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Regulatory Note

Generic Development of Topical Dermatologic Products: Formulation Development, Process Development, and Testing of Topical Dermatologic Products

Rong-Kun Chang,[1] Andre Raw,[1,2] Robert Lionberger,[1] and Lawrence Yu[1]

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Abstract. This review presents considerations which can be employed during the development of a semi-solid topical generic product. This includes a discussion on the implementation of quality by design concepts during development to ensure the generic drug product has similar desired quality attributes to the reference-listed drug (RLD) and ensure batch to batch consistency through commercial production. This encompasses the concept of reverse-engineering to copy the RLD as a strategy during product development to ensure qualitative (Q1) and quantitative (Q2) formulation similarity, as well as similarity in formulation microstructure (Q3). The concept of utilizing *in vitro* skin permeation studies as a tool to justify formulation differences between the test generic product and the RLD to ensure a successful pharmacodynamic or clinical endpoint bioequivalence study is discussed. The review concludes with a discussion on drug product evaluation and quality tests as well as *in vivo* bioequivalence studies.

KEY WORDS: dermatologic product; generic; semi-solid; topical product; quality by design.

INTRODUCTION

The skin is the largest organ of the integumentary system in humans. It covers the entire body and has a surface area of approximately 2 m^2 with thickness ranging from 0.5 to 4 mm or more. The skin is involved in many functions, such as providing a protective barrier from the external environment (e.g., defending against microbial infection, inhibiting the entry of chemicals and toxins, preventing dehydration), regulating body temperature, and producing vitamin D. The skin is also the most exposed organ and is subject to several physical and environmental stressors. Furthermore, autoimmunity, dysregulation of stratum corneum regeneration, drug-induced skin hypersensitivity, and many other reasons can result in skin disorders. As such, the skin is susceptible to various disorders and diseases. Topical dermatologic products, which can be administered easily and are convenient in terms of portability, are used in treating a variety of disorders. Topical preparations exist in many forms, such as ointments, gels, creams, lotions, solutions, suspensions, foams, and shampoos. The most commonly used topical preparations are semisolid dosage forms that include ointments, creams, lotions, and gels, which will be the main focus of this review. Table I shows common skin diseases along with some examples of topical drugs for their treatments.

Depending on the physicochemical properties, desired site of action, and formulation strategies for the drug, drugs incorporated into semisolids can show their activity on the surface layers of tissues or via penetration into deeper layers to reach the site of action or through systemic delivery. In some cases, some topical preparations may be designed to limit their activity on the surface of the skin with no stratum corneum penetration, for example repellents and chemical treatments for pediculosis. In such cases, excipients that inhibit skin penetration can be used to retain the drug on the surface layer of the skin. The barrier nature of the stratum corneum greatly limits the entry of drugs into the systemic circulation. Nonetheless if the drug is to act locally

The opinions expressed in this review by the authors do not necessarily reflect the views or policies of the Food and Drug Administration (FDA).

[1] Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 7500 Standish Place, Rockville, Maryland 20855, USA.

[2] To whom correspondence should be addressed. (e-mail: andre.raw@fda.hhs.gov)

ABBREVIATIONS: Q1, Same components as the reference-listed drug; Q2, Same components in same concentration as the reference-listed drug; Q3, Same components in same concentration with the same arrangement of matter (microstructure) as the reference-listed drug; IIG, Inactive Ingredient Guide; RLD, Reference-listed drug; QbD, Quality by design; MDD, Maximum daily dose; SAR, Structure–activity relationship; NLT, No less than; NMT, No more than; API, Active pharmaceutical ingredient; ICH, International Conference on Harmonization; Q3A, Guidance for industry Q3A impurities in new drug substance; Q3B, Guidance for industry Q3B impurities in new drug product; Q3C, Guidance for industry Q3C impurities: residual solvents; Q1A, ICH topic Q1A stability testing of new drug substances and products; IT, Identification threshold; QT, Qualification threshold; ANDA, Abbreviated new drug application; FDA, Food and Drug Administration; USP, U.S. Pharmacopeia; CFR, Code of Federal Regulations.

Table I. Common Skin Diseases and Some Examples of Topical Drug Products for Their Treatments

General category	Disorders/diseases	Pathogenic conditions/microorganisms	Example of topical drug products
Bacterial infection	Impetigo, forunculosis, cellulitis, folliculitis	*Staphyloccocus Aureus*, *Streptococcus pyogenes*	Mupirocin (Bactroban), Polymyxin B sulfate, Bacitracin zinc, Gentamicin sulfate, Neomycin, Silver sulfadiazine, Sulfanilamide, Nystatin
Fungal/yeast infection	Tinea pedis, cruris, corporis, unguium Candidiasis	*Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Candida albicans*	Clotrimazole (Lotrimin, Mycelex), Terbinafine (Lamisil), Ketoconazole (Nizoral), Butoconazole Nitrate, Ciclopirox Olamine, Halobetasol Propionate, Econazole Nitrate, Terconazole
Viral infection	External genital/ perianal warts Cold sore	*Molluscam contagiosum virus* *Human papillomavirus* *Herpes Simplex virus*	Salicylic acid, Imiquimod (Aldara), Podophyllotoxin, Acyclovir, Docosanol
Inflammatory and pruritic manifestations	Allergic contact dermatitis, atopic dermatitis, seborrheic dermatitis, eczema	The exact cause is unknown, but it is thought to be linked to an overactive response by the body's immune system to external and/or internal triggers.	Triamcinolone 0.1% (Triamcinolone), Fluocinonide (Lidex), Clobetasol (Temovate), Tacrolimus (Protopic), Pimecrolimus (Elidel), Desonide, Alclometasone dipropionate, Mometasone furoate, Desoximetasone, Prednicarbate, Diflorasone Diacetate, Amcinonide
Acne, Rosacea	Acne vulgaris	Acne is caused by the stimulated sebaceous glands at the time of puberty, leading to the inflammation of skin surface. The exact cause of rosacea is still unknown, but many factors, such as genetic, emotional, and sun exposure may trigger and aggravate rosacea.	Metronidazole, Isoretinol (Accutane), Benzoyl peroxide, Dapsone, Azelaic acid, Clindamycin, Erythomycin, Sodium sulfacetamide, Adapalene, Tretinoin
Psoriasis	Psoriasis vulgaris	The exact cause remains unknown. There may be a combination of factors, including genetic predisposition and environmental factors triggering cell proliferation out of control.	Hydrocortisone, Calcipotriene (Dovonex), Anthralin, Lactic acid (AmLactin, Lac-Hydrin), Tacrolimus (Protopic), Pimecrolimus (Elidel)
Vitiligo	Vitiligo	A disorder that causes depigmentation of patches of skin	Corticosteroid, Tacrolimus (Protopic), Pimecrolimus (Elidel)
Actinic/solar keratosis, skin cancer	Actinic/solar keratosis Squamous cell carcinoma Basal cell carcinoma	Due to sun exposure and UV radiation and weakening of the immune system	5-fluouracil (Efudex, Fluoroplex), Imiquimod (Aldara), Diclofenac (Voltaren, Solaraze)
Loss of hair	Androgenic alopecia Cicatricial alopecia Alopecia areata	Due to hormonal changes, inflammation damages/scars, autoimmune disease, and other reasons, hair follicles may have a shorter growth period and produce thinner and shorter hair shafts.	Minoxidil, Anthralin, Cyclosporine
Damaged skin	Fine wrinkling, mottled hyperpigmentation, tactile, roughness of facial skin	Photo-damaged skin	Tretinoin
Local dermal anesthesia	–	Dermal anesthetic product to numb the skin	Benzocaine, Lidocaine, Tetracaine, Prilocaine
Pediculosis	Head lice	Chemical treatment of pediculosis	Lindane, Permethrin, Pyrethrin, Piperonyl Butoxide, Malathion

or systemically, it must first penetrate the stratum corneum. Most topical dermatologic preparations are meant to be locally active, but some preparations have local action as well as a minor/negligible systemic effect, as a small amount of the drug is absorbed systemically. In some cases, drug accumulation in the dermal layer is critical and the drug transport via hair follicles (e.g., liposome) is a potential approach. On the other hand, because of the excellent transdermal permeability of certain drugs and/or suitable formulation modifications, semisolids (e.g., 2% nitroglycerin in a lanolin–petrolatum base, 10% oxybutynin chloride in an alcohol-based gel, 1% or 1.62% testosterone in a clear gel) have been used to deliver the drug systemically, bypassing the destructive hepatic first-pass metabolism. To promote the

systemic availability, penetration enhancers may be used to enhance the drug transport through skin. However, systemic delivery of drugs from topical dosage forms has several problems, including inconvenience of administration, inaccuracy of administered dose, difficulties in removing the residual formulation from the skin, and aesthetic reasons. Owing to these drawbacks, bandage-type transdermal patches have to a large extent replaced the semisolid preparations intended for systemic effect. Transdermal patches and semi-solid products for systemic use, however, are not considered typical topical products and are outside the scope of this article.

Topical Drug Delivery

The major barrier layer of skin, the stratum corneum, consists of an interstitial lipid pathway and a proteinaceous cellular compartment. Drug molecules penetrate the skin primarily through the tortuous and continuous intercellular path. Transport of topical drugs, especially with the aid of solvents and enhancers used in the formulation, may also occur through a transcellular route, the hair follicles, or sweat ducts. Only the drug in the molecular state can penetrate through the skin. Occluded skin, e.g., the application of ointment on the skin, may retain significant amounts of the transepidermal water and facilitate drug transport through the hydrated skin. States with diseased skin, such as atopic dermatitis, psoriasis, and warts, may have effects on the barrier property of skin, which must be considered for the drugs geared toward these skin diseases. From a drug delivery perspective the concentration gradient between the formulation and site of action provides the driving force for penetration of drug through the skin. Thus saturation of the drug in the vehicle having a thermodynamic activity of unity provides a larger driving force for transporting through the skin than a formulation at a lower fraction of saturation (e.g., highly solubilized system). Super-saturated conditions having a thermodynamic activity greater than unity, can further enhance the drug delivery through skin. However, a drug in a super-saturated solution is in a metastable state and, hence, may convert back to its stable form, thus changing the flux of the drug through skin.

Formulation Design of Generic Topical Drug Products

Definitions of semisolid preparations, such as ointments, creams, lotions, gels, *etc*. vary and are ill-defined and imprecise in some cases. Based on rheological behavior, water and volatiles, composition, and thermal behavior, Buhse *et al.* [1] devised new definitions and a system for determination of the appropriate nomenclature for a topical dosage form. Osborne [2] further summarized the topical drug product classification system and discussed the importance of accurately labeling a topical dosage form. It should be pointed out that there are some older topical products described in Pharmacopeia based on imprecise nomenclature to name the drug products. As a result, the labeling for approved topical drug products may not be accurate or commensurate with the current classification. For these reasons, it is important to evaluate the reference-listed drug (RLD) critically based upon its physical chemical characteristics and not rely solely upon labeling for dosage form selection in generic drug development [3, 4].

To ensure pharmaceutical and therapeutic equivalency, generic drug formulas often tend to mainly mimic those of the RLDs. It is prudent to use the drug product information appearing in the packaging insert, patents, and published literature for the RLD, along with data generated by reverse engineering efforts to come up with the initial generic formula. If feasible, the major formulation goal for a generic topical drug product is quantitative sameness (Q1, same components as the RLD) and qualitative sameness (Q2, same components in same concentration as the RLD, *i.e.*, within ±5%) to the RLD [5, 6]. However, even with Q1/Q2 sameness, special attention needs to be directed toward the grade of the excipient, because different grades of excipient can have a significant impact on drug product quality attributes. For example, a low-melting-grade material may melt under accelerated stability conditions and a high-melting-grade excipient can withstand higher storage temperatures; conversely a high-viscosity-grade excipient has a better ability to impart the consistency to semisolid preparations, compared to a low-viscosity-grade material. Another advantage of developing a formulation with Q1/Q2 sameness, is that although topical dosage forms (other than solutions) often require *in vivo* bioequivalence studies, in some instances a biowaiver (for a non-solution product) may be granted with supporting data to demonstrate Q1/Q2 sameness and similar physicochemical characteristics as in the case of topical solutions. Thus, by reverse engineering the RLD, all the potential issues such as critical product attributes, stability, and efficacy for a test generic product may be minimized.

In some cases, due to patent protection or to undesirable product attribute(s) of the RLD formulation, the generic drug firm may choose not to match the RLD formula. The generic firm may choose to reformulate to improve certain product attributes. During generic product development, modifications of the RLD formula in terms of excipient replacement, grade of excipient, or amount of excipient used in the formula, *etc.* needs to be justified by its functionality, the FDA Inactive Ingredient Guide (IIG) [7], pharmacology/toxicology data, and bioequivalence/clinical data. Each inactive ingredient must be justified unless it is ≤0.1% of the total drug product weight.

When developing a formulation, it is reasonable to keep the type of emulsifier, hydrophilic–lipophilic balance value, and solvent to emulsifier ratio similar to those of the RLD. An appropriate emulsifier system is needed for emulsion-type topical drugs to disperse the drug containing solvent phase and to produce the desired type of emulsion (O/W or W/O) with satisfactory appearance and consistency for the final product. To avoid regulatory classification issues, pharmaceutical formulators need to avoid the replacement of water with polar solvents in preparation of emulsion-type semisolids.

Also, formulators should be certain that the excipients and quantity used in the drug product are in IIG list with the same route of administration and no more than the amount listed in the IIG. In case a novel excipient is essential to achieve the desired physicochemical properties and performance characteristics for the drug product, appropriate

toxicological and pharmacological data need to be generated to support its use in drug product formulation. In general, pharmaceutical formulators avoid this costly approach.

Overage is not normally allowed unless it is due to manufacturing losses. The use of a "stability overage" should only be a last resort, and is strongly discouraged. However, some RLDs contain significant amount of overage to compensate for the loss of drug due to its degradation. In such cases, an overage can be allowed up to the overage present in the RLD and the importance of thorough investigation of product attributes for the RLD cannot be over-emphasized.

For formulation design, simplicity is the basis of good formulation design and the shorter the ingredient list, the better. Good formulators eliminate redundant elements and integrate components when possible [8]. Formulation components for topical drug products are briefly summarized in Table II. However, to achieve the delivery of the drug and the consumer's acceptance, a complex combination of excipients is often required for topical drug product formulations. Given the numerous excipients used, it is important to avoid unwanted interactions among the ingredients used in the formula. For example, an anionic surfactant may react with a positively charged drug or *vice versa*; an anionic emulsifier with monovalent salt may be inactivated by multivalent counter ions (e.g., Ca^{++}, Mg^{++}). If the formulation requires solvent(s) to dissolve the API in the manufacturing process, it is prudent to have solvent screening studies to determine the solubility of the drug in the potential solvent systems and to generate the short-term accelerated stability data (e.g., 4 weeks at 40°C) of the drug in the potential solvent system to justify the selection of the solvent system. The amount of the solvent system used in the formula should be cautiously selected to ensure that solubility is below 90% of the saturation solubility of the drug in the solvent system at room temperature to eliminate the drug re-crystallization issue. Furthermore, solvent-screening experiments can be performed using an additional cold condition, e.g., refrigerated temperature, to detect the undesired precipitation.

Gels are relatively easier to prepare compared to emulsion-type creams and lotions. In general, a selected gelling agent, such as Carbomers and xanthan gum, can be dispersed in purified water or hydroalcoholic medium to form uniform lump-free dispersion and subsequently, an active and preservative phase can be added to the gel phase to form a medicated gel.

Table II. Formulation Components for Topical Drug Products

Component functionality	Component description	Example
Emollient/ stiffening agent/ ointment base	Main structure-forming materials for semisolid dosage form Based on their composition and physical characteristics, the USP classifies ointment bases as hydrocarbon bases (oleaginous bases), absorption bases, water-removable bases, and water-soluble bases.	Carnauba wax, Cetyl alcohol, Cetyl ester wax, Emulsifying wax, Hydrous lanolin, Lanolin, Lanolin alcohols, Microcrystalline wax, Paraffin, Petrolatum, Polyethylene glycol, Stearic acid, Stearyl alcohol, White wax, Yellow wax
Emulsifying agent/ solubilizing agent	Surfactants used to reduce the interfacial tension to stabilize emulsions and to improve the wetting and solubility of hydrophobic materials	Polysorbate 20, Polysorbate 80, Polysorbate 60, Poloxamer, Emulsifying wax, Sorbitan monostearate, Sorbitan monooleate, Sodium lauryl sulfate, Propylene glycol monostearate, Diethylene glycol monoethyl ether, Docusate sodium
Humectant (polyols)	Promotes the retention of water in the system	Glycerin, Propylene glycol, Polyethylene glycol, Sorbitol solution, 1,2,6 Hexanetriol
Thickening/ gelling agent	Increases viscosity Main structure-forming materials for gels	Carbomer, Methyl cellulose, Sodium carboxyl methyl cellulose, Carrageenan, Colloidal silicon dioxide, Guar gum, Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose, Gelatin, Polyethylene oxide, Alginic acid, Sodium alginate, Fumed silica
Preservative	Prevents microbial growth	Benzoic acid, Propyl paraben, Methyl paraben, Imidurea, Sorbic acid, Potassium sorbate, Benzalkonium chloride, Phenyl mercuric acetate, Chlorobutanol, Phenoxyethanol
Permeation enhancer	Increases the permeation by promoting the diffusion, partitioning, or the drug solubility of an active ingredient through the stratum corneum	Propylene glycol, Ethanol, Isopropyl Alcohol, Oleic acid, Polyethylene glycol
Chelating agent	Binds metal ions to minimize metal-catalyzed degradation and to enhance the preservative effect	Ethylene diamine tetraacetate
Antioxidant	To minimize oxidative deterioration	Butylated hydroxyanisole, Butylated hydroxytoluene
Acidifying/ alkalizing/ buffering agent	Maintain a proper pH for the dosage form	Citric acid, Phosphoric acid, Sodium hydroxide, Monobasic sodium Phosphate, T`rolamine
Vehicle/ solvent	Facilitate the dispersion and/or dissolution of API	Purified water, Hexylene glycol, Propylene glycol, Oleyl alcohol, Propylene carbonate, Mineral oil

Many excipients used in topical drug products have dual or multiple functionalities

Viscosity modification is an important part of semi-solid formulations. However, viscosity of the test drug product is not required to be identical to that of the RLD, provided that viscosity of the drug product is not a critical quality attribute. Theoretically, viscosity may impact skin retention of the dosage form and drug delivery/penetration via the skin. Therefore, it is prudent to provide data from a well-designed *in vitro* skin permeation study demonstrating that flux is similar between the test product and the RLD. Furthermore, the retentive properties on the skin and patient acceptability need to be evaluated to assess whether the test product with a different viscosity from the RLD has a negative impact on these attributes. Because its effect is multidimensional and not easily predictable, viscosity and spreadability are regarded as critical quality attributes in the initial product development stage.

For drug-dispersion-type semisolid products, small drug particles may dissolve in the continuous phase and deposit onto the larger particles (*i.e.*, Ostwald ripening). A temperature cycling study with cycles from room temperature to 40°C may be used to evaluate the tendency of Ostwald ripening during the product development stage. For emulsion-type semisolid drug products, typically the test products are subjected to alternate freeze–thaw cycles as follows: 24 h at −20°C followed by a 24-h thaw at room temperature, 24 h at −20°C followed by a 24-h thaw at room temperature, and 72 h at −20°C followed by a 24-h thaw at room temperature. The drug products should remain stable with respect to physical appearance, absence of drug crystals (solubilized-type product), particle size of drug crystals, and package integrity following these cycles.

Most topical preparations, especially those with emulsion formulations have a potential for contamination by various bacteria. Hence, antimicrobial preservatives are used to inhibit the growth of bacteria, fungi, and mold. The selection of preservative for a generic semi-solid product is typically based on the RLD. A combination of methylparaben and propylparaben is the most commonly used preservative at levels typically ranging from 0.01% to 0.3%. In some instances there may be concerns about the use of some preservatives in topical drug products. For example, formaldehyde-releasing preservatives like imidurea and hydantoin are known to have a tendency of causing allergic contact dermatitis. Furthermore, formaldehyde is also a human carcinogen and a known sensitizing agent, and in these cases it is necessary to demonstrate that the observed level of free formaldehyde for the drug product is within an acceptable threshold. Benzyl alcohol may degrade to benzaldehyde, and when used in the formulation it is important to include benzaldehyde as part of a related substances test in the drug product release stability testing specifications as a precaution.

Antioxidants, alone or in combination with a chelating agent, are added to semi-solid preparations to prevent oxidative degradation. Addition of a chelating agent and incorporation of an antioxidant for the RLD give a hint of instability of the drug in the formulation matrix. Some excipients, such as white petrolatum also may oxidize at high temperatures during manufacturing of the drug product, and may result in different by-products in addition to the potential oxidative degradants from the pharmaceutical active ingredient.

In developing generic formulations of topical dermatologic preparations that require repeated and long-term use, ultrapure and hypoallergenic ingredients may sometimes be warranted to minimize sensitization and contact dermatitis in patients. Special attention should be paid to the use of fragrance in the formulation, because 1% of the general population suffers from fragrance allergies [9]. Omission of the fragrance components from the RLD may be justified by the SUPAC-SS Guidance, which states that deletion of an ingredient intended to affect fragrance is unlikely to have any detectable impact on formulation quality and performance and is considered as a Level 1 change and no bioequivalence testing would be necessary [10]. If possible, formulators should consider hypoallergenic, fragrance-free, artificial color-free, gluten-free, peanut-free, alcohol-free, preservative-free, latex-free, or ethoxylate surfactant-free components for drug products to make them less harsh on the skin and less concern for end users with ingredient anxiety. Also some emulsifiers, especially when used in large amounts, may cause skin irritation. If in doubt, dermal irritation, corrosivity, and sensitization potential need to be evaluated for ingredients and test drug product using an animal model or *in vitro* model (human epidermal tissue constructs and biobarrier membrane). In addition to the aforementioned considerations, many other points listed in Table III need to be contemplated thoroughly.

Also during development, the volatility and penetration rate of the ingredients in the formula are additional important factors to be considered. As a result of solvent evaporation, skin absorption of the vehicle and interaction among drug substance, changes to the residual formula and skin components may occur after application altering drug properties. For example, due to solvent evaporation, the physical state of drug substance may change (crystallization, dissolution, or polymorph) resulting in a change in the skin drug permeation and retention. Therefore, the proportion of volatile and non-volatile excipients used in the test and RLD formulations and their effects need to be carefully evaluated.

For semi-solid preparations, Q1/Q2 is not a must for generic products to be acceptable by the agency. However, the generic firm will face more regulatory scrutiny for a non-Q1/Q2 formula and need to demonstrate that the physicochemical characteristics, critical quality attributes, and *in vitro* flux rate of its drug products are in line with the RLD, especially considering the insensitivity of clinical endpoint bioequivalence studies. In this respect, two studies for topical drug product development that are considered as the most powerful to ascertain drug flux in dermatologic and transdermal product development include *in vitro* human skin permeation and *in vivo* percutaneous absorption in animal models:

- Flux measurement across human skin is perhaps the most useful and insightful ***in vitro*** information in development of a topical drug product. Based on the physical design of a diffusion cell, they can be classified as horizontal, vertical, or flow-through diffusion cells along with several adaptations to the basic design. The vertical type Franz diffusion cell is the most widely accepted for *in vitro* percutaneous absorption studies. Other than the design of the diffusion cell, a finite dose technique (*i.e.*, ~3 to 5 mg/cm^2) is considered more relevant than infinite dose design as it better represents the clinical situation for topical drug products. The skin obtained from surgery and cadavers can be excised

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