in the US, about 100 are known or reported to be contact sensitizers. The common sensitizers used for patch testing are said to be found in a significant percentage of cosmetic products. Yet, estimates suggest that, at most, four percent of the general population shows positive patch test to these ingredients.

Clearly, identifying clinically relevant fragrance sensitivity can be a challenge. Nonetheless, patients known to be allergic should avoid cosmetics and topical drug products containing sensitizing fragrances, including masking fragrances. When a patient has a known fragrance allergy, the practitioner may specify on the prescription "Brand necessary: Patient allergic to fragrance." In such cases, it is unlikely that the insurance company or pharmacist will be able to identify a suitable generic product to substitute.

Restrictions on Prescribing), so direct evidence of safety and efficacy has been lacking. Nonetheless, consideration of the available data, empirical evidence, and clinical experience typically guide the safe use of many topical formulations in patients as young as full-term infants. An exception may be the pre-term infant where the barrier is not fully formed and significantly increased percutaneous absorption and toxicity have been well-documented.

Diaper wearing can affect skin barrier function due to occlusion and potential for tissue maceration, and in children there may be some enhanced drug absorption at certain anatomic sites compared to adults. For this reason caution is advised in treating the diaper area with topical drugs on a chronic basis. Practical considerations, such as tolerability and ease of application, may also influence the treatment of children. Parents may be more likely to comply with applications of formulations that are spreadable, soothing, and can be applied quickly, (i.e., hydrocortisone butyrate 0.1% lotion [water-in-oil emulsion] [Locoid Lotion, Triax Pharmaceuticals]).

A parent is not likely to apply to a child’s skin a formulation that causes stinging or burning. For example, when topical hydrocortisone 1% was formulated with urea 10%, it offered efficacy equivalent to a mid-potency steroid for atopic dermatitis, but it had low tolerability.

Ethnicity. Although largely not studied, and while significant differences may not be evident on the cellular level, practical considerations may influence management of patients based on ethnicity. Petroleum jelly has been shown to reduce transepidermal water loss by 98 percent, making it a favorable occlusive moisturizer. While some will not tolerate use of a petrolatum-based ointment to some anatomic sites for cosmetic reasons, some patients prefer petrolatum-based products at some anatomic sites. Clinicians
Age Restrictions on Prescribing

Roughly only one-fifth of all drugs on the US market are labeled for use by infants and children, and only 30 to 40 percent of drugs have an indication for use in children under age 12. Consequently, one study found, 62% of outpatient pediatric visits (0-17 years of age) in the US resulted in off-label prescribing (67% of pulmonary and dermatologic medication prescriptions were off-label). Prescribing information for currently-marketed topical corticosteroids may contain age limits (from a lower limit of three months up to 18 years of age and often an upper limit of 65 years of age).

These apparently arbitrary age limits are artefacts of the regulatory review and approval process. Trial designers typically excluded patients over age 65 because the increasing risk of death due to cardiovascular or other natural causes inherent in this older population increases the risk that a subject may die or experience a serious medical event during the trial. Even if the death or event is not related to therapy, it is thereafter associated with the drug labeling.

Until fairly recently, FDA had not required pediatric testing of drugs subject to the review of an NDA. Since December 1998, when FDA made the pediatric rule effective, drug manufacturers are now required to conduct some studies of new products in the pediatric population or obtain a “pediatric waiver.” The extent of studies conducted in the pediatric population for NDA approval these days depends on prevalence of the disease at various ages within the pediatric population, the extent of the required animal safety studies needed to support such pediatric testing, and negotiations between the manufacturer and FDA. Topical corticosteroids are commonly used in subjects younger than two, e.g., in the management of atopic dermatitis. FDA currently requires testing of corticosteroids in pediatric subjects if the labeled indication includes atopic dermatitis. The clinical safety of some corticosteroid products have extended to children as young as two years of age, while others have data down to three months of age. The differences in pediatric age limitations among products is the result of the labeling sought by the particular manufacturer and actual data supporting safety in that age cohort. Studying the HPA axis effects of topical corticosteroids in very young patients builds a foundation of data to support their safe use in children and also helps to assure access to therapy for very young patients.

<table>
<thead>
<tr>
<th>Examples of Topical Corticosteroids with Specific Age Allowances Below 2 Years</th>
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<tbody>
<tr>
<td><strong>3 Months or older</strong></td>
</tr>
<tr>
<td>• Desonate Gel (desonide), 0.05%; Intendis</td>
</tr>
<tr>
<td>• Derma-Smoothe/FS Topical Oil (flucinolone acetonide), 0.01%; Hill Dermaceuticals</td>
</tr>
<tr>
<td>• Locoid Lipocream/Lotion (hydrocortisone butyrate), 0.1%; Triax Pharmaceuticals, LLC</td>
</tr>
<tr>
<td>• Verdeso (desonide) Foam, 0.05%; Stiefel</td>
</tr>
<tr>
<td><strong>1 Year or older</strong></td>
</tr>
<tr>
<td>• Aclovate Cream or Ointment (alclometasone dipropionate), 0.05%; GlaxoSmithKline</td>
</tr>
<tr>
<td>• Cutivate Lotion (fluticasone propionate), 0.05%; PharmaDerm</td>
</tr>
<tr>
<td>• Cutivate Cream (fluticasone propionate), 0.05%; PharmaDerm</td>
</tr>
</tbody>
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anecdotally have reported regional and ethnic trends in certain vehicle preferences.

Ethnic differences in clinical response to topical therapies have been documented but are poorly understood. In the original trials for tacrolimus ointment 0.03% (Protopic, Astellas) for adult atopic dermatitis, active treatment was not superior to vehicle in African-American adults. Tacrolimus was superior to vehicle in Caucasian adults, and there was no difference in response between African-American and Caucasian children. Wedig and Maibach reported a 34 percent lower in vivo absorption of 14C-labeled dipyrrithione following topical application to four male African American subjects relative to four male Caucasian subjects. However, Lotte et al., using the same methodology, reported no statistically significant differences in the in vivo absorption of 14C-benzoic acid, 14C-caffeine, and 14C-acetyl-salicylic acid following topical application to African American


Topically applied medications can reach the US market in one of three ways: a new drug application (NDA), an abbreviated new drug application (ANDA) for generics, or by compliance with an OTC Monograph as an over-the-counter (OTC or non-prescription) product (see Sidebar: OTC Monograph). Other topically applied products are either cosmetics, which FDA does not approve for marketing, or devices granted 510K marketing clearance. (See “Divining the Details of Device Clearance,” available online at VehiclesMatter.com).

Drugs that had been marketed prior to passage of the Food, Drug, and Cosmetics Act in 1938, were permitted to remain on the market. Ultimately, some were submitted for approval in NDAs in their existing or new formulations. Others were shown to be ineffective or dangerous and were abandoned. In 1968, FDA established “Drug Efficacy Study Implementation” or DESI with the aim of evaluating drugs that had not yet undergone clinical trials and review. About 160 drugs have still not been reviewed yet are available on the market. Known as DESI drugs, many are still used in dermatology—coal tar, sulfur, sodium sulfacetamide, and hydroquinone, among them. Sometimes these drug products based on very old active ingredients are known as “grandfathered” drugs or unapproved prescription products.

Since the passage of the Food, Drug, and Cosmetics Act of 1938, FDA has established strict processes for the review and approval of new drugs. FDA approves a specific drug formulation on the basis of a New Drug Application; it does not approve a chemical entity or compound. For example, although the FDA had approved oral dapsone more than five decades earlier, topical dapsone gel could not come to market based on that filing. An NDA for dapsone gel 5% was submitted to FDA with data supporting...
its strength, dosage form and new indication.

The costs associated with bringing a new prescription product to market have risen significantly over the past decade. The development costs for a new chemical entity (NCE) as a dermatological, starting with formulation development through NDA approval, is currently estimated to be $40-50 million or more, exclusive of the significant research costs associated with discovery and synthesis of the compound. Because a new formulation containing an already-approved drug for a new indication, strength, or dosage form can bypass some safety studies, development costs may be decreased to around $15-25 million. Combination drug products for dermatologic use (a clindamycin/benzoyl peroxide formulation, for example) can be expected to be intermediate in cost. The developer and/or intended marketer must demonstrate that the new drug formulation is safe and effective for the intended indication in a systematic step-wise manner. Among the many aspects that must be addressed during the typical four to seven year development period of the vehicle (from initial design to market approval) are stability and lack of unsafe levels of impurities and degradation.

A generic drug product seeks to match an approved drug formulation in terms of active ingredient, concentration, and dosage form. Besides chemistry documentation (e.g., demonstration of stability), such products must demonstrate bioequivalence to the Reference Listed Drug (RLD) or innovator through relatively inexpensive tests. Bioequivalence signifies that “the rate and extent of absorption are not statistically different when pharmaceutical equivalents are administered to patients or subjects at the same molar dose under similar experimental conditions.”

In order to demonstrate bioequivalence to an oral RLD, a generic oral formulation must demonstrate equivalent bioavailability through comparable plasma concentrations. For topical medications, methods for demonstrating bioequivalence are more complex than for oral products and controversial. For example, plasma concentrations are usually very low and fail to demonstrate that a topical drug is available at the necessary site of activity. There are three ways a generic topical product can meet the bioavailability requirement: 1.) by a bioequivalence waiver from FDA (commonly allowed for solution dosage forms), 2.) by a show of “equivalence” of a corticosteroid in the vasoconstriction bioassay (described in more detail below), or 3.) by a demonstration of clinical bioequivalence for all non-corticosteroid topical products in a three-arm study (generic product v. RLD v. vehicle). Clinical measures are variable, difficult to control for, and may lack sensitivity. Thus, such clinical bioequivalence trials are quite large and expensive.

If the generic formulation demonstrates bioequivalence, its safety and efficacy are assumed to be equivalent to those of the innovator. The generic product must meet most of the same chemistry and pharmacologic criteria required of the RLD, including establishing a stability-based shelf life. Costs to bring generic topical formulations to market today can be from $500,000 to $1.5 million, unless a clinical bioequivalence study is required, thus increasing the development cost to an estimated $4-6 million.

Topical corticosteroids are among the drugs most commonly prescribed by dermatologists and represent a tremendous proportion of the generic topical prescription market and therefore represent a suitable focus for exploring generic drug approvals. The US topical corticosteroid market was $1.5 billion in 2009 as a result of more than 35 million prescriptions, of which slightly more than 90% were for generics.

The standard bioassay adopted by FDA for demonstrating bioequivalence of topical corticosteroids is the vasoconstriction assay using the Area Under the Effect Curve or AEUC. This bioassay is based on the findings of Stoughton and McKinzie that corticosteroids cause skin blanching and that this surrogate pharmacodynamic response is related to potency and clinical efficacy. FDA has adapted the original bioassay to serve as a bioequivalence assay with specific test
A chromameter is used to measure skin blanching effect over an established period of time as elicited by a topically applied test formulation (T), the reference drug (R), and at untreated control sites. To establish bioequivalence, FDA requires that the 90% confidence interval for the ratio of the AUEC due to the test product and the AUEC due to the reference product does not differ significantly; significance is defined as 20%. As such:

- The lowest limit for T/R = 80/100 or 80%.
- The maximum limit for R/T = 100/80 or 125%.

There are concerns about the clinical significance of the -20/+125 variability permitted for bioequivalence measures. This wide percentage variability in the delivered dose of an innovator compared to its generic can be expected to correlate with a difference in clinical efficacy. Possibly more concerning is the potentially significant difference between two generics formulations. Suppose challenge product A tests in the -15% range, relative to the innovator, while challenge product B tests in the +20% range. The potential clinical implications for a patient switched from A to B—such switches occur frequently—are obvious. Furthermore, while bioassay data demonstrate the effects of a topical corticosteroid at the conclusion of a set period of time after a single micro-dose, it does not provide clinically important information, such as minute-to-minute and hour-to-hour pharmacodynamics of a drug; effects of multiple doses on the skin; or the impact of the physical properties of the generic vehicle on patient compliance. The latter two can vary significantly based on the vehicle.

Application time is an important consideration in topical therapy, as a drug must be given the opportunity to absorb through the stratum corneum. In clinical practice, some vehicles have been found to virtually slide off the skin, permitting little time for drug absorption. Application site matters, as well. If not properly formulated, a vehicle applied to the hands, for example, may be transferred rather quickly to objects or other anatomic sites or washed off. Two formulations could have comparable AUECs as demonstrated in a laboratory, but if one does not remain on the affected skin for an adequate time, the clinical implications are obvious. Unfortunately, FDA requires no test for clinical utility of the vehicle of a generic dosage form.

As noted, except for the case of bioequivalence waivers, generic manufacturers must match the dosage form but not necessarily the excipients that comprise the vehicle. In order to establish equivalency, formulators may incorporate high proportions of penetration enhancers in their products to disrupt the stratum corneum and encourage drug absorption. There is no requirement for assessing the

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**OTC Monograph**

FDA oversight of OTC drugs differs significantly from that for prescription drugs. The Office of Nonprescription Products maintains a list of more than 80 therapeutic categories of OTC drugs. The Center for Drug Evaluation and Research oversees these agents to assure they comply with safety and labeling. The OTC Monograph outlines the permitted active ingredients, dosages appropriate for OTC marketing, indications, and label language. The OTC Monograph, in a sense, provides a recipe for OTC products, with rare specifications or restrictions on dosage form or formulations. Any manufacturer who creates a formulation under the parameters outlined and with the labeling indicated is able to bring that formulation to market without FDA review and approval. OTC products must comply with the Monograph and Good Manufacturing Practices (GMP) including documentation of stability.

Among OTC Monograph categories, which include antacids and aphrodisiacs, are multiple categories of relevance to dermatology:

- Acne (benzoyl peroxide, salicylic acid)
- Antimicrobials
- Dandruff/seborrheic dermatitis
- Pediculicides
- Skin protectants (diaper rash, cold sores, insect bites, poison ivy, oak, sumac)
- Wart removers

OTC Monograph categories, which include antacids and aphrodisiacs, are multiple categories of relevance to dermatology:

- Acne (benzoyl peroxide, salicylic acid)
- Antifungals
- Antiperspirants
- External analgesics (poison ivy, oak, sumac)
- Sunscreens
- Acne (benzoyl peroxide, salicylic acid)
important local safety parameters of irritancy and skin barrier function of generic corticosteroid creams, lotions, gels, ointments or foams.

The laboratory assays described above are intended to demonstrate bioequivalence—that is, they show that the formulations provide similar bioavailability of active drug at specific time points. Bioequivalence is one component of “Therapeutic equivalence,” a term which would seem to suggest that two formulations will have equivalent efficacy in clinical use. However, according to FDA, head-to-head clinical trials of formulations to treat active disease in human subjects are not required to demonstrate therapeutic equivalence.

Generic corticosteroid formulations need not repeat HPA axis testing, which is required of innovator or reference drugs. Although HPA axis suppression is rarely a significant clinical concern for adults, HPA axis suppression in children can have numerous systemic side effects, including an effect on long-term growth, and bone formation. Increasingly, evidence suggests that the vehicle can help to modulate rate and extent of systemic absorption associated with topical corticosteroid delivery.

Given advancements in molecule engineering and formulation development, most modern reference low-potency topical corticosteroids are not associated with significant risks of HPA axis suppression, therefore claims of safety based on comparison of HPA axis results for reference formulations within the same potency class may be misleading. Yet, when modern formulations are compared to older formulations (especially considering that pre-clinicaltrials.gov some results were never published; See Sidebar: ClinicalTrials.gov), enhanced safety is evident.

Characteristics of the vehicle can profoundly modulate the local and systemic safety (as previously described) as well as the potency of a corticosteroid. For example, betamethasone dipropionate 0.05% is characterized in four different potency classes, depending on the vehicle (See Table 2).

### ClinicalTrials.gov

Nearly every clinical trial undertaken in the US today (and a majority of those conducted around the world) is registered at ClinicalTrials.gov. An important beneficial consequence of this public registry is that it has created a checks-and-balances system within the clinical studies community. Studies are listed during early phases and researchers are required to post updates (including discontinuation) and to provide access to published results. In the past, researchers could simply bury sub-optimal or unexpected results because few people knew that a trial was ever underway. Now, because every trial is recorded in a searchable public database, researchers today do not have that liberty.

ClinicalTrials.gov is a project of the US National Institute of Health (NIH) administered through the National Library of Medicine (NLM) in collaboration with all NIH Institutes and the FDA. The stated mission of the website is to provide “patients, family members, health care professionals, and members of the public easy access to information on clinical trials for a wide range of diseases and conditions.” The database was mandated in the Food and Drug Administration Modernization Act (1997) which required the Department of Health and Human Services, through the NIH, to establish a registry of clinical trials for both federally and privately funded trials.

The site is intended to help potential participants identify enrolling studies as well as to disseminate information about trials. ClinicalTrials.gov currently contains 85,508 trials sponsored by the National Institutes of Health, other federal agencies, and private industry. Studies listed in the database are conducted in all 50 States and in 171 countries.

### Table 2. Betamethasone Dipropionate 0.05% Potency Categorizations

<table>
<thead>
<tr>
<th>Class</th>
<th>Formulation</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Diprolene Cream, 0.05%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diprolene Ointment, 0.05%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Diprolene Cream AF, 0.05%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diprosone Ointment 0.05%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Diprosone Cream 0.05%</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Diprosone Lotion 0.05%</td>
<td></td>
</tr>
</tbody>
</table>

### Conclusion

The development of an appropriate topical formulation for a given active drug is a complex, time-consuming, and costly process.
Yet this laborious and multi-step process is necessary to assure efficacy, enhance compliance, and decrease the possibility of adverse events. For a field such as dermatology that has seen the introduction of relatively few new chemical entities in recent years, new therapeutic development initiatives have largely focused on improving vehicles to optimize treatment. Part II of this series (June 2010) will further investigate specific dosage forms used in dermatology with an emphasis on vehicle development challenges and the potential for real clinical benefits.