

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-844

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3.5.2 Patent Certification

Desonide Gel, 0.05% Paragraph II Certification

The Sponsor, Skin Medica, seeks marketing approval of Desonate[®] Hydrogel, 0.05% in the treatment of atopic dermatitis via a 505(b)(2) application.

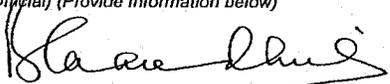
Desonate[®] Hydrogel, 0.05% is protected under US Patent No. 6,387,383 B1, issued May 14, 2002. Since the patent was filed on August 3, 2000 and does not claim priority from any earlier filed application, the expiration date of the patent will be August 3, 2020.

To the best of Skin Medica's knowledge, any other patents relating to desonide gel have expired and Desonate[®] Hydrogel, 0.05% does not infringe on any existing patents. There is not a patent in effect for Des Owen[®] Lotion.

**APPEARS THIS WAY
ON ORIGINAL**

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
		NDA NUMBER 021844	
		NAME OF APPLICANT / NDA HOLDER Skin Medica	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) Desonate® Hydrogel			
ACTIVE INGREDIENT(S) Desonide, micronized		STRENGTH(S) 0.05%, w/w	
DOSAGE FORM Topical Gel			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number No. 6,387,383		b. Issue Date of Patent 5/14/2002	c. Expiration Date of Patent 8/3/2020
d. Name of Patent Owner Dow Pharmaceutical Sciences		Address (of Patent Owner) 1330 Redwood Way	
		City/State Petaluma, California	
		ZIP Code 94954	FAX Number (if available) 707.793.0145
		Telephone Number 707.793.2600	E-Mail Address (if available) bchaudhuri@dowpharmsci.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.	
2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) Claim No. 18, 19, 20	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Indication: Atopic Dermatitis Directions: Desonate® Hydrogel, 0.05% should be applied to the affected areas as a thin film two times daily. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, reassessment of diagnosis may be necessary.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

6. Declaration Certification	
<p>6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>12/8/05</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input checked="" type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Dow Pharmaceutical Sciences</p>	
<p>Address 1330 Redwood Way</p>	<p>City/State Petaluma, California</p>
<p>ZIP Code 94954</p>	<p>Telephone Number 707.793.2600</p>
<p>FAX Number (if available) 707.793.0145</p>	<p>E-Mail Address (if available) bchaudhuri@dowpharmsci.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	



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(12) **United States Patent**
Dow et al.

(10) **Patent No.:** US 6,387,383 B1
(45) **Date of Patent:** May 14, 2002

(54) **TOPICAL LOW-VISCOSITY GEL
COMPOSITION**

(75) **Inventors:** Gordon J. Dow, Santa Rosa; Robert W. Lathrop, Novalo; Debra A. Dow, Petaluma, all of CA (US)

(73) **Assignee:** Dow Pharmaceutical Sciences, Petaluma, CA (US)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** 09/632,508

(22) **Filed:** Aug. 3, 2000

(51) **Int. Cl.7** A61K 7/00; A61K 47/00

(52) **U.S. Cl.** 424/401; 514/772; 514/859; 514/886; 514/887

(58) **Field of Search** 424/401, 404, 424/78.02, 78.03, 78.06; 514/772, 844, 859, 886, 861, 887, 863, 871

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(57) **ABSTRACT**

A composition is provided that has a viscosity of less than about 15,000 cP and a pH of about 3.0 to 9.0 for treating a skin disorder in a human subject. The composition consists essentially of (a) a therapeutically-effective amount of at least one compound useful for treating such disorder, (b) a pharmaceutically-acceptable, lightly cross-linked poly-acrylic acid polymer compatible with the compound, (c) optionally a water miscible solvent, (d) optionally a preservative, (e) optionally an oil phase component and suitable surfactant, and (f) water. The composition is useful for treating an inflammatory skin disorder, acne, or rosacea. The low viscosity composition has an advantage of being administered more accurately when combined with a container that administers the composition as drops.

59 Claims, No Drawings

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TOPICAL LOW-VISCOSITY GEL
COMPOSITION

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to a composition for treating a skin disorder in a human, and a method of administering and preparing such composition.

2. Background

Skin disorders are a common problem in childhood, adolescence and adulthood. Skin disorders can include, for example, acne, inflammatory diseases such as atopic eczema, or rosacea.

Acne vulgaris is a follicular disease characterized by pilosebaceous inflammations such as comedones, papules, pustules, cysts and nodules. Chiefly a disease of adolescence (and often a cause of emotional distress), acne originates endogenously and stems for multifactorial influences. Major progressive factors in the development acne include hyperkeratosis of the follicular epithelium, increased sebum production, and proliferation of *Propionibacterium acnes*. These factors are primarily responsible for hyperkeratosis of the follicle lining, including retention of keratin and sebum, as well as the free fatty acid by-products of *P. acnes* metabolism which can lead to inflamed acne papules and pustules.

Although acne may also be influenced by exogenous and hormonal factors, research has been centered around eliminating *P. acnes*, the most common cause of inflammation. To date, the pathogenesis of acne is not fully understood, and there is currently no cure for the disease. Many systemic and topical medications, such as tetracycline, have been used to manage and control acne. None, however, is universally successful.

Acne treatment is typified by "polypharmacy", whereby physicians employ simultaneous treatment with a variety of modalities. The search for improved acne treatments has been widespread and continuous during the past several decades. Enhanced cosmetic properties to encourage user compliance, the use of topical therapies in place of systemic drugs to reduce toxicity and side effects, and the introduction of new drugs and formulations represent the forefront of acne treatment advances.

The first use of a topical antibiotic, erythromycin, for the treatment of acne was reported by Fulton (Fulton, J. E. Jr. and Pablo, G. *Topical antibacterial therapy for acne*. Study of the family of erythromycins. Arch. Dermatol. 110:83-86, 1974). Topical administration of these potent agents has the advantage of reduced side effects, particularly those caused by systemic drug effects, e.g., nausea, gastrointestinal upset, diarrhea, and vaginal yeast overgrowth.

Lincomycin antibiotics have been employed in the topical treatment of acne (U.S. Pat. No. 3,969,516). Lincomycin was commercialized by Upjohn Co. (now Pharmacia & Upjohn) as Cleocin T Solution, Gel, Lotion and Pledgets. Cleocin T Gel was an improvement over Cleocin T Solution because of the elimination of alcohol and the ease of application to the facial skin for the treatment of acne. This gel is based on carbomer 934, NF.

Atopic dermatitis is a polygenic disease with an inherited predelection and strongly influenced by environmental factors. The condition affects infants, children, adolescents and adults and is allergic in nature. The distribution is symmetrical, typically involving the face, neck and flexural areas. Atopic dermatitis is chronic, relapsing and usually

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pruritic. Topical treatment frequently includes topical corticosteroids, such as desonide, hydrocortisone valerate, fluocinonone acetonide, triamcinolone acetonide, betamethasone valerate, hydrocortisone butyrate, halobetasol propionate, betamethasone dipropionate, clobetasol propionate, difloransone diacetate, fluticasone propionate, budesonide or the like.

Rosacea is a chronic inflammatory eruption of the nose, face and other flushing areas of the skin. The disease is most common in middle aged women and is characterized by erythema, papules, pustules, telangiectasia and enlarged sebaceous glands. The cause etiology is not totally clear; however vasomotor lability and menopause are predisposing factors. The organism *Demodex folliculorum* is found frequently in the contents of inflamed pustular follicles, and has a possible role in this skin disorder. Treatments include topical metronidazole and oral tetracycline type antibiotics.

SUMMARY OF THE INVENTION

One aspect of this invention is a composition having a pH of about 3.0 to about 9.0 and a viscosity of less than about 15,000 centipoise (cP) for treating a skin disorder in a human subject. The composition comprises (a) a therapeutically-effective amount of at least one compound useful for treating such disorder, (b) a pharmaceutically-acceptable polyacrylic acid polymer compatible with the compound, (c) optionally a water miscible solvent, (d) optionally a preservative, (e) optionally an oil phase and surfactant, and (f) water.

Another aspect of the invention is a composition described above in combination with a container that accurately administers a portion of the composition for topical administration to a patient.

Another aspect of the invention is a composition described above in combination with labeling instructions for use in treating the skin disorder.

Still another aspect of the invention is a method for treating a skin disorder in a human subject, which method comprises administering a composition described above to an affected area of the subject's skin having such disorder in an amount and for a period of time sufficient to improve the skin disorder.

Still another aspect of the invention is a method for preparing a composition of this invention by combining water with a therapeutically-effective amount of a suitable compound and the polymer and optionally a water-miscible solvent and preservative. If a lotion is desired an oil phase is formed for integration with the aqueous phase.

Other aspects of the invention may be apparent upon further reading the specification and claims of the patent application.

SPECIFIC DESCRIPTION

This invention provides a novel topical gel or lotion delivery system for the treatment of skin diseases, particularly acne vulgaris. One unique aspect of the system is the use of a polymeric material that provides a gel material that has a very low viscosity but which is cosmetically elegant and aids in the administration process by providing a pourable composition that flows through a dropper tip easily.

The Composition

One aspect of this invention is a composition having a pH of about 3 to about 9 and a viscosity of less than about 15,000 cP for treating a skin disorder in a human subject.

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The composition comprises a therapeutically-effective amount of at least one compound useful for treating such disorder, a pharmaceutically-acceptable, lightly cross-linked polyacrylic acid polymer compatible with the therapeutically-effective compound, optionally a water miscible solvent, optionally a preservative, and water. The composition may include a solution of the active compound or a suspension. A lotion will also include a pharmaceutically-acceptable oil phase emulsified with one or more surfactants.

The composition is useful to treat skin disorders, e.g. acne, rosacea, or inflammatory skin diseases such as atopic dermatitis. The composition will include an active agent that will be one compound alone or two or more compounds in combination. The active agent can be an antibiotic, a corticosteroid, a retinoid, an anti-inflammatory imidazole, a non-steroidal anti-inflammatory agent (NSAID), or a combination.

An antibiotic is generally viewed as a drug that inhibits the growth of an unwanted microorganism. Representative examples of topical antibiotics include lincomycins, (e.g. clindamycin), erythromycin, minocycline, and tetracycline, and the pharmaceutically-acceptable salts, esters, or prodrugs thereof. Preferred is clindamycin phosphate.

A "retinoid" is a keratolytic drug related to retinoic acid and generally includes chemical entities such as retinol and its esters and closely related naturally-occurring derivatives and structurally-related synthetic analogs. This includes, for example, retinol, retinal, tretinoin (all-trans retinoic acid), isotretinoin, adapalene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid), and the like. Of these, tretinoin is preferred.

Generally, a topical corticosteroid is a compound that is a structural modification of hydrocortisone (also known as cortisol) and that shows topical anti-inflammatory activity. Representative examples include those set forth in Table 65-1 at page 1575 of "Goodman & Gilman's The Pharmacological Basis of Therapeutics," Eighth Edition, McGraw-Hill, Inc. (1993). Specific, non-limiting examples of topical corticosteroids include those mentioned in the "background" section of this application. Preferred corticosteroids, when used as a single active agent, include diflorasone diacetate, fluticasone propionate, halobetasol propionate, or budesonide. Halobetasol propionate is most preferred when used as a single active ingredient.

Nonsteroidal anti-inflammatory agents (NSAIDs) are compounds that suppress the inflammatory response when topically applied by inhibiting prostaglandin synthesis or by other mechanisms of action. Examples may be found in Goodman and Gilman, *Ibid*. Representative examples include ibuprofen, indomethacin, diclofenac, and naproxen and their salts. Preferred is diclofenac.

An anti-inflammatory imidazole is an imidazole compound that suppresses a topical inflammatory response. Metronidazole is a representative imidazole compound suitable for this invention.

In describing the details of the composition, the numerical ranges given herein are those amounts that provide the functional results in the composition. Thus, the ranges are generally introduced with the term "about" to indicate a certain flexibility in the range, i.e. $\pm 10\%$ or less at the lower and upper numerical ranges given.

As mentioned, the active agent may be present alone or in combination. For example, a topical antibiotic, such as clindamycin phosphate, may be combined with a topical corticosteroid. Where a formulation is designed primarily

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for application to the facial area, to treat acne for example, it is preferred to combine an antibiotic (e.g. clindamycin phosphate) with a less potent corticosteroid, such as desonide, hydrocortisone valerate, fluocinolone acetonide, hydrocortisone butyrate, or triamcinolone acetonide. The topical antibiotic can also be combined with a retinoid, e.g. clindamycin phosphate and tretinoin or adapalene.

The composition of the invention will include a polymeric material that will be present in an amount sufficient to bring the viscosity of the composition to a level of not more than about 15,000 cP, preferably between about 100 and about 12,000, and more preferably between about 300 and about 10,000. The viscosity is determined at room temperature (20-25° C.) using a Brookfield viscometer model DV-1+, spindle #27 at 12 revolutions per minute (rpm). If the measured viscosity is less than 4,000 cP, spindle #21 should be used instead of #27. By keeping the viscosity below about 15,000 cP, the advantages of more appealing cosmetic characteristics and ease of accurate application through improved flow and pourability are achieved.

The polymers that have been found to be particularly useful in the composition of the present invention are lightly cross-linked polyacrylic acid polymers which are available from B.F. Goodrich under the tradename CARBOPOL®. They are generically referred to as carbomers. The CARBOPOL polymers are hydrophilic polymers based on a polyacrylic acid structure. For use in the present invention the lightly cross-linked polymers include CARBOPOL 910, 941, 971, and 981 and CARBOPOL ETD 2050.

Either CARBOPOL 941 or 981 is particularly valuable for the present invention because the viscosity of a gel based on CARBOPOL 941 or 981 is low relative to its concentration. This feature is the result of the low level of cross-linking within the polymer structure in a neutralized aqueous system. In contrast polyacrylic acid polymers which display a high level of cross-linking, such as CARBOPOL 980 or 974P, produce gels with higher viscosity at comparable concentrations.

A 0.5% solution of either CARBOPOL 941 or 981 at pH 7.5 has a viscosity measurement of from 4,000 to 11,000 cP (Brookfield viscometer at 20 rpm) compared to a viscosity measurement of from 40,000 to 60,000 cP for a comparable 0.5% solution of either CARBOPOL 940 or 980 (reference: B.F. Goodrich Product Guide, Bulletin 2).

This lower-level viscosity feature of the lightly cross-linked polyacrylic acid polymers, e.g. CARBOPOL 941 and 981, offers two advantages to the composition of the present invention. A gel made from one of these lightly cross-linked polymers provides better skin feel and lubricity than a gel of comparable viscosity made from a highly cross-linked polymer. Second, a low viscosity gel can be administered very accurately by a dropper or drip-type dispenser as compared to other commercial products which are thicker gels that do not provide as accurate an application.

CARBOPOL 941 NF resin and its cosolvent polymerized alternative, CARBOPOL 981 NF resin, provide permanent emulsions and suspensions at low viscosities. The gels produced with these resins have excellent clarity. In ionic systems, they perform better than most of the other CARBOPOL resins and at concentrations below 1.5% in solvent systems. The polymers are available from B.F. Goodrich Specialty Chemicals, 9911 Brecksville Road, Cleveland, Ohio 44414-3247.

CARBOPOL resins are polymers of acrylic acid crosslinked with polyalkenyl ethers or divinyl glycol. The polymers are flocculated powders of primary particles aver-

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aging about 0.2 micron in diameter. The flocculated powders are agglomerates that average 2 to 7 microns as determined by Coulter Counter. These agglomerates cannot be broken down into the primary particle once produced.

Each primary particle can be viewed as a network structure of polymer chains interconnected by crosslinks. Without the crosslinks, the primary particle would be a collection of linear polymer chains intertwined but not chemically bonded. These linear polymers are soluble in a polar solvent, such as water. They swell in water up to 1000 times their original volume (and ten times their original diameter) to form a gel, especially when exposed to a pH environment above about 4-6. Since the pK_a of these polymers is 6.0 ± 0.5 , the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative particles, which adds to the swelling of the polymer. Highly crosslinked polymers of this type do not dissolve in water, rather they form gels by forming homogeneous dispersions.

The glass transition temperature of CARBOPOL resin is 105°C . (221°F) in powder form. However, the glass transition temperature drops dramatically as the resin comes into contact with water. The polymer chains start gyrating and the radius of gyration becomes bigger and bigger. Macroscopically, this phenomenon manifests itself as swelling.

The aqueous composition of the invention, will optionally include a water miscible solvent and a preservative. The water miscible solvent (i.e. a cosolvent) will be present if needed, to assist in dissolving the active agent. The cosolvent may be a single component or a mixture. Examples include those that are miscible with water such as ethanol, propylene glycol, glycerin, polyethylene glycol 400, and the like. Certain water-miscible solvents, such as glycerin or propylene glycol, also add beneficial humectant properties to the composition. Drug delivery and penetration into the skin can be modified by the water-miscible cosolvent composition.

The preservative useful in the composition is material that aids in ensuring a stable composition and/or prevents growth of bacteria. Thus, a preservative may be one or more of an antioxidant, a chelator, an antibacterial, or the like. Suitable preservatives include methylparaben, butylparaben, propylparaben, benzyl alcohol, sorbic acid, imidurea, thimerisal, propyl gallate, BHA, BHT, citric acid, disodium edetate, and the like. Another optional additive is a fragrance. Generally, this will be present in a trace amount only and has no effect on the functioning of the composition.

A preferred composition, particularly for the treatment of acne, will exhibit a pH of about 3 to 9, preferably about 4 to 7, and most preferably at about 5 to 6. Thus, the composition may also include a pH-adjusting agent as needed at a level to adjust the pH to the desired range. Such agents include many pharmaceutically-acceptable organic or inorganic bases, e.g., sodium hydroxide and tromethamine. The pH chosen will depend in part on the pH tolerance of the active agent chosen for the composition. The examples provide guidance for certain compounds and suitable pH values for the compositions.

Another aspect of this invention is an emollient embodiment, i.e., a fluid emulsion or lotion. This aspect of this invention is a composition having an internal oil phase dispersed with the aid of at least one surfactant, e.g. an emulsifier, in water. Suitable surfactants are well known in the art and include those referred to as anionic and nonionic agents. These are described in Remington: The Science and Practice of Pharmacy, Nineteenth Edition, Vol. 1 at p. 251.

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Representative surfactants include polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, sorbitan laurate, sorbitan oleate, sorbitan stearate, polyoxyethylene stearate, sodium laureth sulfate, and laureth-10. Oil phase components include those that are commonly used in the art such as mineral oil, petrolatum, stearyl alcohol, cetyl alcohol, isopropyl myristate, diisopropyl adipate, stearic acid, white wax, and the like.

The following Table sets forth operational and preferred ranges of the various components for a gel composition having an active ingredient, which may be a single compound or a combination of two or more compounds. The term surfactant means one or more surfactants, which includes wetting agents and emulsifiers.

TABLE A

Component	% w/w		
	Operational	Preferred	More Preferred
Active ingredient	0.005-10.0	0.01-5.0	0.05-2.0
Polycrylic Polymer Acid	0.05-3.0	0.05-1.0	0.1-0.5
Cosolvent	0.0-70.0	0.0-40.0	0.0-25.0
Preservative	0.0-3.0	0.01-1.0	0.05-0.25
Surfactant*	0.0-8.0	0.0-5.0	0.0-3.5
Oil phase*	0.0-50.0	0.0-25.0	0.0-15.0
Water	QSAD 100	QSAD 100	QSAD 100
Base	QS pH	QS pH	QS pH

*Present for lotion

The following Table B sets forth the operational, preferred, and more preferred concentrations of representative active ingredients that can beneficially be used in practicing our invention, whether alone or in combination. The exact amount will be readily determined by one of ordinary skill by referencing standard texts such as the Physicians Desk Reference or Goodman and Gilman's referred to hereinbefore.

TABLE B

Component	% w/w		
	Operational	Preferred	More Preferred
Antibiotic	0.1-5.0	0.5-2.0	0.5-1.0
Corticosteroid	0.005-2.5	0.01-1.0	0.05-0.1
Retinoid	0.005-0.5	0.05-0.1	0.025-0.05
Imidazole	0.1-5.0	0.5-2.0	0.75-1.0
NSAID	0.1-3.0	0.2-2.0	0.2-1.0

To make an emulsion (i.e., lotion) form of our invention as broadly set forth in Table A, the surfactant and oil phase component are included in the composition. The following table illustrates the manner in which the composition is modified to form a lotion.

TABLE C

Component	% w/w		
	Operational	Preferred	More Preferred
Surfactant	0.1-8.0	0.5-5.0	1.0-3.5
Oil phase	1.0-50.0	2.5-25.0	5.0-15.0

The preferred formula of the composition would either be preservative-free or have a decreased level of preservatives as compared to material that is commercially available. This is important because the presence of preservatives in a composition can result in irritation or allergic reaction of the

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skin. Reducing the possibility of skin irritation or allergic reaction in a composition provides a better product. Regarding compositions that contain clindamycin phosphate, the leading product is Cleocin T Gel. It is a clear viscous gel that tests have shown is not as well accepted as the less viscous material of the invention made with a more lightly cross-linked polymer. By controlling the viscosity of the gel at a low level it can be accurately dispensed from a clear plastic squeeze bottle rather than from an ointment tube. The advantage is two-fold. One is accurate dosage control by using a reduced orifice tip and improved product presentation for marketing. In addition, tests have shown that the less viscous material is cosmetically more elegant and will result more regular use.

In preparing a composition of this invention general formulation techniques known in the art of pharmaceutical science will be used. See, for example, Remington: The Science and Practice of Pharmacy, Nineteenth Edition, Mack Publishing Company (1995). Preparation of specific formulations may be found in the examples.

To prepare a gel with two active ingredients where one is suspended and the other is dissolved, first add the insoluble active to a water-miscible ingredient, or a portion of the water with a surfactant, to disperse. Separately, dissolve the other active and any other preservative ingredients in the purified water. Disperse the gelling agent in the aqueous solution with appropriate stirring. Then add the dispersion of the first active ingredient to the gel and mix well to blend. Last, add a pH adjusting agent to adjust the pH to the desired range. The preparation of a gel when both active ingredients are dissolved is similar, varying only in the first step. First, add the active with lower aqueous solubility to a solvent, blend of solvents, or water. Mix to dissolve. Separately, dissolve the other active and any preservative ingredients in the purified water. Disperse the gelling agent in the aqueous solution with appropriate stirring. Then add the solution of the first active to the gel and mix well to blend. Last, add a neutralizing agent to adjust the pH to the desired range.

For a combination of an antibiotic e.g. clindamycin phosphate with a retinoid, such as tretinoin, three formulation approaches can be applied to a composition of the invention: 1) an aqueous gel, formed from a lightly crosslinked carbomer gelling agent, with the clindamycin phosphate dissolved and the tretinoin suspended; 2) an oil-in-water emulsion with the clindamycin phosphate dissolved in the water thickened with a lightly cross-linked carbomer gelling agent and the tretinoin dissolved in an internal liquid oil phase; and 3) a solution consisting of water and water-miscible organic solvents with the clindamycin phosphate and tretinoin both dissolved.

The following compositions are given as representative as the types of compositions useful in this invention.

Where the composition contains an antibiotic alone, for example clindamycin phosphate, the composition has a pH of about 4 to 7 and contains

- (a) about 0.5% to 2.0% w/w clindamycin phosphate,
- (b) about 0.1% to 0.4% w/w of the polymer,
- (c) the base to adjust pH,
- (d) about 15.0% to 25.0% w/w of a water miscible solvent,
- (e) less than about 0.2% w/w of a preservative, and
- (g) QSAD purified water to 100% w/w.

Preferably such a composition has a pH of about 5 to 6 and contains

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- (a) 1.0 to 1.5% w/w clindamycin phosphate,
- (b) 0.2% w/w of the polymer,
- (c) the base to adjust pH,
- (d) 15.0% w/w propylene glycol and 5.0% w/w polyethylene glycol 400,
- (e) 0.1-0.15% w/w methylparaben, and
- (g) QSAD purified water to 100% w/w.

A gel composition where the antibiotic in clindamycin phosphate and the retinoid is tretinoin may contain

- (a) (i) about 0.5% to about 2.0% w/w clindamycin phosphate, and
- (ii) about 0.01% to about 0.05% w/w tretinoin;
- (b) about 0.1% to about 0.5% w/w of the polymer;
- (c) the base to adjust pH;
- (d) about 10% to about 30% w/w of a water-miscible solvent;
- (e) less than about 0.2% of a preservative; and
- (g) QSAD purified water 100% w/w.

A lotion composition of clindamycin phosphate and tretinoin usefully will contain

- (a) (i) about 0.5% to about 2.0% w/w clindamycin phosphate and
- (ii) about 0.01% to about 0.05% w/w tretinoin;
- (b) about 0.1% to about 0.5% w/w of the polymer;
- (c) the base to adjust pH;
- (d) about 5% to about 30% w/w of a water-miscible solvent;
- (e) less than about 0.2% of a preservative;
- (f) an oil phase in combination with at least one surfactant to form an emulsion; and
- (g) QSAD purified water 100% w/w.

Treatment

Another aspect of the invention is a method for treating a skin disorder in a human, which method comprises administering a composition to an affected area of the subject's skin having such disorder in an amount and for a period of time sufficient to improve the skin disorder, wherein the composition is described in this patent application. Preferably, the composition is administered once a day over the treatment period. Depending on the patient's improvement, the treatment may extend for less than a week to two months or more. The progress of improvement may be monitored by the patient or by a physician.

The skin disorders which are treatable with the composition of the invention include acne vulgaris, rosacea, and various inflammatory conditions including atopic dermatitis. A discussion of these conditions may be found in the Merck Manual. For example, acne vulgaris is an inflammatory disease affecting hair follicles and sebaceous glands. Lesions are most common on the face, but the neck, chest, upper back, and shoulders may also be affected.

The affected area of the subject's skin can be anywhere on the body in which the skin disorder exists. The amount of composition and period of administration time sufficient to improve the skin disorder will be dependent on the subject and skin condition. Generally, a sufficient amount will be squeezed from a dropper tip of a squeeze bottle or an eye dropper onto the area affected and rubbed gently into the skin. Usually, no more than a few drops will be needed to apply to an affected area.

Article of Manufacture

Another aspect of the invention is an article of manufacture that comprises a composition for treating a skin disorder

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as described above in a suitable container, preferably in a dropper bottle, in combination with labeling instructions. The dropper bottle can be made of any material, for example, glass, rigid plastic, or flexible plastic. Other means of administration are an eyedropper, or tube with a suitable small orifice size, such as an extended tip tube.

The composition of this invention may be, for example, filled and packaged into a plastic squeeze bottle (i.e., 42 g). A suitable container-closure system for the package presentation for the composition described in Table D.

TABLE D

NOMINAL SIZE	OVERFLOW CAPACITY	MATERIAL DESCRIPTION	MANUFACTURER
1 oz	46 cc	Natural cylinder, round polypropylene bottle, 15/415 finish, Wheaton B-21411 White low density polyethylene 15 mm dropper tip plug, Wheaton B-11048 White polypropylene extended tip closure, Wheaton B-15044	Wheaton Plastic Products 1101 Wheaton Avenue Milville, NJ 08332

The labeling instructions can come in the form of a pamphlet, a label applied to or associated with the packaging of the article of manufacture.

The labeling instructions provide for administering a composition of the invention to an affected area of a subject's skin having a skin disorder, in an amount and for a period of time sufficient to improve the skin disorder. Printed labeling instructions are functionally related to the composition of the invention inasmuch as such labeling instructions describe a method to treat a skin disorder. The labeling instructions are an important aspect of the invention in that before a composition can be approved for any particular use, it must be approved for marketing by the United States Food and Drug Administration. Part of that process includes providing a label that will accompany the pharmaceutical composition which is ultimately sold. While the label will include a definition of the composition and such other items such as the clinical pharmacology, mechanism of action, drug resistance, pharmacokinetics, absorption, bioavailability, contraindications and the like, it will also provide the necessary dosage, administration and usage. Thus, the combination of the composition with the dropper bottle with appropriate treatment instructions is important for the proper usage of the drug once it gets on the market. Such treatment instructions will describe the usage in accordance with the method of treatment set forth herein before.

Having now generally described this invention, the same will be better understood by reference to certain specific examples which are included herein for purposes of illustration only and are not intended to be limiting of the invention or any embodiment thereof, unless so specified.

In the following examples, the viscosity is determined at room temperature (20-25° C.) using a Brookfield viscometer model DV-1+, spindle #27 at 12 revolutions per minute (rpm). If the measured viscosity is less than 4,000 cP, spindle #21 should be used instead of #27.

EXAMPLES

Example I

This example sets forth a pourable gel composition of this invention. The procedure set forth in steps a-f produces a

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composition according to Table I. The composition is referred to as "Clindagel." An application to designate Clindagel as a trademark has been filed.

TABLE I

COMPONENT	% w/w
Clindamycin phosphate, USP (equivalent to 1% clindamycin)	1.19
Methylparaben	0.15
CARBOPOL® 941 (or 981)	0.20
Propylene glycol	15.0
Polyethylene glycol 400	5.0
Sodium hydroxide (10% solution)	QS pH 5.3 to 5.7
Purified water	QSAD 100.00

The viscosity of this composition is about 1,000 cP.

- Weigh approximately 90% of the purified water into a stainless steel kettle. Add the propylene glycol and polyethylene glycol 400. Stir with propeller mixer.
- At room temperature add methylparaben to step a) with continued stirring. Mix until dissolved.
- While continuing to mix, add clindamycin phosphate to step b). Mix until dissolved.
- While continuing to mix, add CARBOPOL® 981 or 941 slowly to step c), avoiding clumping. Mix vigorously at room temperature until a uniform and lump-free dispersion is achieved.
- While mixing, add sufficient sodium hydroxide, 10% solution, to achieve a pH of 5.3 to 5.7. Mix until uniform.
- Add the remaining water to make 100% and mix until uniform.

Example II

This example shows the composition of a commercially available product containing clindamycin phosphate. The product is sold by Pharmacia as Cleocin T® Gel. The components and amounts were analyzed to be as follows:

TABLE II

COMPONENT	% w/w
Clindamycin phosphate	1.19
Carbomer 934 P	0.8
Propylene glycol	4.9
Polyethylene glycol 400	10.2
Sodium hydroxide	QS pH 5.4
Methylparaben	0.3
Allantoin	0.2
Purified water	QSAD 100

The viscosity of this composition is about 20,000 cP.

Example III

Comparison of Clindagel and Cleocin-T® Gel

This example provides clinical data showing the advantages of a composition of the invention as compared to a known commercial composition.

A multi-center investigator-blind clinical trial was conducted comparing a composition of this invention (see Example I) Clindagel, once daily, and Cleocin-T® Gel (see Example II), twice daily (according to manufacturer's directions), in acne vulgaris. Three hundred and twenty four patients, half in each group, were treated for up to 12 weeks.

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The investigator was "blinded" in that she/he did not know which treatment the patient used before the investigator evaluated the condition of the patient's acne.

Evaluations included inflammatory lesion count, total lesion count, physician's global assessment and skin-related side effects. Papules and pustules were considered inflammatory lesions. Total acne lesions included open and closed comedones in addition to inflammatory lesions. The physician's global severity assessment was based on a nine-point scale. At study end (12 weeks or last evaluation) it was concluded that Clindagel used once a day was equal in effectiveness to Cleocin-T® used twice daily and Clindagel had significantly fewer side effects. The data on lesion counts are summarized in Table III.

TABLE III

Improvement in Acne Lesions at Endpoint: Clindagel™ Once Daily vs. Cleocin-T Gel Twice Daily.			
	Clindagel™ Once Daily	Cleocin-T® Gel Twice Daily	95% Confidence Lower Bound
ACNE LESIONS			
Inflammatory	-50.90 (2.62)	-50.02 (2.62)	0.897
Total	-37.27 (2.44)	-39.52 (2.44)	0.801

The physician's global assessment is summarized in Table IV.

TABLE IV

Summary of Number of Patients with a Two-Category Improvement from Baseline in the 9-Point Physician's Global Severity Assessment at Endpoint			
PHYSICIAN'S GLOBAL Assessment	Clindagel™ Once Daily Number of Patients	Cleocin-T® Gel Twice Daily Number of Patients	95% Confidence Lower Bound
Improved by 2 categories	84	84	0.833
Same or Worsened	72	73	
TOTAL	156	157	

The frequency of dermal side effects from Clindagel™ once daily and from Cleocin-T® twice daily are tabulated in Table V.

TABLE V

Summary Results of Frequency of Adverse Events Comparing Clindagel™ Once Daily and from Cleocin-T® Twice Daily.			
Category	ADVERSE EVENTS		Fisher's Exact Test
	Clindagel™ Once Daily	Cleocin-T® Gel Twice Daily	
Number of patients in safety evaluation	168	165	
Number of patients with at least one skin/appendage disorder reported	2	13	0.003
Frequency of local adverse reactions	1.2%	7.9%	

Example IV

This example sets forth the results of a user preference test (with vehicles, not actives) comprising a composition of this

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invention is shown in Example I (with CARBOPOL® 981) with the commercially available composition of Example II, (with Carbomer 934 P). Table VI sets forth the formulation compositions.

The study was conducted amongst a normal subject patient population of 10 in order to evaluate the functional and cosmetic attributes using a half-face, paired, and symmetrical design.

TABLE VI

Component Vehicle Formulae:	% w/w Clindagel	Cleocin-T Gel
Carbomer 934P	—	0.8
Carbomer 981	0.2	—
Propylene glycol	15.0	4.9
Polyethylene glycol 400	5.0	10.2
Sodium hydroxide	qs to pH 5.5	qs to pH 5.4
Methylparaben	0.15	0.3
Allantoin	—	0.2
Purified water	QSAD 100	QSAD 100

Test articles (gel vehicles) were identified by blinded identification code, thereby preventing test subject from knowing the identity of the test articles being applied. Each test pair involved test articles L vs. R, which were used on the left and right sides of the face respectively. The test articles assigned to L and R codes were varied so that each test article was randomly evaluated on R and L test locations and by order of application.

The subjects were equally balanced for sex. The mean age of the population was 34 years old within an age range of 25-44 years.

The following attributes were assessed during and after application: spreadability, feel/texture during application, ease of application, ability to rub the gel into the skin, drying time on the skin, skin feel after application, overall cosmetic preference, and usability of the product. Each gel was evaluated for its functional and cosmetic attributes on a scale of 1-6, with 1 being Unacceptable and 6 being Excellent.

Of the nine subjects with a preference for one of the test articles, 67% preferred Clindagel vehicle over Cleocin-T vehicle. The degree of preference of Clindagel over Cleocin-T was judged "moderate" to "great" in 100% of those tested. The data are tabulated in Table VII.

TABLE VII

Subject	Vehicle Preference By Subject										TOTAL
	1	2	3	4	5	6	7	8	9	10	
Age	26	39	44	42	25	28	42	35	33	26	
Sex	F	F	M	M	F	F	M	F	M	M	
Cleocin-T							P	P	P	NP	3
Clindagel	P	P	P	P	P	P				NP	6

P = Preferred
NP = No Preference
F = Female
M = Male

There was a significantly higher score for Clindagel vehicle than for Cleocin-T gel vehicle in four of the specific attributes, and no significant difference in two of those attributes (Table VIII). Clindagel vehicle scored marks of "Very Good" in three of the six attribute categories and marks of "Good" in three other. Cleocin-T gel vehicle scored marks of "Very Good" in one category, "Good" in four categories and "Fair" in one category.

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TABLE VIII

Functional and Cosmetic Attribute:	Frequency of Higher Score of Clindagel Vehicle and Cleocin-T Gel Vehicle		No Preference
	CLINDAGEL	CLEOCIN-T	
Spreadability	30%	30%	40%
Feel/texture during application	50%	30%	20%
Ease of application	20%	30%	50%
Ability to rub gel into skin	50%	20%	30%
Length of drying time	70%	20%	10%
Skin feel after application	50%	30%	20%

Forty percent of test subjects commented independently that the Clindagel vehicle was "runny" or "watery" upon application. This was also reflected in the "Ease of Application" attribute, where Cleocin-T had a slightly higher score. 50% of test subjects commented independently on their face feeling "sticky" after application of the Cleocin-T vehicle. 80% of test subjects indicated that they would use the Clindagel vehicle as a facial medication product. Only 30% of those tested indicated that they would use Cleocin-T vehicle as a facial medication product.

Example V

Stability Study of Clindagel™ with Clindamycin Phosphate as Active Ingredient

This example provides laboratory data showing stability of Clindagel (Example I) for at least 18 months at 25° C. Clindagel was tested for the stability of the active ingredient, clindamycin phosphate, over time at controlled room temperature (i.e., 25° C. and 60% relative humidity). A stability-indicating, high performance liquid chromatography assay was used to assess remaining clindamycin phosphate potency, expressed as clindamycin, during the experiment. Based on the data shown in Table IX, Clindagel is projected to have a commercial shelf life of about 24 months.

The estimated shelf life was calculated from the 95% confidence interval around the least squares fit to the available data. The projected shelf life is the time at which the drug potency reaches 90% of label claim (as allowed by the USP). The software used for the statistical analysis is named "SLIMStat+" and is sold by Metrics, Inc., P.O. Box 4035, Greenville, N.C. 27836, phone 252-752-3800.

TABLE IX

Percent Clindamycin by Weight	Room Temperature Stability Assessment of Clindamycin Potency in Clindagel™, 1%					
	Initial	1 month	2 months	6 months	12 months	18 months
Clindamycin Phosphate Assay	1.028	1.017	1.009	1.004	0.983	0.959

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Example VI

Clindamycin Phosphate-Tretinoin Combination Composition

Section 1

This section of this example describes two gel compositions of the invention in which the active ingredients are clindamycin phosphate and tretinoin.

Two pourable gel compositions containing a combination of clindamycin phosphate and tretinoin were made according to the invention. In Formulation A, the gel had a pH of about 5.5 and a viscosity of about 6100 cP. In Formulation B, the gel exhibited a pH of about 4.7 and a viscosity of about 6,000 cP. See quantitative formulae in Table X. This example illustrates the utility of our invention in the preparation of physically and chemically stable gel formulations.

TABLE X

Component	Quantitative compositions of two combination Clindamycin Phosphate/Tretinoin gel formulations:	
	A % w/w	B % w/w
Tretinoin	0.025	0.025
Clindamycin Phosphate	1.21	1.21
Propyl Gallate	—	0.02
BHA	0.02	—
Citric Acid	—	0.05
Disodium Edetate	0.05	0.05
Polysorbate 80	5.0	0.08
Propylene Glycol	5.0	—
PEG 400	20.0	—
Glycerin	—	10.0
Methylparaben	0.1	0.15
CARBOPOL 981	0.5	0.5
Tromethamine (10% in water)	QS to pH 5.5	QS to pH 4.5
Purified Water	QSAD 100	QSAD 100

Method of preparation: Formula A

- Combine the propylene glycol, polyethylene glycol 400, and polysorbate 80. Add the tretinoin and stir to dissolve.
- In a separate container dissolve the disodium edetate, methylparaben, and butylated hydroxyanisole in the purified water.
- Add the clindamycin phosphate to the aqueous solution of step b and stir to dissolve.
- Disperse the CARBOPOL 981 into the aqueous solution with high-speed stirring.
- Add the tretinoin drug phase to the aqueous CARBOPOL dispersion with stirring and then add the tromethamine and mix to form a homogeneous gel.

Method of Preparation of Formula B

- Combine the glycerin and polysorbate 80. Add the tretinoin and stir to wet and disperse.
- In a separate container dissolve the propyl gallate, citric acid, disodium edetate, methylparaben, and butylated hydroxyanisole in the purified water.
- Add the clindamycin phosphate to the aqueous solution of step b and stir to dissolve.
- Disperse the CARBOPOL 981 into the aqueous solution with high-speed stirring.
- Add the tretinoin drug phase to the aqueous CARBOPOL dispersion with stirring and then add the tromethamine and mix to form a homogeneous gel.

Section 2

This Section of this example describes two additional compositions that are slight modifications of Formulas A and B, wherein the preservatives have been changed or adjusted.

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The formulas are given below. C is similar to A, and D is similar to B.

TABLE XI

Component	C % w/w	D % w/w
Clindamycin Phosphate	1.24	1.24
Tretinoin	0.025	0.025
Propyl Gallate	—	0.02
BHA	0.02	—
Citric Acid	—	0.05
Disodium Edetate	0.05	0.05
Methylparaben	—	0.15
Propylparaben	—	0.03
Benzyl Alcohol	1	—
Polysorbate 80	5	0.08
Propylene Glycol	5	—
PEG 400	20	—
Glycerin	—	10
Tromethamine (10%)	qs to pH 5.5	qs to pH 4.5
CARBOPOL 981	0.5	0.5
Purified Water	qsad 100	qsad 100

In making formula C, the 0.1% methylparaben preservative in Formula A was replaced with 1.0% benzyl alcohol. In Formula D, 0.03% propylparaben was added as an additional preservative (because the combination of methylparaben and propylparaben is sometimes a better preservative system). Methods of preparation:

Formula C is prepared similarly to Formula A, except that methylparaben would be omitted from step "b," and the benzyl alcohol would be added to step "a."

Formula D is prepared similarly to Formula B; propylparaben would be added to step "b."

The Formula C gel has a pH about 5.5 and a viscosity about 9000 cP. The Formula D gel has a pH about 4.6 and a viscosity about 4100 cP.

Example VII

Assessment of Chemical Stability of Tretinoin in Formulations A and B from Example VI

This example provides laboratory data showing the stability of tretinoin in two compositions of the invention under accelerated test conditions.

Tretinoin is known to be relatively unstable, therefore, the chemical stability of these combination formulations was assessed in a 12-week accelerated stability study. The gels were packaged in amber glass vials, 8 grams each, and stored at 40° C. High performance liquid chromatography assays were performed initially and at 2, 4, and 12 weeks using the method for tretinoin cream (USP 24, page 1684). Both compositions were found to retain their potency in this accelerated study. Table XII summarizes the chemical stability results.

TABLE XII

Tretinoin Concentration (% w/w)	Accelerated Temperature (40° C.) Stability Assessment of Tretinoin Potency in Formulations A and B, Example VI.			
	TIME IN WEEKS			
	0	2	4	12
Formula A	0.0210	0.0228	0.0236	0.0231
Formula B	0.0236	0.0231	0.0234	0.0234

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Example VIII

Composition of Combination Gel Formulation

This example teaches how to modify a known commercial composition of Example II to include tretinoin.

A combination gel formulation of tretinoin 0.025%, and clindamycin 1% was made by spatulating tretinoin powder and propyl gallate (an antioxidant to retard oxidative loss of tretinoin) into Cleocin®T gel (Example II). The quantitative formula is shown in Table XIII.

TABLE XIII

Component	Amount
Tretinoin	0.0074 g
Propyl Gallate	0.0145 g
Cleocin® T gel	28.0000 g
TOTAL	28.0219 g

The tretinoin and propyl gallate were accurately weighed, placed on a glass plate, and incorporated into the Cleocin®T gel with a spatula. During spatulation, the product was protected from light. The resulting product was a smooth, clear light yellow gel with a pH of 5.7 and a viscosity of about 20,000 cP.

Example IX

Physical Stability Studies of the Compositions of Example VI (Formula A) and Example VIII

This example compares a composition of the invention (Example VI, Formula A) with a modified commercial composition (Example VIII) with regards to crystal growth.

The physical stability of Example VI, Formula A and Example VIII, was assessed over a 4-week period at 5° C., 40° C. and 50° C. The stability evaluation was based on careful physical examination for description at initial, 2 week and 4 week times. At study end, microscopic examination was performed to check for precipitation of tretinoin and crystal growth. As illustrated in the data summary below (Table XIV), the modified commercial formulation, Cleocin®T gel, was physically unstable compared to a composition of the invention, Example VI (Formula A).

TABLE XIV

Description: Clear-Light-Yellow Gel			
	Initial	2 weeks	4 weeks
	Example VI (Formula A)		
5° C.	Clear	Clear	Clear - no crystals
40° C.	Clear	Clear	Clear - no crystals
50° C.	Clear	Clear	Clear - no crystals
	Example VIII		
5° C.	Clear	Hazy	Hazy - Crystals to 1200 microns
40° C.	Clear	Translucent	Hazy - Crystals to 1200 microns
50° C.	Clear	Translucent	Hazy - Crystals to 1200 microns

Example X

This example sets forth a lotion composition of this invention comprising two active ingredients: an antibiotic, i.e., clindamycin phosphate, and a retinoid, i.e., tretinoin. The components for this lotion are set forth in Table XIV.

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TABLE XIV

Component	% w/w
Clindamycin Phosphate	1.21
Tretinoia	0.025
Stearyl Alcohol	5.00
Diisopropyl Adipate	6.00
PEG 40 Stearate (Myrj 52)	2.00
Sorbitan Stearate (Span 60)	2.00
Butylated Hydroxytoluene	0.02
Propylene Glycol	5.00
Methylparaben	0.15
Propylparaben	0.03
Citric Acid	0.05
Disodium Edetate	0.10
CARBOPOL 981	0.10
Tromethamine (10%)	qs pH 5.5
Purified Water	qsad 100

The viscosity of this composition is about 7,000 cP.

Method of Preparation:

- a. Combine the propylene glycol and purified water. Add the methylparaben, propylparaben, citric acid, and disodium edetate and stir to dissolve.
- b. Add the clindamycin phosphate to step "a" and stir to dissolve.
- c. Add the Carbopol 981 to step "b" and stir to form a homogeneous dispersion.
- d. Warm step "c" water phase to between 60° C. and 70° C.
- e. Combine the stearyl alcohol, PEG 40 stearate, sorbitan stearate, and butylated hydroxytoluene and warm to melt at between 60° C. to 70° C.
- f. Add the tretinoia to the diisopropyl adipate and stir to dissolve.
- g. With high-speed stirring add step "e" oil phase and step "f" drug phase sequentially to step "d" water phase and mix well.
- h. Cool emulsion with continued stirring.
- i. Add the tromethamine solution and stir to form a homogeneous emulsion. Cool to room temperature with continued stirring.

Example XI

This example sets forth a pourable gel composition of this invention which gel contains a corticosteroid. Such formulation is suitable for treating inflammatory skin conditions such as atopic dermatitis.

Component	% by weight
Halobetasol propionate, micronized	0.05
Docusate sodium	0.10
CARBOPOL® 981	0.3
Propylene glycol	12
Methylparaben	0.1
Propylparaben	0.02
Tromethamine	QS pH 6.5
Purified water	QSAD 100.00

The viscosity of this composition is about 6200 cP.

- a. Dissolve the methylparaben and propylparaben in the propylene glycol at room temperature using a propeller mixer.
- b. Weigh 70% of the formula weight of purified water and slowly add the solution from step "a" while mixing with propeller mixer.

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- c. While continuing to mix, add CARBOPOL® 981 slowly to step "b." Mix at room temperature until a smooth and uniform dispersion is produced.
- d. To 10% of the formula weight of water add the docusate sodium and mix until fully dissolved. To facilitate dissolution the mixture may be warmed to 40-50° C., and then cooled to room temperature when dissolution is complete.
- e. Disperse the micronized halobetasol propionate in step "d" with a propeller mixer or preferably a homogenizer of the rotor-stator type.
- f. Add step "e" to step "c" using propeller mixer to uniformly disperse the drug material.
- g. Dissolve the tromethamine in 10 times its weight in purified water. While mixing, use the tromethamine solution to adjust the pH and thicken the gel. Continue incremental additions until a pH of about 6.5 is attained.
- h. Add water to make 100% of the batch size and mix until homogeneous with a propeller-type mixer.

Example XII

This example sets forth yet another pourable gel composition of this invention. The formulation contains metronidazole for topical application to the skin areas affected, for example, with rosacea.

Component	% by weight
Metronidazole	0.75
Methylparaben	0.12
Propylparaben	0.03
CARBOPOL® 981	0.25
Glycerin	5.00
Trolamine	QS pH 8
Purified Water	QSAD 100

The viscosity of this composition is about 4700 cP.

- a. Weigh 90% of the formula weight of purified water, metronidazole, glycerin, methyl-paraben and propylparaben into a suitable stainless steel container. Mix vigorously at room temperature until all components are dissolved. A propeller-type mixer is particularly suitable.
- b. While continuing to mix, slowly add the CARBOPOL®. Mix until a lump-free dispersion is attained.
- c. Mix the trolamine with an equal part of purified water. Use this solution to adjust the pH to about 8 with incremental additions while mixing.
- d. Add the balance of the purified water to make 100% and mix until a homogeneous gel is produced.

Example XIII

This example sets forth a pourable gel composition of this invention which gel contains a NSAID agent.

Component	% by weight
Naproxen	1.00
Octoxynol 9	0.10
CARBOPOL® 981	0.30
Propylene glycol	5.00

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-continued

Component	% by weight
Glycerin	5.00
Benzyl alcohol	1.00
Sodium hydroxide, 10% solution	QS pH 3.0 to 3.5
Purified water	QSAD 100.00

The viscosity of this composition is about 4200 cP.

- a. Mix the benzyl alcohol, glycerin and propylene glycol together at room temperature using a propeller mixer.
- b. Weigh 70% of the formula weight of purified water and slowly add the solution from step "a" while mixing with propeller mixer.
- c. While continuing to mix, add CARBOPOL® 981 slowly to step "b." Mix at room temperature until a smooth and uniform dispersion is produced.
- d. To 2-5% of the formula weight of water add the octoxynol 9 and mix until fully dissolved.
- e. Disperse the naproxen in step "d" with a propeller mixer or a homogenizer.
- f. Add step "e" to step "c" using propeller mixer to uniformly disperse the drug material.
- g. While mixing, use the sodium hydroxide solution to adjust the pH. Continue incremental additions until a pH of 3.0 to 3.5 is attained.
- g. Add water to make 100% of the batch size and mix until homogeneous with a propeller-type mixer.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A topical aqueous gel composition having a pH of about 3 to about 9 and a viscosity of less than about 15,000 cP for treating a skin disorder in a human subject, which composition consists essentially of

- (a) a therapeutically-effective amount of at least one compound useful for treating such disorder,
- (b) a hydrophilic pharmaceutically-acceptable, lightly cross-linked polyacrylic acid polymer compatible with the compound,
- (c) a pharmaceutically-acceptable base to adjust pH,
- (d) optionally a water miscible solvent,
- (e) optionally a preservative, and
- (f) water.

2. The composition of claim 1, wherein the compound is an antibiotic, imidazole, retinoid, corticosteroid, or a non-steroidal anti-inflammatory drug (NSAID).

3. The composition of claim 2, wherein the compound is an antibiotic alone or in combination with a corticosteroid or a retinoid.

4. The composition of claim 3, wherein the compound is an antibiotic alone.

5. The composition of claim 4, wherein the antibiotic is clindamycin phosphate.

6. The composition of claim 5 having a pH of about 4.0 to 7.0, which composition consists essentially of

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- (a) about 0.5% to 2.0% w/w clindamycin phosphate,
- (b) about 0.1% to 0.4% w/w of the polymer,
- (c) the base to adjust pH,
- (d) about 15.0% to 25.0% w/w of a water miscible solvent,
- (e) less than about 0.2% w/w of a preservative, and
- (f) purified water in a quantity sufficient to make (QSAD) 100% w/w.

7. The composition of claim 6 having a pH of about 5.0 to 6.0, which composition consists essentially of:

- (a) about 1.0 to 1.5% w/w clindamycin phosphate,
- (b) about 0.2% w/w of the polymer,
- (c) the base to adjust pH,
- (d) about 15.0% w/w propylene glycol and about 5.0% w/w polyethylene glycol 400
- (e) about 0.1-0.15% w/w methylparaben, and
- (g) QSAD purified water to 100% w/w.

8. The composition of claim 3, wherein an antibiotic is combined with a corticosteroid, the antibiotic is clindamycin phosphate, and the corticosteroid is desonide, hydrocortisone valerate, fluocinolonone acetonide, hydrocortisone butyrate, or triamcinolone acetonide.

9. The composition of claim 3, wherein an antibiotic is combined with a retinoid, the antibiotic is clindamycin phosphate, and the retinoid is tretinoin.

10. The composition of claim 9 having a pH of about 4 to 7, which composition is a gel consisting essentially of

- (a) (i) about 0.5% to about 2.0% w/w clindamycin phosphate, and (ii) about 0.01% to about 0.05% w/w tretinoin;
- (b) about 0.1% to about 0.5% w/w of the polymer;
- (c) the base to adjust pH;
- (d) about 10% to about 30% w/w of a water-miscible solvent;
- (e) less than about 0.2% of a preservative; and
- (g) QSAD purified water 100% w/w.

11. The composition of claim 1, wherein the compound is a non-steroidal anti-inflammatory drug.

12. The composition of claim 11, wherein the compound is naproxen or diclofenac or a pharmaceutically-acceptable salt thereof.

13. The composition of claim 2, having a corticosteroid as the sole active agent.

14. The composition of claim 13, wherein the corticosteroid is diflorasone diacetate, fluticasone propionate, halobetasol propionate, or budesonide.

15. The composition of claim 14, wherein the corticosteroid is halobetasol propionate.

16. The composition of claim 1 in combination with a container that accurately administers a portion of the composition for topical administration to a patient.

17. The composition of claim 16 in combination with labeling instructions for use in treating the skin disorder.

18. A method for treating a skin disorder in a human subject, which method comprises topically administering an aqueous gel composition having a pH of about 3 to about 9 and a viscosity of less than about 15,000 cP to an affected area of the subject's skin having such disorder in an amount and for a period of time sufficient to improve the skin disorder, wherein the composition consists essentially of

- (a) a therapeutically-effective amount of at least one compound useful for treating such disorder,
- (b) a hydrophilic, pharmaceutically-acceptable lightly cross-linked polyacrylic acid polymer compatible with the pharmaceutical active material,

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- (c) a pharmaceutically-acceptable base to adjust pH
 - (d) optionally a water miscible solvent,
 - (e) optionally a preservative, and
 - (f) water.
19. The method of claim 18, wherein the skin disorder is an inflammatory skin disorder, acne, or rosacea.
20. The method of claim 19, wherein the composition is administered once a day for the period of time sufficient to improve the skin disorder.
21. The method of claim 19, wherein the skin disorder is acne.
22. The method of claim 19, wherein the compound of the composition is an antibiotic, imidazole, retinoid, corticosteroid, or NSAID.
23. The method of claim 22, wherein the compound is an antibiotic alone or in combination with a corticosteroid, or a retinoid.
24. The method of claim 23, wherein the compound is an antibiotic alone.
25. The method of claim 24, wherein the antibiotic is clindamycin phosphate.
26. The method of claim 18, wherein the composition has a pH of about 4.0 to 7.0 and consists essentially of
- (a) about 0.5% to 2.0% w/w clindamycin phosphate,
 - (b) about 0.1% to 0.4% w/w of the polymer,
 - (c) a base to adjust pH,
 - (d) about 15% to 25.0% w/w of a water miscible solvent,
 - (e) less than about 0.2% w/w of a preservative,
 - (f) QSAD purified water to 100% w/w.
27. The method of claim 26, wherein the composition has a pH of about 5.0 to 6.0 and has the following components:
- (a) about 1.0 to 1.5% w/w clindamycin phosphate,
 - (b) about 0.2% w/w of the polymer,
 - (c) a base to adjust pH,
 - (d) about 15% w/w propylene glycol and 5 w/w polyethylene glycol 400,
 - (e) about 0.1-0.15% w/w methylparaben, and
 - (f) QSAD purified water to 100% w/w.
28. The method of claim 22, wherein the compound is an antibiotic in combination with a corticosteroid.
29. The method of claim 28, wherein the antibiotic is clindamycin phosphate and the corticosteroid is desonide, hydrocortisone valerate, fluocinolone acetonide, hydrocortisone butyrate, or triamcinolone acetonide.
30. The method of claim 23, wherein the antibiotic is clindamycin phosphate and is combined with tretinoin.
31. The method of claim 30, wherein the composition is a gel having a pH of about 4 to 7, consisting essentially of
- (a) (i) about 0.5% to about 2.0% w/w clindamycin phosphate, and (ii) about 0.01% to about 0.05% w/w tretinoin;
 - (b) about 0.1% to about 0.5% w/w of the polymer;
 - (c) the base to adjust pH;
 - (d) about 10% to about 30% w/w of a water-miscible solvent;
 - (e) less than about 0.2% of a preservative; and
 - (g) QSAD purified water 100% w/w.
32. The method of claim 18, wherein the compound is an NSAID.
33. The method of claim 32, wherein the compound is diclofenac or naproxen or a pharmaceutically acceptable salt thereof.
34. The method of claim 19, wherein composition contains a corticosteroid as the sole active agent.

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35. The method of claim 34, wherein the corticosteroid is diflorasone diacetate, fluticasone propionate, halobetasol propionate, or budesonide.
36. The method of claim 35, wherein the corticosteroid is halobetasol propionate.
37. A method of preparing an aqueous gel composition having a viscosity of less than about 15,000 cP and a pH of about 3 to 9 useful for treating a skin disorder in a human subject, which method comprises
- (a) combining water with a therapeutically-effective amount of at least one compound useful for treating such disorder and a hydrophilic, pharmaceutically-acceptable, lightly cross-linked polyacrylic acid polymer compatible with the compound,
 - (b) adjusting the pH to about 3 to 9, and
 - (c) optionally combining a water-miscible solvent and a preservative to form the composition.
38. The method of claim 37, wherein the compound is an antibiotic, imidazole, retinoid, corticosteroid, or a NSAID.
39. The method of claim 38, wherein the compound is an antibiotic alone or in combination with a corticosteroid or a retinoid.
40. The method of claim 39, wherein the compound is an antibiotic alone.
41. The method of claim 40, wherein the antibiotic is clindamycin phosphate.
42. The method of claim 41, wherein the composition has a pH of about 4 to 7, and consists essentially of
- (a) about 0.5% to 2.0% w/w clindamycin phosphate,
 - (b) about 0.1% to 0.4% w/w of the polymer,
 - (c) the base to adjust pH,
 - (d) about 15.0% to 25.0% w/w of a water miscible solvent,
 - (e) less than about 0.2% w/w of a preservative, and
 - (f) QSAD purified water to 100% w/w.
43. The method of claim 42, wherein the composition has a pH of about 5 to 6, and consists essentially of:
- (a) 1.0 to 1.5% w/w clindamycin phosphate,
 - (b) 0.2% w/w of the polymer,
 - (c) the base to adjust pH,
 - (d) 15.0% w/w propylene glycol and 5.0% w/w polyethylene glycol 400
 - (e) 0.1-0.15% w/w methylparaben, and
 - (f) QSAD purified water to 100% w/w.
44. The method of claim 39, wherein the antibiotic is combined with a corticosteroid, the antibiotic is clindamycin phosphate, and the corticosteroid is desonide, hydrocortisone valerate, fluocinolone acetonide, hydrocortisone butyrate, or triamcinolone acetonide.
45. The method of claim 39, wherein the antibiotic is combined with a retinoid, the antibiotic is clindamycin phosphate, and the retinoid is tretinoin.
46. The method of claim 45, wherein the composition is a gel having a pH of about 4 to 7 and consists essentially of
- (a) (i) about 0.5% to about 2.0% w/w clindamycin phosphate, and (ii) about 0.01% to about 0.05% w/w tretinoin;
 - (b) about 0.1% to about 0.5% w/w of the polymer;
 - (c) the base to adjust pH;
 - (d) about 10% to about 30% w/w of a water-miscible solvent;
 - (e) less than about 0.2% of a preservative; and
 - (f) QSAD purified water 100% w/w.

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47. The method of claim 38, wherein the compound is a NSAID.

48. The method of claim 47, wherein the compound is naproxen or diclofenac or a pharmaceutically-acceptable salt thereof.

49. The method of claim 38, wherein the composition has a corticosteroid as the sole active agent.

50. The method of claim 49, wherein the corticosteroid is diflorasone diacetate, fluticasone propionate, halobetasol propionate, or budesonide.

51. The method of claim 50, wherein the corticosteroid is halobetasol propionate.

52. The method of claim 37, which method further comprises placing the composition in a container from which drops are accurately administered for topical administration to a patient.

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53. The method of claim 52, which method further comprises combining the container with labeling instructions for use in treating the skin disorder.

54. The composition of claim 13, wherein the corticosteroid is desonide.

55. The composition of claim 54, wherein the desonide is present at about 0.01% w/w to about 1.0% w/w.

56. The method of claim 34, wherein the corticosteroid is desonide.

57. The method of claim 56, wherein the desonide is present at about 0.01% w/w to about 1.0% w/w.

58. The method of claim 49, wherein the corticosteroid is desonide.

59. The method of claim 58, wherein the desonide is present at about 0.01% w/w to about 1.0% w/w.

* * * * *

EXCLUSIVITY SUMMARY

NDA # 21-844

SUPPL # N/A

HFD # 540

Trade Name Desonate (desonide) Gel 0.05%

Generic Name desonide gel 0.05%

Applicant Name SkinMedica

Approval Date, If Known pending

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

study 403 and study 105

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

study 403 and study 105

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 67548 YES ! NO
! Explain:

Investigation #2
IND # 67548 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Shalini Jain, PA-C

Title: Regulatory Health Project Manager

Date: October 19, 2006

Name of Office/Division Director signing form: Susan Walker, M.D.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

1.3.5.3 Exclusivity Request

Pursuant to 21 CFR 314.108, Desonate[®] Hydrogel, 0.05% qualifies for three years of exclusivity, since a clinical investigation was essential in showing effectiveness of Desonate[®] Hydrogel, 0.05% in twice-a-day applications for the treatment of atopic dermatitis, and the clinical investigation was conducted by the sponsor (as per IND No. 67,548).

Pursuant to 21 CFR 314 and 505A of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355a), Desonate[®] Hydrogel, 0.05% also qualifies for an additional 6 months pediatric exclusivity.

**APPEARS THIS WAY
ON ORIGINAL**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA #: 21-844 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 12/21/06 PDUFA Goal Date: 10/21/06

HFD 540 Trade and generic names/dosage form: Desonate™(desonide) Gel 0.05%

Applicant: SkinMedica Therapeutic Class: 3S

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: atopic dermatitis

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. 3 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 21-844

Page 3

This page was completed by:

(See appended electronic signature page)

Shalini Jain, PA-C
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)



Dow Pharmaceutical Sciences

The D in Topicals R&D

Since 1977

DEBARMENT CERTIFICATION

Skin Medica herewith certifies that the services of any persons debarred under Section 306(a) or (b) were not and will not be used in any capacity in conjunction with this application.

Signed:

A handwritten signature in black ink, appearing to read "Barry M. Calvarese", written over a horizontal line.

Date:

12/12/05

Barry M. Calvarese, MS
Dow Pharmaceutical Sciences, Inc.
Vice President
Regulatory and Clinical Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Form Approved: OMB No. 0910-0396 Expiration Date: February 28, 2006.															
TO BE COMPLETED BY APPLICANT																
<p>With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).</p> <div style="text-align: center; border: 1px solid black; width: fit-content; margin: 10px auto; padding: 2px;"> Please mark the applicable checkbox. </div> <p><input checked="" type="checkbox"/> (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).</p> <table border="1" style="width: 100%; border-collapse: collapse; margin: 10px 0;"> <tr> <td style="width: 20px; text-align: center; vertical-align: middle; font-size: x-small;">Clinical Investigators</td> <td style="width: 50%; padding: 5px;">SEE ATTACHED LIST</td> <td style="width: 30%;"></td> </tr> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> </tr> </table> <p><input type="checkbox"/> (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).</p> <p><input type="checkbox"/> (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.</p> <table border="1" style="width: 100%; border-collapse: collapse; margin: 10px 0;"> <tr> <td style="width: 50%; padding: 5px;"> NAME Barry M. Calvarese, MS </td> <td style="width: 50%; padding: 5px;"> TITLE Vice President, Regulatory and Clinical Affairs </td> </tr> <tr> <td colspan="2" style="padding: 5px;"> FIRM / ORGANIZATION Dow Pharmaceutical Sciences, Inc. </td> </tr> <tr> <td style="width: 65%; padding: 5px;"> SIGNATURE </td> <td style="width: 35%; padding: 5px;"> DATE 12/2/05 </td> </tr> </table>		Clinical Investigators	SEE ATTACHED LIST								NAME Barry M. Calvarese, MS	TITLE Vice President, Regulatory and Clinical Affairs	FIRM / ORGANIZATION Dow Pharmaceutical Sciences, Inc.		SIGNATURE 	DATE 12/2/05
Clinical Investigators	SEE ATTACHED LIST															
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FIRM / ORGANIZATION Dow Pharmaceutical Sciences, Inc.																
SIGNATURE 	DATE 12/2/05															
<p style="text-align: center; font-weight: bold; font-size: small;">Paperwork Reduction Act Statement</p> <p style="font-size: x-small;">An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:</p> <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 60%; font-size: x-small;"> Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857 </div> </div>																

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DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS		
<i>TO BE COMPLETED BY APPLICANT</i>		
<p>The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:</p> <p style="text-align: center;"><i>Name of clinical investigator</i></p> <p style="text-align: center;"><i>Name of clinical study</i></p>		
<div style="border: 1px solid black; padding: 2px; display: inline-block;"><i>Please mark the applicable checkboxes.</i></div>		
<p><input type="checkbox"/> any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;</p> <p><input type="checkbox"/> any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;</p> <p><input type="checkbox"/> any proprietary interest in the product tested in the covered study held by the clinical investigator;</p> <p><input checked="" type="checkbox"/> any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.</p>		
<p>Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests. <i>The investigator is an employee and stockholder of the sponsor</i></p>		
NAME _____		TITLE _____
FIRM / ORGANIZATION Dow Pharmaceutical Sciences		
SIGNATURE _____		DATE 11/25/05
Paperwork Reduction Act Statement		
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FIRM / ORGANIZATION Dow Pharmaceutical Sciences			
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NAME _____		TITLE _____	
FIRM / ORGANIZATION Dow Pharmaceutical Sciences			
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<i>TO BE COMPLETED BY APPLICANT</i>	
The following information concerning _____, who participated as a clinical investigator in the submitted study _____, 0.05% v _____'s submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:	
<div style="border: 1px solid black; padding: 2px; display: inline-block;"><i>Please mark the applicable checkboxes.</i></div>	
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Team Leader Memo for NDA 21-844
Desonate (desonide) Gel, 0.05%

Letter date: 12/19/05

CDER Stamp date: 12/21/05

Applicant: Dow Pharmaceuticals.

Indication sought: mild to moderate atopic dermatitis in patients 3 months of age and older

The applicant has requested approval for Desonate Gel for the topical treatment of mild to moderate atopic dermatitis in patients 3 months of age and older. In support of this indication, the applicant has submitted results from a two pivotal safety and efficacy trials and two supportive safety trials. The applicant proposed the tradename Desonate **Hydrogel**, however the accepted tradename is Desonate (desonide) Gel, 0.05%.

Regulatory Background

The applicant pursued a 505(b)(2) pathway for their drug product, based on reliance on published literature for nonclinical data needs. In an attempt to construct a clinical bridge to the Agency's findings of safety and efficacy for DesOwen Cream (reference listed drug), using DesOwen Lotion as the comparator, the applicant conducted a three-arm safety and efficacy trial (study 4-03). In this trial, Desonate Gel demonstrated superiority to vehicle but failed to demonstrate non-inferiority to DesOwen lotion. Because the applicant did not establish a clinical bridge for efficacy, a second trial was conducted in which superiority of Desonate Gel to vehicle was demonstrated. The sponsor conducted an open-label HPA axis suppression study with test product only; the sponsor did not assess systemic desonide levels of either test or comparator. In addition to submitting data from clinical and non-clinical studies that the applicant has conducted, the applicant has submitted literature to address non-clinical data needs (the reader is referred to the Pharmacology/Toxicology Review and Supervisory Memorandum by Drs. Barbara Hill and Paul Brown, respectively).

Efficacy

The applicant submitted data from two randomized, well controlled studies to demonstrate the safety and efficacy of their product used twice daily for four weeks for the treatment of atopic dermatitis in patients 3 months of age and older. The reader is referred to Dr. Kathleen Fritsch's biostatistical review and Dr. Elektra Papadopoulous' clinical review for a thorough discussion of the trials and results. Both reviewers found that the applicant convincingly demonstrated that their product, Desonate gel, is superior to vehicle in the treatment of atopic dermatitis.

In brief, the pivotal trials were of similar but not identical design. The first, study 4-03, was a multi-center, prospective, randomized, evaluator-blind, parallel group three-arm study of 666 subjects aged 3 months and older who were randomized 3:3:1 to receive Desonate Gel, DesOwen lotion, or vehicle gel treatment twice daily for four weeks. Efficacy was assessed at week 4 using an Investigator's Global Severity Score, a 6-grade

scale incorporating erythema, induration/papulation, and oozing/crusting. The primary efficacy endpoint, treatment success, was defined as achieving a score of 0 or 1 on the IGSS at week 4. The second, study 1-05, was a multi-center, prospective, randomized, evaluator-blind, parallel group two-arm study of 201 subjects aged 3 months and older who were randomized 2:1 to receive Desonate Gel or vehicle gel treatment twice daily for four weeks. Efficacy was assessed at week 4 using the Investigator's Global Severity Score, which in study 1-05 was a 5-grade scale incorporating erythema, induration/papulation, and oozing/crusting. The primary efficacy endpoint, treatment success, was defined (in study 1-05) as achieving a score of 0 or 1 on the IGSS (clear or almost clear) with at least 2 grades of improvement at week 4. In both pivotal trials, Desonate Gel was superior to vehicle gel in the treatment of atopic dermatitis. In addition, *post hoc* analysis of study 04-03 using more stringent criteria for the primary endpoint parallel to the criteria used in study 1-05 (0 or 1 on IGSS and two-grade improvement), demonstrated Desonate Gel was superior to vehicle gel in study 4-03 under these more stringent criteria.

In both pivotal trials individual signs of atopic dermatitis were assessed as secondary endpoints. In study 4-03, erythema, induration and oozing/crusting were the individual signs that were assessed, each on a four-category scale, and in study 1-05, in addition to erythema, induration and oozing/crusting, lichenification and scaling were also assessed, each on a five-category scale. The secondary endpoints were analyzed as percent reduction from baseline. For each of the individual signs in both pivotal trials, Desonate Gel was significantly superior compared to vehicle gel.

The robustness of the pivotal trial data for the primary efficacy endpoints, as well as the support and consistency of the results from the secondary endpoints, allow a determination of efficacy.

Safety

The safety population included 465 subjects with atopic dermatitis who were treated with Desonate Gel. The integrated safety data base included 425 subjects with atopic dermatitis who were treated with Desonate Gel in phase 3 vehicle-controlled trials. There were no deaths or serious adverse events attributed to study drug. Treatment related adverse events occurred in 2% of subjects treated with Desonate and 8% of subjects treated with vehicle gel. The most common treatment-related adverse events occurred at the application site (application site burning and application site pruritus). Collection of adverse events and assessment of local tolerance did not reveal unexpected safety signals.

Special safety studies included a repeat insult patch test study to assess cumulative irritation and sensitization potential, and a hypothalamic-pituitary-adrenal (HPA) axis suppression study. In the provocative repeat insult patch test study to assess cumulative irritation and contact sensitization potential (study 1-03), Desonate gel and vehicle gel had similar cumulative skin irritation scores (454/7924 and 602/7928, respectively), and 0.3% sodium laurel sulfate (positive control) and DesOwen Lotion (comparator) had roughly similar cumulative skin irritation scores (3061/7928 and 4424/7928, respectively). The presence of sodium laurel sulfate in the vehicle of the comparator,

DesOwen Lotion, may explain the irritation score for that product. Desonate Gel did not produce significant cutaneous irritation under the provocative conditions of study 1-03. In the challenge phase of study 1-03, one subject demonstrated sensitization to Desonide Gel vehicle which was confirmed by re-challenge, and four subjects demonstrated reactions consistent with sensitization to Desonate Gel which were not confirmed because rechallenge was not completed. The occurrence of sensitization and probable sensitization reactions to Desonate Gel and Desonate Gel vehicle under the provocative conditions of study 1-03 is not surprising, as Desonate Gel contains several known sensitizers: desonide, methylparaben, and propylparaben. Desonate Gel labeling contains information about the potential for sensitization with the use of Desonate Gel.

The HPA axis suppression study, study 3-03, enrolled 40 subjects, ages 6 months to 6 years, with moderate to severe atopic dermatitis affecting at least 35% body surface area. Subjects were treated with Desonate Gel twice daily for four weeks, and underwent cosyntropin stimulation testing of their adrenal axis at baseline and end of treatment. Of 37 evaluable subjects, one subject demonstrated adrenal suppression, based on a stimulated cortisol level of $\leq 18 \mu\text{g/dL}$ ($8.1 \mu\text{g/dL}$) at the end of treatment. Repeat cosyntropin stimulation testing to assess the reversibility of suppression was not performed. Product labeling describes the risk for HPA axis suppression with use of Desonate Gel in the CLINICAL PHARMACOLOGY and PRECAUTIONS sections.

The reader is referred to the clinical review by Dr. Elektra Papodopoulos and the biopharmaceutics review and amendment by Dr. Tapash Ghosh for a fuller discussion of the safety of this product.

Special Populations--Pediatrics

Atopic dermatitis is primarily a pediatric disease. The two pivotal safety and efficacy trials, as well as the special safety studies, were conducted in pediatric subjects, the most relevant population for this indication. Efficacy and safety can be extrapolated from the pediatric to the adult population, as the disease may persist into adulthood in a minority of patients.

Post-marketing Commitments

From Dr. Barbara Hill's pharmacology/toxicology review: "The applicant commits to conducting a dermal carcinogenicity study in Tg.AC mice with Desonate (desonide) gel...[and] a study to determine the photoco-carcinogenic potential of Desonate (desonide) gel (**13-week photosafety study in mice**).

Conclusion

In a two adequate and well-controlled clinical studies, in combination with supportive safety and non-clinical studies, the applicant has demonstrated the safety and efficacy of Desonate Gel applied twice daily for up to four weeks for the treatment of atopic dermatitis in patients 3 months of age and older. I concur with the recommendations of the multi-disciplinary review team for approval for marketing.

Jill Lindstrom, MD

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jill Lindstrom
10/17/2006 11:32:14 AM
MEDICAL OFFICER

Stanka Kukich
10/17/2006 11:38:33 AM
MEDICAL OFFICER

Jain, Shalini

From: Katie Ditton [KDitton@dowpharmsci.com]
Date: Thursday, September 14, 2006 8:06 PM
To: Jain, Shalini
Cc: Barry Calvarese
Subject: Desonate (NDA 021844)
Attachments: proposed-desonate-package-insert.doc; proposed-desonate-package-insert.pdf

Shalini,

Attached please find the revised Desonate PI. I have included the MS Word version and the PDF containing a clean copy and the redline.

DPSI is officially submitting the updated labeling as SN0008 to the eCTD tomorrow. Included in that submission will be the following:

- 3.5g Sample, 15g, 30g and 60g Carton text and artwork
- 3.5g Sample, 15g, 30g and 60g Container (Tube) text and artwork
- Proposed Package Insert
- Proposed Patient Information Sheet

In addition, DPSI accepts the Phase 4 commitment dates proposed in the 09/13/06 facsimile from the Agency.

Please let me know if you have any questions.

Regards,

Katie Ditton
Associate Manager, Regulatory Affairs
Dow Pharmaceutical Sciences
1330 Redwood Way
Petaluma, CA 94954
707-285-1540

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 9/12/06

For Shalini Jain

To: Barry Calvarese	From: Mary Jean Kozma-Fornaro Supervisor, Project Management Staff
Company: Dow	Division of Dermatology & Dental Products
Fax number: 760 448-3615	Fax number: (301) 796-9894/9895
Phone number: 707 793-2600	Phone number: (301) 796-2110
Subject: NDA 21-844 Phase 4 commitment comments for submission received August 30, 2006	

Total no. of pages including cover:

Please see attached and submit agreement to listed timelines.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2110. Thank you.

NDA 21-844 September 13, 2006

The Division acknowledges receipt of the sponsor's proposed timeline for the nonclinical post-marketing commitments for Desonate (desonide) gel submitted to NDA 21-844 on August 30, 2006. The revised timeline appears acceptable. However, actual dates are needed for the timeline for tracking in the Post-marketing study database. Therefore, the Division recommends the following timeline for the nonclinical post-marketing commitments which incorporates dates into the timeline that correspond with the timeline proposed by the sponsor.

1. The applicant commits to conducting a dermal carcinogenicity study in Tg.AC mice with Desonate (desonide) gel.

4-week dose range finding study report (plus TPA feasibility study):	By May 1, 2007
Study protocol submission:	By November 1, 2007
Study start date:	By August 1, 2008
Final report submission:	By May 1, 2010

2. The applicant commits to conducting a study to determine the photoco-carcinogenic potential of Desonate (desonide) gel (13-week photosafety study in mice).

3-week pilot study report (plus single dose SKH1-hr mice studies for PK, irritancy and UVR response):	By May 1, 2007
Study protocol submission:	By August 1, 2007
Study start date:	By February 1, 2008
Final report submission:	By February 1, 2009

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Jean Kozma Fornaro
9/13/2006 10:42:37 AM
CSO

MEMORANDUM OF TELECON

DATE: August 17, 2006

APPLICATION NUMBER: NDA 21-844, Desonide Gel, 0.05%

BETWEEN:

Name: Barry Calvarese, Ph.D.
Phone: 707-665-4610
Representing: Dow Pharmaceutical Sciences

AND

Name: Ernest Pappas, Chemist
Division of Pre-Marketing Assessment II, Branch III

SUBJECT: FDA requests an acceptance criteria (upper and lower limits) for viscosity to be added to the Desonide Gel, 0.05% release and stability specifications.

BACKGROUND:

There were no limits in the release and stability specifications for the viscosity.

— CALL: At the request of the reviewing chemist, Ernest Pappas, and concurrence of the Branch Chief, FDA's Chemist for Dermatology and Dental, Ernest Pappas explained to the firm that they need to establish upper and lower limits in the release and stability specifications. The firm stated that they did not have that information earlier but they do now and they will submit an amendment to the file and send an electronic copy to Linda Athey, FDA's Regulatory Health Project Manager for Quality.

{See appended electronic signature page}

Linda Athey
Regulatory Health Project Manager for Quality

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/s/

Linda D Mullins-Athey
8/18/2006 09:58:48 AM
PROJECT MANAGER FOR QUALITY

MEMORANDUM**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research**

To: Susan Walker, MD
Director, Division of Dermatology and Dental Products
HFD-540

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: August 8, 2006

Subject: OSE Review # 06-0173, Desonate (Desonide Gel) 0.05%; NDA 21-844

This memorandum is in response to a May 11, 2006 request from the Division of Dermatology and Dental Products (HFD-540) for a final review of the proprietary name, "Desonate". Additionally, the package insert labeling was submitted for review and comment. Revised container labels and carton labeling have not been submitted at this time.

DMETS initially found the proprietary name "Desonate Hydrogel" acceptable from a safety perspective in ODS Consult # 05-0102 dated August 18, 2005. Additionally, DMETS recommended that the Division contact the CDER Labeling and Nomenclature Committee for acceptability of the dosage form "Hydrogel". Subsequently, on December 12, 2005, the Division sent two faxes to the sponsor communicating the following, (1) DMETS had no objections to the use of the proprietary name, Desonate Hydrogel and (2) the following comments from Chemistry, Manufacturing and Control (CMC):

"The Agency does not approve a trade name during IND stages, however, when you submit an NDA with the tradename, Desonate Hydrogel, we have the following concerns:

- The term 'hydrogel' is not regulatory terminology for a topical dosage form and because of that using the term as part of the trade name might be considered to be a fanciful name which could imply extra efficacy of the product.
- 'Desonate' sounds very similar to the established name, 'desonide', and our regulations strongly discourages a trade name containing similar syllables or already approve drugs or established names."

The sponsor submitted a response to CMC's concerns in subsequent correspondences dated February 1, 2006 and March 20, 2006, and portions of their response were included in this request for consultation sent from your Division. Following discussions with your Division, we have confirmed that the sponsor will not include Hydrogel in their proprietary name. However, the sponsor states that DPSI still maintains that "Desonate is not misleading, confusing, or deceptively similar for the reasons listed in serial submission 0044 to IND 67,548 dated February 1, 2006, and consequently, would like to obtain FDA approval for Desonate". DMETS did not consider the similarity between Desonate and Desonide to be a problem because desonide is the active ingredient in Desonate. Thus, DMETS will not respond to the sponsor's request with respect to the concerns of confusion between Desonate and Desonide. We defer this review to CMC. DMETS will only review the proprietary name, Desonate, from a sound-alike and look-like perspective to other marketed products. In

reviewing Desonate, we have not identified any additional names that may have the potential for name confusion with "Desonate" since our initial review of Desonate Hydrogel.

In the review of the package insert of Desonate, we have identified the following area of possible improvement, which might minimize potential user errors.

Dosage and Administration Section: Revise the statement "Desonate (desonide gel) 0.05% should be applied..." to read "Desonate (desonide gel) 0.05% should be applied as a thin film to the affected areas two times daily and rubbed in gently."

In summary, DMETS has no objections to the use of the name, Desonate. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name Desonate acceptable from a promotional perspective. Please submit the container label and carton labeling for review and comment when available. If you have further questions or need clarification, please contact Diane Smith at 301-796-0538.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Kristina Arnwine
8/11/2006 01:22:08 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
8/11/2006 02:01:44 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/11/2006 04:07:43 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM OF TELECON

DATE: June 30, 2006

APPLICATION NUMBER: NDA 21-844

BETWEEN:

Name: Barry M. Calvarese, VP Regulatory and Clinical Affairs
David Osborne, PhD, VP Product Development
Charles G. Chavdarian, PhD, Senior Director, Analytical Services
Phone: 1-800-561-4946 Pass: 361249
Representing: Skin Medica

AND

Name: Ernest Pappas, Ph.D., Review Chemist
Division of Pre-Marketing Assessment II, HFD-540
Karl Stiller, Regulatory Health Project Manager
Division of Pre-Marketing Assessment III

SUBJECT: Clarification request related to the Chemistry section of the NDA submission; agglomeration and homogeneity in-process testing.

FDA contacted Skin Medica for clarification and further explanation of Steps [redacted] as shown in Figure 2.3.P.3.3.1.1, Desonide Gel 0.05% Manufacturing Process Schematic Flow Chart for Registration Batches ([redacted]) and Commercial Batches ([redacted]). Specifically, explanation as to the absence of microscopic testing for agglomeration and the absence of a potency assay to ensure homogeneity was requested.

Step [redacted] states " [redacted] ". The FDA asked if a microscopic examination of the product at this point was feasible in order to verify the absence of agglomerates. Skin Medica stated that in Step [redacted]

[redacted] Skin Medica stated that desonide is very [redacted]

[redacted]

[redacted] (containing Purified Water, Edetate Disodium Dihydrate, glycerine and Carbopol 981).

Skin Medica stated that " [redacted] "

FDA stated that the reasoning given for Steps [redacted] was clear. Skin Medica offered to send a

desk copy of Sections 2 and 3 with a cover letter detailing the location therein of the rationale for the manufacturing process. FDA thanked Skin Medica, and the teleconference was concluded.

{See appended electronic signature page}

Moo Jhong Rhee, PhD.
Branch Chief
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Karl Stiller
7/6/2006 01:07:37 PM
PROJECT MANAGER FOR QUALITY

Moo-Jhong Rhee
7/7/2006 02:52:26 PM
CHEMIST
Chief, Branch III

REQUEST FOR CONSULTATION

TO (Division/Office):
DDRE, HFD-430

FROM: Shalini Jain, Regulatory Project Manager

DATE
05/11/06

IND NO.

NDA NO.
21-844

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
12/21/05

NAME OF DRUG
Desonide Gel 0.05%

PRIORITY CONSIDERATION
S

CLASSIFICATION OF DRUG
3

DESIRED COMPLETION DATE
PDUFA Goal Date: 10/21/06

NAME OF FIRM: SKINMEDICA

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
X OTHER (SPECIFY BELOW): (PPI, Carton/Container, PI) |
|--|--|--|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

-
- TYPE A OR B NDA REVIEW
-
-
- END OF PHASE II MEETING
-
-
- CONTROLLED STUDIES
-
-
- PROTOCOL REVIEW
-
-
- OTHER (SPECIFY BELOW):

-
- CHEMISTRY REVIEW
-
-
- PHARMACOLOGY
-
-
- BIOPHARMACEUTICS
-
-
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

-
- DISSOLUTION
-
-
- BIOAVAILABILITY STUDIES
-
-
- PHASE IV STUDIES

-
- DEFICIENCY LETTER RESPONSE
-
-
- PROTOCOL-BIOPHARMACEUTICS
-
-
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

-
- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
-
-
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
-
-
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
-
-
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

-
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
-
-
- SUMMARY OF ADVERSE EXPERIENCE
-
-
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

See Sponsor comments below: (this was received as an eCTD and is in EDR)

DPSI sent in the initial request for review of the Desonate trade name in Serial Submission 0037 to IND 67,548 dated 19 April 2005. DPSI received comments from the Agency on 12 December 2005 and replied to the comments in Serial Submission 0044 to IND 67,548 dated 01 February 2006.

DPSI then submitted the trade name to NDA 021844 in Sequence Number 0002 dated 20 March 2006 and respectfully requested a response to the proposed trade name by 03 April 2006.

DPSI has taken all Agency comments into consideration in determining its recommendation for a trade name for Desonide Gel 0.05%. DPSI has decided to remove the word "HydroGel" from the trade name.

DPSI still maintains that "Desonate" is not misleading, confusing, or deceptively similar for the reasons stated in Serial Submission 0044 to IND 67,548 dated 01 February 2006 and, consequently, would like to obtain FDA approval for:

Desonate™ (desonide gel) 0.05%

DPSI started the request for trade name review over a year ago because our packaging lead time and promotional campaign is predicated upon this singular name. For the commercial realities involved in launching a product (lead time to print, etc.), we would like to proceed to develop our packaging and promotional launch materials. If we wait any longer, we will suffer commercial harm due to the delays imposed by the FDA. DPSI acknowledges the importance of this review and would appreciate that if the FDA has any objections to our position, we respectfully request that it be made as soon as possible.

Can you please give us an update on the status of the review?

Note:

The sponsor SKINMEDICA is working with Dow Pharmaceuticals (DPSI)

SIGNATURE OF REQUESTER Shalini Jain	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL DFS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Shalini Jain

5/11/2006 07:47:14 PM

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

FROM: Shalini Jain, Regulatory Project Manager

DATE
05/11/06

IND NO.

NDA NO.
21-844

TYPE OF DOCUMENT
original NDA

DATE OF DOCUMENT
12/21/05

NAME OF DRUG
Desonate Hydrogel (
Desonide gel 0.05%)

PRIORITY CONSIDERATION
S

CLASSIFICATION OF DRUG
3

DESIRED COMPLETION DATE
PDUFA GOAL DATE
10/21/06

NAME OF FIRM: SKINMEDICA

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

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CLINICAL

PRECLINICAL

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Can you please give us an update on the status of the review?

PDUFA DATE: 10/21/06

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA

HFD- /Division File

HFD- /RPM

HFD- /Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER

Shalini Jain

301-796-0692

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

5/28/05

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/s/

Shalini Jain
5/11/2006 07:40:36 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-844

Dow Pharmaceutical Sciences
Attention: Barry M. Calvarese, MS
Vice President, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954-1169

Dear Mr. Calvarese:

Please refer to your December 19, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Desonide Gel, 0.05%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 30, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry and Manufacturing Controls:

1. A statement regarding facilities' readiness for inspection was not provided.
2. It is noted in the label/labeling section that the dosage form "gel" is not included in the proposed established name for the drug product, and the word "HydroGelTM" appears as a part of the trade name. The word "HydroGelTM" may not be acceptable as a part of the trade name.

Pharmacology/Toxicology:

A comprehensive timeline for the conduct of the nonclinical studies to evaluate the dermal carcinogenic and photo-carcinogenic potential of desonide gel, 0.05%, as post marketing commitments was not submitted.

Biostatistics:

The details of the calculations for the confidence intervals for the noninferiority comparisons in Study 7001-G3HP-04-03 need to be clarified.

We also request that you submit the following information:

Chemistry and Manufacturing Controls:

1. Please provide a statement regarding facilities' readiness for GMP inspection.
2. The proper dosage form nomenclature for the proposed drug product is "gel". Therefore, the word "Gel" should be a part of the established name for the proposed drug product. Please submit labeling incorporating the proper dosage form nomenclature of "gel".

Pharmacology/Toxicology:

Please provide a comprehensive timeline for conduct of the nonclinical studies to evaluate the dermal carcinogenic and photoco-carcinogenic potential of desonide gel, 0.05%, as postmarketing commitments (i.e., conduct of dose range finding studies, submission of nonclinical protocols, initiation of studies and submission of final study reports).

Biostatistics:

Please submit details (such as the exact formulas) of how the Wald's confidence intervals with Yates' continuity correction were calculated in Study 7001-G3HP-04-03.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Maria M. Anderson, Regulatory Project Manager, at (301) 796-2110.

Sincerely yours,

{See appended electronic signature page}

Stanka Kukich, M.D.
Acting Division Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Stanka Kukich

2/28/2006 01:09:52 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 2/16/06

For Maria Anderson

To: Barry Calvarese

From: Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff

Company: Dow

Division of Dermatology & Dental Products

Fax number: 760 448-3615

Fax number: (301) 796-9894/9895

Phone number: 707 793-2600

Phone number: (301) 796-2110

Subject: NDA 21-844 Chemistry Information Request

Total no. of pages including cover:

Please provide the formulation composition, formulation #, and lot # for the drug product batches used in the Phase 3 pivotal clinical studies. If the information has already been provided in the NDA, please point out where it is.

Document to be mailed:

YES

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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/s/

Mary Jean Kozma Fornaro
2/16/2006 10:10:19 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-844 Supplement # NA Efficacy Supplement Type SE-

Trade Name: Desonate Hydrogel
Established Name: Desonide gel
Strengths: 0.05%

Applicant: Skin Medica
Agent for Applicant: Dow Pharmaceuticals

Date of Application: December 19, 2005
Date of Receipt: December 21, 2005
Date clock started after UN: NA
Date of Filing Meeting: January 30, 2006
Filing Date: February 19, 2006
Action Goal Date (optional): NA

User Fee Goal Date:
October 21, 2006

Indication(s) requested: atopic dermatitis

Type of Original NDA: (b)(1) (b)(2) x
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S x P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES x NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health) X
12/20/05

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO
NA

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- ****Need foreign applicant signature**
Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? ALL AND REQUIRED PAPER FORMS SUBMITTED IN HARD COPY

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- | | | | | | | |
|-----------------------------------|-----|--------------------------|-----|-------------------------------------|----|--------------------------|
| • Is it an electronic CTD (eCTD)? | N/A | <input type="checkbox"/> | YES | <input checked="" type="checkbox"/> | NO | <input type="checkbox"/> |
|-----------------------------------|-----|--------------------------|-----|-------------------------------------|----|--------------------------|
- If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments: VERIFIED

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X [NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
**** NEED FOREIGN APPLICANT SIGNATURE**

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
SIGNED BY APPLICANT

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y X NO
- PDUFA and Action Goal dates correct in COMIS? YES X NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. YES

- List referenced IND numbers: 67548

- End-of-Phase 2 Meeting(s) Date(s) NOVEMBER 20, 2003 NO
 If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) REQUESTED BUT CODED AS GUIDANCE: FEBRUARY 10, 2005 NO
 If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES X NO
 If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
 WILL CONSULT AFTER FILING MTG YES X NO
- Risk Management Plan consulted to ODS/IO? N/A X YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y X NO
 WILL CONSULT AFTER FILING MTG
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A X YES NO

If Rx-to-OTC Switch application: NOT APPLICABLE

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO NA

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
CHEMISTRY REVIEWER WILL INITIATE
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT

MEMO OF FILING MEETING

DATE: JANUARY 30, 2006

BACKGROUND: Desonide first approved in the 1970s for treatment of steroid responsive dermatoses. Topical formulations that are approved and available are cream, ointment, and lotion. This application is a gel formulation and studied a pediatric population for treatment of atopic dermatitis.

ATTENDEES: Mary Jean Kozma Fornaro, Stanka Kukich, Jill Lindstrom, Bindi Nikhar, Shalini Jain, Paul Brown, Barbara Hill, Shulin Ding, Kathleen Fritsch, Mat Soukoup.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	J. Porres/reassigned to E. Papadopoulos
Secondary Medical:	B. Nikhar
Statistical:	M. Soukoup
Pharmacology:	B. Hill
Statistical Pharmacology:	
Chemistry:	E.Pappas
Environmental Assessment (if needed):	NA
Biopharmaceutical:	T. Ghosh
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	NA
DSI:	
Regulatory Project Management:	M. Anderson
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site inspection needed? YES NO
Planned clin/stat future meeting will determine
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A x YES NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A FILE X REFUSE TO FILE

BIOPHARMACEUTICS FILE X REFUSE TO FILE

- Biopharm. inspection needed? YES NO X

PHARMACOLOGY

N/A FILE X

REFUSE TO FILE

- GLP inspection needed?

YES NO X

CHEMISTRY

FILE X

REFUSE TO FILE

- Establishment(s) ready for inspection? NEED ADDRESSES
- Microbiology

YES NO
YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- x The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- x Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. X Convey document filing issues to applicant by Day 74, March 3, 2006.

Mary Jean KozmaFornaro, Chief
Project Management Staff for Maria
Anderson

Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**APPEARS THIS WAY
ON ORIGINAL**

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
DES OWEN LOTION ANDA 72354 which used the innovator Desowen Cream N 19048 for approval via a suitability petition. (Discussed with Don Hare)

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). Dosage form is a Gel
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO x
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO x
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO x
10. Are there certifications for each of the patents listed for the listed drug(s)? All patents and exclusivity expired YES NO x
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

- Patent number(s): NO ORANGE BOOK LISTINGS
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? Patent certification states no existing patent/exclusivity
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 67548 NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?
Kim Colangelo and Racquel peat notified

YES NO

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Jean Kozma Fornaro
2/7/2006 02:11:52 PM
CSO
Regulatory Filing review & memo

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVER SHEET	Form Approved: OMB No. 0910-0297 Expiration Date: December 31, 2006.				
See Instructions on Reverse Side Before Completing This Form							
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdofa/default.htm							
1. APPLICANT'S NAME AND ADDRESS Skin Medica 5909 Sea Lion Place, Suite H Carlsbad, CA 92008	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 021844						
2. TELEPHONE NUMBER (include Area Code) (877) 944-1412	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).						
3. PRODUCT NAME Desonide Gel, 0.05%	6. USER FEE I.D. NUMBER						
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.							
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box.) </td> </tr> <tr> <td style="vertical-align: top; padding: 5px;"> <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.) </td> <td style="vertical-align: top; padding: 5px;"> <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) </td> </tr> </table>				<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)
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8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <div style="text-align: right;"> <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO </div> (See Item 8, reverse side if answered YES)							
<p>Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 </td> <td style="width: 33%; vertical-align: top; text-align: center;"> and </td> <td style="width: 33%; vertical-align: top;"> Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 </td> </tr> </table> <p style="text-align: right; font-size: small;">An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</p>				Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852					
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Vice President, Regulatory & Clinical Affairs Dow Pharmaceutical Sciences, Inc.	DATE 11/30/2005					



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 67,548

Dow Pharmaceutical Sciences
Attention: Barry Calvarese, MS
Vice President, Regulatory and Clinical Affairs
1330A Redwood Way
Petaluma, CA 94954-1169

Dear Mr. Calvarese:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Desonide Gel, 0.05%

We also refer to the meeting between representatives of your firm and the FDA on February 10, 2005. The purpose of the meeting was to discuss the briefing document submitted January 10, 2005.

The official minutes of that meeting are enclosed.

If you have any questions, call Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: February 10, 2005 **Time:** 1 PM
Location: 9201 Corporate, N225
Application: IND 67,548, Desonide Gel, 0.05%
Subject: Guidance Meeting
Meeting ID: 14441
Sponsor: Dow Pharmaceutical Sciences
Meeting Chair: Jonathan Wilkin, M.D., Division Director, DDDDP, HFD-540
Meeting Recorder: Jacquelyn Smith., Project Manager, DDDDP, HFD-540

FDA Attendees, Titles, and Office/Division:

Jonathan Wilkin, M.D., Division Director, DDDDP, HFD-540
Markham Luke, M.D., Team Leader, Dermatology, DDDDP, HFD-540
Joseph Porres, M.D., Medical Officer, DDDDP, HFD-540
Ramesh Sood, Ph.D., Team Leader, Chemistry, DNDCIII, HFD-830
Joel S. Hathaway, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DBIII, HFD-725
Mat Soukup, Ph.D., Biostatistics Reviewer, HFD-725
Shiowjen Lee, Ph.D., Biostatistics Reviewer, DBIII, HFD-725
Tapash Ghosh, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer, DPEIII, HFD-880
Jonca Bull, M.D., Director ODE V, HFD-105
Jacquelyn Smith, Regulatory Project Manager, DDDDP, HFD-540

External Constituent Attendees and Titles:

Gordon J. Dow, PharmD, Founder, Chief Technical Officer
Barry M. Calvarese, MS, Vice President Regulatory and Clinical Affairs
Charles G. Chavdarian, Ph.D., Senior Director of Analytical Services

Sarmistha Basu, Ph.D., Project Manager (via teleconference)

Ron Trancik, Vice President, Research & Development, Skin Medica
A.J. Acker, Associate Manager, Regulatory Affairs, DPS (via teleconference)
Shawna Lemke, Associate Manager, Regulatory & Clinical Affairs (via teleconference)

Dianne Denton, Executive Director, Strategic Marketing, Skin Medica

Purpose:

To provide general guidance on content and format of the investigational New Drug Application under 21 CFR 312. The briefing document provides background and questions for discussion.

Chemistry, Manufacturing and Controls:

The sponsor has provided a summary of information regarding the drug substance and drug product, as well as an outline of the stability studies currently being conducted and the projected extent of data available at the time of NDA submission. The sponsor had only one CMC-related question: "Does the outlined stability program meet with the Agency's approval?"

The planned stability protocol proposed for the NDA submission appears to be adequate. The design conforms to or exceeds the ICH recommended design. The post-approval stability plan is not adequate, however, as it does not describe the frequency of initiating stability studies. Routinely, a minimum of one lot per year of a marketed package size is expected to be placed on stability after approval, though a given product may have a higher frequency depending on its individual stability characteristics. This should be revised in the NDA submission to address this expectation.

Not all of the CMC comments from the End-of-Phase-2 meeting were addressed in this briefing package. We have the following comments:

1. The proposed drug product specification has been revised to a somewhat lower impurity level for the identified _____ impurity, but this level is still set at NMT _____ without apparent justification. CMC Response #1, regarding qualification of impurities at the specified levels, has not been submitted for CMC review. If these data have been submitted, the sponsor is asked to provide the date and page numbers of the pertinent submission. We expect that actual lot analyses of pre-clinical or clinical trial lots are necessary to qualify any specified impurity.
2. In the release specification for desonide _____ drug substance, the acceptance criterion for particle size is "mean particle size less than _____." This does not serve as a limit for maximum particle size, which we feel is important since the drug substance is _____, i.e. _____. A maximum limit for particle size should be added to this specification acceptance test.
3. In the release specification for desonide (_____) drug substance, the Related Substances tests for "any single impurity". Have any impurities been identified? If not, has any attempt been made to identify unknown impurities? Referring to _____, recurring impurities in the drug substance should be individually specified, whether identified or unidentified, and the acceptance limit justified on the basis of observed levels. This specification item should be revised to address these concerns.
4. In the release specification for Desonide Gel drug product, the acceptance criterion for particle size is "NLT _____% LTE _____ and NLT _____% LTE _____." This does not serve as a

limit for maximum particle size, which we again feel is important since the drug substance is _____, i.e. _____. A maximum limit for particle size should be added to this specification acceptance test.

Pharmacology/Toxicology:

Sponsor's Question:

Does the Agency agree that the information provided in this package is sufficient to support the 505(b)(2) filing for Desonide?

Agency Response:

The nonclinical toxicology information provided in the Pre-NDA package appears to be sufficient to support the submission of a 505(b)(2) NDA for Desonide gel, 0.05%. The adequacy of this information for filing a 505(b)(2) NDA application will be determined after submission of the NDA.

The Division recommends that the Sponsor include a timeline for conduct of the previously agreed upon Phase 4 dermal carcinogenicity study in Tg.AC mice with Desonide gel in the NDA submission.

The Division acknowledges that the Sponsor has changed their _____

_____ The Sponsor now proposes conduct of a 13 week photosafety study in rats as a phase 4 commitment. While this strategy may be acceptable, the adequacy of the proposed study will be determined after review of the study protocol. The Division recommends that the Sponsor include a timeline for conduct of the study to determine the photoco-carcinogenic potential of Desonide gel, 0.05%, (a 13-week photosafety study in rats) in the NDA submission.

Clinical Pharmacology & Biopharmaceutics:

Sponsor's Question:

Does the Agency require an electronic version of the data (SAS data set) contained in the report from phase 2 clinical study, "A Multi-Center, Open Label Evaluation of the Adrenal Suppression Potential of Topically Applied Desonide Gel 0.05% in Pediatric Subjects with Moderate to Severe Atopic Dermatitis?"

Agency Response:

Skin blanching (vasoconstriction) and HPA-axis suppression study results will be reviewed in detail during NDA review. Electronic data set for these studies will be helpful. The sponsor is

requested to include line listings of amount of drug used and involved body surface area of each patient in these studies.

The sponsor also needs to address the systemic exposure of Desonide and its metabolites following application of final market formulation of Desonide Gel, 0.05% under maximal usage condition in the target patient population.

Clinical:

Sponsor's Question 1:

On March 10, 2004 the clinical reviewer sent the following comment: **"Efficacy: to be determined as success, patients who at baseline present a PGS score = 2 need to present at the end of treatment a PGS score = 0, and patients who at baseline have a PGS score = 3 need to have at the end of treatment a PGS score = 0 or 1."**

The Sponsor believes that this more rigorous definition is now the primary endpoint and that non-inferiority has been established in the ITT group at the 2-week time-point. Is this acceptable?

Agency Response:

No, this type of analysis was not pre-specified. Per the protocol, pre-specified time to assess efficacy is after 4 weeks of treatment. The criteria for determination of success, as described by the sponsor, is to be applied at 4 weeks, rather than at 2 weeks.

The sponsor stated plans to conduct an additional 4-week vehicle controlled study, which would be acceptable.

Sponsor's Question 2:

The safety profile of Desonide gel 0.05% as shown in the Phase 3 study and the HPA Axis study is comparable to that of the Reference product. The Phase 3 study was well designed and executed. This study provides strong support for the safety and efficacy of Desonide gel 0.05% in the treatment of mild to moderate atopic dermatitis in children. Given the relatively large sample sizes of this study and the significant superiority of a 4-week dosing regimen compared to a 2-week regimen, a second independent pivotal trial demonstrating efficacy compared to placebo would appear superfluous. If a second Phase 3 study were conducted comparing Desonide gel 0.05% to vehicle and the same trend of superiority of 4-week treatment compared to 2-week treatment is maintained, is a 4-week treatment labeling claim achievable?

Sponsor's Question 3:

Does the Agency agree that the clinical data presented are adequate to support the filing of a 505(b)(2) application for Desonide?

Agency Response (Questions 2 & 3):

The clinical informational needs for an NDA are as follows (whether the application is a 505(b)1 or a 505(b)2):

a) Dermal safety studies with the final to-be-marketed drug product, of which you have conducted a combined irritation/sensitization study. As desonide gel, 0.05% absorbs light in the

UVB spectrum, photoirritancy and photosensitization studies will be needed on NDA submission. The results of the topical safety study should be reported as line listings and as the number of patients experiencing a positive reaction, rather than the cumulative index.

b) HPA suppression study with the final to-be-marketed drug product. Systemic levels should also be determined in such a study (see comments above under Clinical Pharmacology).

c) Pivotal safety and efficacy studies conducted with the final to-be-marketed drug product (see below).

If the application is submitted as a 505(b)1 two independent studies demonstrating superiority to vehicle at the pre-specified time of assessment. In the second Phase 3 vehicle controlled study, the investigators, centers, and patients should be different from those who participated in previous studies of desonide gel.

If the application is submitted as a 505(b)2 with a bridge for both safety and efficacy:

One multi-armed study (product, vehicle, and reference listed drug product) demonstrating superiority to vehicle and non-inferiority to a reference listed product at the pre-specified time of assessment. (A small ersatz vehicle for the reference listed drug product may also be included for blinding purposes if desired.) If the pre-specified time of assessment is 4 weeks, to achieve a labeling claim of 4 weeks the assessment should be conducted at 4 weeks.

If the application is submitted as a 505(b)2 with a bridge for safety only:

Two independent studies demonstrating superiority to vehicle at the pre-specified time of assessment are needed. In addition, a comparative bridging study to the reference listed product demonstrating lack of superiority is needed to allow the Agency to use its findings for local safety for the reference listed product. The study to compare to the reference listed product may be incorporated into the study design for one of the two pivotal clinical studies if desired. Also, systemic safety may be inferred if an HPA axis suppression study and/or desonide blood levels comparing test and reference products show no greater systemic exposure with your test product.

Sponsor's Question 4:

Does the Agency agree that the proposed formats for line listings, draft table, and statistical plan for the Phase 3 study are adequate?

Agency Response:

The Biostatistical plan should agree with the pre-specified plan for primary analysis (please see Biostat comments below).

The summary tables of the subject baseline data in your proposed amended statistical plan omit the total signs and symptoms scores. It is recommended that your line listings include the signs and symptoms scores at baseline, at Week-2, and Week-4 (with individual signs & symptoms and total).

Please include in the list of ITT patients a column indicative of the number of treatment applications for each patients. Patients who were dispensed medication but never used it should be listed here with treatment applications = "0"

The Sponsor should provide site-breakdown of the data from the pivotal multicenter study.

It is recommended that the Sponsor provide efficacy and safety subset analysis for each of the following populations in their studies:

- a) Racial background
- b) Age Groups (including pediatric and geriatric)
- c) Gender

Sponsor's Question 5:

A total of approximately 319 patients with atopic dermatitis and 257 healthy subjects will have been exposed to Desonide Gel, 0.05%, during the clinical development program. Do 319 subjects with atopic dermatitis exposed to Desonide Gel, 0.05%, for 4 weeks provide sufficient exposure to support the safety of the proposed new product?

Agency Response:

The Sponsor should describe how long term safety evaluation is to be addressed by the studies conducted or data available. The Sponsor is reminded of **ICH E1A** guidelines for chronic use products.

The sponsor could extend the new Phase 3 trial beyond the 4 weeks to provide long term safety data for review.

To support the long term safety, the sponsor may supply for review data from the open public literature or other sources. Then a determination could be made as to whether other studies could be needed.

Sponsor's Question 6:

Does Dow plan to submit only the case report forms of patients who died, experienced a serious adverse event, discontinued the study due to an adverse event, or who dropped from the Phase 3 study. Does the Agency find this acceptable?

Agency Response:

The case report forms of patients who died, experienced serious adverse events, discontinued the study for any reason should be submitted for all studies conducted in support of this NDA rather than just from Phase 3 studies. The Sponsor should provide annotated Case Report forms with the data sets.

Per patient line listings should be provided for all reports of serious adverse events in addition to the case reports.

Additional Clinical Comments:

Please clarify whether the Phase 3 clinical study and the dermal safety studies were conducted with the final to-be-marketed product

The Sponsor should provide any investigator training materials.

The PDF documents should be editable rather than image based.

It would be helpful to the reviewer if the Sponsor would also provide MS Word files of the proposed label.

In a new Phase 3 vehicle-controlled study, the inclusion criteria could be an IGA score of "moderate." There should be congruence between the entry criteria of "moderate" and the baseline signs and symptom scores for the secondary endpoints.

Biostatistics:

Sponsor's Question 4:

Does the Agency agree that the proposed formats for line listings, draft table, and statistical plan for the Phase 3 study are adequate?

Agency Response:

The formats of draft table and statistical plan for the Phase 3 trial are generally acceptable. Please refer to clinical comments for the format of line listings.

The following are statistical comments concerning the meeting briefing.

1. Comments on the primary efficacy endpoint and non-inferiority margins which were conveyed to the sponsor before:
 - a. The Division's recommended primary efficacy endpoint is the proportion of patients with "clear" or "almost clear" at Week 4 in Investigator's Global Severity Score that has at least a 2-point improvement from baseline.
 - b. For non-inferiority assessment of Desonide Gel to Desowen Lotion with respect to the primary efficacy endpoint, the Division had made comments that the proposed non-inferiority margin of 10% was equivalent to maintaining only about 33% of treatment efficacy over vehicle with the sponsor's assumption about the expected success rates of 20% vs. 5% for active vs. vehicle (EOP-2 meeting and SN-008). The Division had recommended that the sponsor consider a smaller non-inferiority margin and re-calculated the sample size needed for the trial.

For non-inferiority assessment with respect to the secondary efficacy endpoints, the sponsor used a margin of 15%. The Division had requested the sponsor to provide the justification for using different non-inferiority margins, and estimates of treatment effect for the secondary efficacy endpoints at the IND stage (7/15/04 and 10/19/04).

However, no information was received from the sponsor concerning these points.

2. If the sponsor plans to submit an NDA, please include the following items in the NDA:
 - a. For the dichotomized Investigator's Global Severity Score, efficacy results by imputing missing at week 4 as failures in one analysis and as successes in another analysis.
 - b. Subgroup results for the primary and secondary efficacy endpoints by race, where race is categorized according to the Guidance, but not White vs. non-White.

- c. For the Phase 3 trial, please also submit copies of
- original study protocol and amendments;
 - original randomization list generated prior to the start of the study;
 - list of ITT patients with treatment assignment and time/date of enrollment for each individual according to patient's ID.
 - electronic SAS data sets in transport file format and, SAS data dictionary that describes the variables used in the data sets.

Project Management:

1. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.
2. The Sponsor is reminded to please submit appropriate patent certification at the time of NDA submission.
3. Comments shared today with the Sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the NDA might identify additional comments or informational requests.

**APPEARS THIS WAY
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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jonathan Wilkin

3/10/05 01:43:35 PM

MEMORANDUM OF MEETING MINUTES



Meeting Date: November 20, 2003 **Time:** 10:00 AM
Location: 9201 Corporate, N225 **Meeting ID:** 11641
Topic: IND 67,548, Desonide Gel, 0.05%
Subject: End-of-Phase 2 Meeting
Sponsor: Dow Pharmaceutical Sciences
Meeting Chair: Jonathan Wilkin, M.D., Division Director, DDDDP, HFD-540
Meeting Recorder: Jacquelyn Smith., Project Manager, DDDDP, HFD-540

FDA Attendees:

Jonathan Wilkin, M.D., Division Director, DDDDP, HFD-540
Markham C. Luke, M.D., Ph.D., Team Leader, Clinical, DDDDP, HFD-540
Joseph Porres, M.D., Clinical Reviewer, DDDDP, HFD-540
Michael Albert, M.D., Clinical Reviewer, DDDDP, HFD-540
Wilson DeCamp, Ph.D., Team Leader, Chemistry, DNDCIII, HFD-830
Mohamed Alish, Ph.D., Team Leader, Biostatistics, DBIII, HFD-725
Shiowjen Lee, Ph.D., Biostatistician, DBIII, HFD-725
Dennis Bashaw, Pharm.D./Team Leader, Pharmacokinetics, DPEIII, HFD-880
Barbara Hill, Ph.D./Pharmacology Reviewer, DDDDP, HFD-540
Jiaqin Yao, Ph.D., Pharmacology Reviewer, DDDDP HFD-540
Jonca Bull, M.D., Director, ODE V, HFD-105
Terri Rumble, R.N., B.S.N, Associate Director of Regulatory Affairs, ODE V, HFD-105
Jacquelyn Smith, Regulatory Project Manager, DDDDP HFD-540

Sponsor Attendees:

Gordon J. Dow, PharmD, Founder, Chief Technical Officer
Karl Beunter, M.D., Ph.D., Chief Medical Officer (via teleconference)
Barry M. Calvarese, MS, Vice President Regulatory and Clinical Affairs
Charles G. Chavdarian, Ph.D., Senior Director of Analytical Services
Elena Serbinova, Ph.D., Associate Director of Regulatory Affairs

Dianne Denton, Executive Director, Strategic Marketing, Skin Medica
Sarmistha Basu, Ph.D., Project Manager (via teleconference)

Purpose:

To provide general guidance on content and format of the investigational New Drug Application under 21 CFR 312. The briefing document provides background and questions for discussion.

Chemistry, Manufacturing and Controls:

Sponsor's Question #1:

Does the Agency agree with the proposed CMC plan?

Agency Response: Yes, subject to your response to the following comments regarding your briefing package:

1. The proposed regulatory specifications and methods for desonide gel, 0.05% (briefing book, Table 1.7; pg. 13) reported limits for the degradation products _____, individual unknowns, and total unknowns, as NMT _____%, NMT _____%, and NMT _____%, respectively. These limits appear to be too high. Per Guidance for Industry (Q3B, "Impurities in New Drug Products"), these impurities should be adequately tested and qualified during the product development to assure their safe use during the clinical studies. The acceptance criteria in the specification should be related to the level at which each impurity is qualified.

Sponsor Response:

The impurities will be qualified at the stated levels by the time of the NDA submission.

FDA Response:

This is not necessarily satisfactory. We will defer to the pharmacology reviewer on the timing of such a submission, since this qualification data may be needed earlier, possibly prior to the phase 3 studies.

2. The stability protocol plan as submitted in the briefing package (item 1.8.2, pp. 13-17) should be followed for the primary stability batches. It appears that the results of the stability data as reported in the IND submission (Vol. 1; pg. 0239) for the desonide gel, 0.05% for use in Phase I/II clinical studies to support of the NDA filing, did not follow this stability protocol. Specifically, two batches (#742 and #743), were not assayed for _____ and other related degradants. In this regard, these data should not be considered as your primary stability batches; only the stability data as collected per your stability protocol in the briefing package are considered as the primary stability batches.

Sponsor Response:

The stability protocol has been amended. The data on the referenced batches does include the degradants.

Additional CMC Comments from the IND:

1. A page is missing in Volume 1 (original IND submission, between pgs. 0147 and 0148).
2. The drug substance specification listed related substances for a single impurity (original IND, vol. 1, pg. 144, Table 7.2) as NMT _____%. This specification does not

conform to the USP requirements for reporting unlabeled impurities in excess of 0.1% when a chromatographic method is used.

Sponsor Response:

They recognize the USP requirement for unlabeled impurities. A revised specification will be submitted shortly.

3. During phase 3, please clarify the in-process control for the pH stated in the original IND submission (vol. 1, pg. 147). This should be related to the pH required for the stability of the _____ in the drug substance. This will assist in establishing the criticality of this parameter.
4. Please consider adding an in-process control at the end of step 3 of the manufacturing procedure (vol. 1, pg. 147) for the _____ since the manufacturing step indicates that " _____ "
5. Please note that CDER has a Data Standards Manual that provides definitions and standards for dosage form descriptions, in addition to the dosage form descriptions published in USP. An effort is currently under way to develop a unified set of terms to be used in describing topical dosage forms, along with objective criteria for their determination. We recommend that you keep abreast of these efforts, which were discussed at a meeting of the Advisory Committee for Pharmaceutical Sciences on March 12, 2003. Ultimately, this work may require revision to the labeling description of your dosage form.

Sponsor Response:

They believe their product is a gel. Is this comment just advisory?

FDA Response:

Our purpose is only to keep you informed of our ongoing efforts (in collaboration with USP) to establish objective and consistent criteria for dosage form descriptions.

6. In our telecon on August 7, 2003, we committed to provide you with comments on your stability protocol dated July 11, 2003, and included in your submission of August 4, 2003. Our comments are:
 - The testing of the _____ g size at _____ months at both _____ indicated that testing for assay and degradation compounds (_____) is optional; this testing should be routine.
 - The testing schedule for the 15g and 60g sizes appears adequate to support your proposed expiration, depending upon our review of the data.
7. Your bracketing proposal as described in your August 4 submission is acceptable.

Pharmacology/Toxicology:

Pharmacology/Toxicology Question 2:

The following toxicology tests were conducted with the proposed new formulation:

- Primary eye and skin irritation studies in rabbits
- Primary eye irritation studies in rabbits
- *In Vitro* Bacterial Reverse Mutation Assay

- *In Vitro* Mammalian Cell Gene Mutation Test
- *In Vivo* Mammalian Erythrocyte Micronucleus Test

Summaries from these studies are included in this document. The Agency agreed with Dow's proposal to use nonclinical pharmacology and toxicology data available from the literature (using Medline and Toxline databases) for Desonide to support the registration of this product.

Does the Agency agree that the information provided in this package is sufficient enough to support the 505(b)(2) NDA filing for Desonide Gel 0.05%?

Pharmacology/Toxicology Response to Question 2:

- 1) No carcinogenicity studies have been conducted for desonide. Treatment of corticosteroid responsive dermatoses is considered a chronic indication. Therefore, a dermal carcinogenicity study for desonide gel is recommended as a phase 4 commitment. The sponsor is referred to the existing ICH guidelines (ICH-S1A, ICH-S1B, ICH-S1C, ICH-S1C(R)) and CDER guidance for industry (Carcinogenicity study protocol submissions) available that discuss recommendations for conduct of carcinogenicity studies.
- 2) No studies have been conducted to determine the photoco-carcinogenic potential of desonide gel. Treatment of corticosteroid responsive dermatoses is considered a chronic indication to a sun exposed treatment area. Therefore, a study to determine the photoco-carcinogenic potential of desonide gel is recommended as a phase 4 commitment. The sponsor is referred to the CDER guidance for industry titled "Guidance for Industry - Photosafety testing" for additional guidance.
- 3) The need for the recommended dermal carcinogenicity study for desonide gel and the study to determine the photoco-carcinogenic potential of desonide gel can be waived only if it is determined that potential safety concerns for desonide gel would limit its use so that it is not used chronically. In this case, the desonide gel label would need to contain appropriate restriction guidelines for the potential safety concerns.
- 4) These recommendations have been previously relayed to the sponsor via fax on 7-16-03 after review of the original IND submission. The sponsor did not provide their plan to address these recommendations in the briefing package. It is requested that the sponsor inform the division of their plan to address these recommendations prior to an NDA submission.

Discussion during the meeting:

The Sponsor stated that they accept the Pharmacology/Toxicology recommendations. The Sponsor informed the Division that they did not submit their plan to address the dermal carcinogenic potential and photoco-carcinogenic potential of desonide gel, 0.05% in the End of Phase 2 briefing package because these studies would be Phase 4 commitments. The Sponsor inquired whether conduct of the dermal carcinogenicity study in a transgenic animal model would be acceptable. The Division informed the Sponsor that their proposal would be acceptable and requested that the Sponsor submit their plan to the IND for evaluation. The Sponsor stated that they will submit their plan to the IND prior to the NDA submission.

The Sponsor informed the Division that they would like to conduct a _____

Biopharmaceutics:

In the current package the sponsor does not address the in vivo biopharmaceutic needs of this application that were outlined during the Pre-IND meeting in 2001. The sponsor should provide an update on the status of both the requested vasoconstrictor and HPA axis trials for this product.

Clinical:

Clinical Question 3. The sponsor is proposing a Phase 3 non-inferiority study comparing Desonide Gel 0.05% to the reference listed drug (RLD) DesOwen Lotion. The proposed protocol is provided in Attachment 1-4.

Does the Agency find the design of this study acceptable to support a 505(b)(2) NDA.?

Agency Response:

To obtain the indication "corticosteroid-responsive dermatosis", a pivotal study in atopic dermatitis and another in psoriasis will be needed.

During the meeting, the Sponsor clarified that only the indication of "atopic dermatitis" is being pursued.

The proposed protocol seems generally appropriate for a Phase 3 study.

The following are comments to the proposed draft protocol:

3.1. Study arms: A Desowen Lotion simulated vehicle arm may be used for blinding purposes. *During the meeting, the Sponsor clarified that a simulated vehicle arm for the RLD will likely not be added to the protocol because the investigators will be blinded to the treatment. However, the Sponsor will take this under further consideration.*

3.2. Inclusion criteria: To facilitate demonstration of efficacy, it is recommended that, for study entry, a minimum BSA involvement greater than the proposed 5% is recommended. *During the meeting, the Sponsor stated that consideration will be given to requiring a 10% BSA at baseline for study entry. The Agency suggested that, to facilitate demonstration of efficacy, a minimum score for erythema, induration, and oozing/crusting be required for study entry. In any case, no patient should be enrolled that could be defined as success at baseline.*

3.3 Exclusion criteria:

3.3.1 It is recommended that patients who have taken antihistamines within 1-2 weeks prior to study entry be excluded because their effect may interfere with assessment of efficacy. *During the meeting it was further clarified that the use of antihistamines would make it difficult to make claims on efficacy for pruritus for desonide gel. The Sponsor clarified that pruritus will not be evaluated as an efficacy endpoint.*

3.3.2. Please provide a rationale for excluding patients who previously failed topical steroid therapy. Phase 3 studies should mimic clinical use and accept "all comers" except when safety reasons would dictate otherwise.

4. Treatment: Please identify the amount of medication to be dispensed to each patient and, to assess actual use, provide for weighing of returned unused medication.

Clinical Question 4. The reference listed drug (RLD) in the proposed Phase 3 non-inferiority study is DesOwen Lotion. The proposed primary endpoint for this study is Desonide Gel 0.05% non-inferior to DesOwen Lotion in the percent of subjects who clear (Score=0) or almost clear (Score=1) at Week 2, as judged by a 0-5 point dichotomized Evaluator's Global Severity Scale.

Does the agency agree with this endpoint?

Agency Response:

- 4.1 During the meeting the Agency clarified that, as specified in the protocol, the primary endpoint for this study is that desonide gel 0.05% should be superior to its own vehicle and non-inferior to DesOwen Lotion in the percent of subjects who clear (Score=0) or almost clear (Score=1) at Week 2, as judged by a 0-5 point dichotomized Evaluator's Global Severity Scale.
- 4.2 The use of the EASI score as a secondary efficacy criteria is not acceptable. The assessment of the individual signs and symptoms would be a more valid reflection of actual disease activity. The following are recommended: erythema, induration, and oozing/crusting.

Clinical Question 5. The Sponsor is proposing to include a claim of _____ properties for Desonide Gel 0.05% in the Description section of the package insert stating "Desonide Gel 0.05% is a _____ aqueous gel suitable for use in adults and children (3 months of age or older). In addition to its _____, Desonide Gel 0.05% possesses _____ properties". In order to substantiate this claim, the Sponsor is proposing to conduct two studies in patients with mild to moderate atopic dermatitis: i) a Controlled Usage Study to evaluate vehicle effects on _____ using _____ measurements, and ii) a biophysical assessment of the _____ potential of Desonide Gel Vehicle.

Do these two studies support inclusion of a _____ claim in the package insert for Desonide Gel 0.05%?

Agency Response:

5.1 _____ itself is a cosmetic rather than clinical claim. It would be difficult to design a study to support a _____ claim unless the can identify the ingredient responsible for the effect, and can design a protocol to demonstrate such effect and its contribution in the treatment of atopic dermatitis.

During the meeting the Sponsor clarified further that the intent was to indicate in labeling that the gel formulation (which are usually considered to be _____) was not _____. The Agency indicated that the _____ effect should be evaluated during clinical trials as part of adverse events. Patients should be evaluated for dry skin or xerosis as part of the side effects (local safety) of the medication (for both the product and vehicle).

5.2 _____ is not a recognized medical claim. The Sponsor was referred to 21 CFR 201.57(c).

5.3 The Sponsor was referred to 21 CFR 201.10: Drugs; misleading statements:
(c) The labeling of a drug may be misleading by reason (among other reasons) of:

(4) The featuring in the labeling of inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation.

5.4 ~~_____~~ study will not mitigate local safety evaluations for _____ and would not have regulatory utility.

5.3 Protocols provided as a synopsis do not provide sufficient detail for the Agency to offer comments.

5.4 Claims of multiple clinical effects. If you are considering claiming multiple effects, the drug product may need to be considered as a "combination" and the contribution of each vehicle ingredient would need to be assessed, as described in 21 CFR 300.50(a)(1).

Additional Clinical Comments:

For the NDA, the following will be needed:

1. Topical clinical safety studies of irritancy and sensitization.
2. HPA suppression studies. *As an action item from the meeting, the item was discussed internally and it was determined that for the desonide containing drug product, the study could begin with children in the age 3-6 years old, and then progress to the next lower age group, adding appropriate safety measures as needed. The HPA axis suppression data may be extrapolated to older patients. It is recommended the duration for the HPA suppression study be four weeks. Further recommendations are included as an addendum below.*
3. Atopic dermatitis is considered a chronic condition affecting primarily children. For this type of indication long term safety studies on sufficient numbers of patients are needed, as per ICHE1a. This information could be derived from an open study, continuing treatment on patients enrolled for the Phase 3 pivotal trial.
4. It is recommended that the non-inferiority margin be reduced, in agreement with the Agency, to allow for a 10% margin.

During the meeting, the Sponsor considered extending the treatment to 4 weeks to facilitate demonstration of efficacy. The Sponsor further stated that, at this time, they were unable to adequately evaluate the relative efficacy of their product. The Agency commented that a comparative Phase 2 study may help to obtain an idea of the effect, and to select the appropriate sample size for pivotal trials.

[Addendum:

The RLD should be used as per labeling, and therefore, the treatment during efficacy studies should be for 2 weeks.]

To facilitate review of submissions, include Word (or other editable) type documents for the protocols which are being submitted.

The comments provided here are based on the brief submitted for this meeting. Please submit an SPA of the final protocol to obtain additional comments from the Agency.

Please identify the IRB and investigators, and provide a copy of the consent form.

[Addendum: The following are additional recommendations for the conduct of HPA suppression studies:

The following information should be collected and submitted to the Agency:

- 1) Each patient identified by identifier number, age, height, and weight.
- 2) The dose of cosyntropin used.
- 3) Baseline cosyntropin test results (pre-dose and 30 minute post-dose serum cortisol concentrations). *Baseline concentrations of cortisol both before and after cosyntropin administration must be in the normal range, i.e. potential study subjects who have previously been receiving corticosteroid therapy, and who demonstrate evidence of HPA axis suppression at baseline/screening, should be excluded from a clinical trial designed to assess the impact of a new corticosteroid drug product on the HPA axis. – Before such patients may be studied, the previously administered corticosteroid must be tapered and recovery of the HPA axis documented by cosyntropin stimulation testing prior to study entry.* Any concomitant medications which may affect cortisol levels of the accuracy of measurement should be noted.
- 4) End-of-treatment (and intermediate-time-point, as appropriate) cosyntropin testing results. *See below regarding repeated administration of cosyntropin in the same subjects.*
- 5) Demonstration of recovery of the HPA axis in patients with abnormal cosyntropin stimulation testing during and/or after conclusion of the study.
- 6) Precise time intervals between cosyntropin stimulation and blood draw for cortisol measurements (alternatively, cosyntropin stimulation clock time and blood draw clock time could be recorded).
- 7) Name and address of laboratory along with laboratory reference values for baseline cortisol concentrations (and stimulated concentrations, if listed).
- 8) For dermatologically applied topical corticosteroids, information about the percent body surface area applied and frequency of application. *Topical corticosteroids for treatment of steroid-responsive dermatoses should be studied in patients with diseased skin.*

Strict adherence to dosing and timing of cosyntropin administration and blood drawing is important; any deviations during the study need to be described. Cosyntropin administration and blood draws for serum cortisol should be performed as labeled, i.e. at baseline and 30 minutes after stimulation.

Administration of cosyntropin to the same subject repeatedly at intervals less than four weeks may result in higher stimulated cortisol levels after each successive cosyntropin injection, leading to invalid data. Evaluation of HPA axis function should be performed at baseline and at the end of treatment at a minimum. For studies longer than 4 weeks, cosyntropin testing should be performed no more frequently than every four weeks.]

Biostatistics:

Clinical Questions #3:

The sponsor is proposing a Phase 3 non-inferiority study comparing Desonide Gel 0.05% to the reference listed drug (RLD) DesOwen Lotion. The proposed protocol is provided in Attachment 1-4.

Does the Agency find the design of this study acceptable to support a 505 (b)(2) NDA?

Agency Response:

Sponsor's populations analyzed, missing data handling, and proposed statistical methods seem acceptable. The following are statistical comments in regard to the proposed Phase 3 study.

1. For blinding purpose, a 4th arm DesOwen Lotion simulated vehicle may be included in the study. This treatment arm needs not be large and does not involve in any statistical analyses.
2. With the sponsor's assumptions about the expected response rates for success in Evaluator's Global Severity score (i.e. 20% vs. 5% for active vs. vehicle), the proposed non-inferiority margin of 10% is equivalent to maintaining only about 33% of treatment efficacy over vehicle. The sponsor should consider a smaller non-inferiority margin. Consequently, sponsor's sample size/power needs to be re-calculated.
3. The use of EASI score as a secondary efficacy endpoint is not acceptable to the Division. Please see clinical comments for the secondary efficacy endpoints that are suitable for labeling.
4. Sponsor's plan of recruiting 653 patients from 20-30 study centers might not achieve the objective of minimum 10 patients per arm per center. The Division recommends that the study should be planned to enroll minimum 10 subjects per treatment arm per center to assess a meaningful center effect.
5. The sponsor indicates that a separate randomization code will be used to enroll a minimum of 280 pediatric subjects (page 55 of the protocol). Does this mean that stratification will be used? Please provide details about the randomization.

Administrative Comments:

1. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.
2. The Sponsor is encouraged to submit the protocol to the IND as Special Protocol through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review, comment and agreement, prior to study initiation.
3. Comments shared today with the Sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or informational requests.
4. The Pediatric Final Rule (21 CFR Parts 201, 312, 314 and 601; Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule) is no longer in effect and therefore the provision in the regulation allowing the FDA to grant or deny waivers/deferrals no longer exists. However, FDA still encourages sponsors to conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

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this page is the manifestation of the electronic signature.**

/s/

Jonathan Wilkin
12/15/03 12:01:39 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-844	Efficacy Supplement Type SE-	Supplement Number
Drug: Desonate™ (desonide) Gel 0.05%		Applicant: SkinMedica
RPM: Shalini Jain	HFD- 540	Phone # 301-796-0692
<p>Application Type: () 505(b)(1) (<input checked="" type="checkbox"/>) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>(x) Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p>	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 	(<input checked="" type="checkbox"/>) Standard () Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 	3	
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 	N/A	
❖ User Fee Goal Dates		
October 21, 2006		
❖ Special programs (indicate all that apply)		
<input checked="" type="checkbox"/> None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2		
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 	() Paid UF ID number	
<ul style="list-style-type: none"> • User Fee waiver 	<input checked="" type="checkbox"/> Small business () Public health () Barrier-to-Innovation () Other (specify)	
<ul style="list-style-type: none"> • User Fee exception 	() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)	
Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 	() Yes (<input checked="" type="checkbox"/>) No	

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

() Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

() Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	No
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	RPM-10/17/06

General Information

General Information	
Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	October 17, 2006
• Most recent applicant-proposed labeling	October 18, 2006
• Original applicant-proposed labeling	September 6, 2006
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	DDMAC 9/13/06, DMETS 8/8/06 & 8/25/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	none
• Applicant proposed	October 17, 2006
• Reviews	See DMETS, Chemistry and DDMAC reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	September 12, 2006 (fax)
• Documentation of discussions and/or agreements relating to post-marketing commitments	September 13, 2006
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	September 12, 2006 (fax)
❖ Memoranda and Telecons	6/30/06 & 8/17/06
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	November 20, 2003
• Pre-NDA meeting (indicate date)	February 10, 2005
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Medical Team Leader - 10/17/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	October 17, 2006
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	October 18, 2006
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	October 2, 2006
❖ Biopharmaceutical review(s) (indicate date for each review)	April 28, 2006 & September 22, 2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	September 13, 2006
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See CMC review
• Review & FONSI (indicate date of review)	See CMC review
• Review & Environmental Impact Statement (indicate date of each review)	See CMC review
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	(x) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	December 21, 2005 & August 30, 2006
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A