

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-819

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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: 07/31/08 See OMB Statement on Page 3.	
		NDA NUMBER 050819	
		NAME OF APPLICANT / NDA HOLDER Dow Pharmaceutical Sciences, Inc.	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) Clindaben Gel			
ACTIVE INGREDIENT(S) Clindamycin Phosphate, USP Benzoyl Peroxide, USP		STRENGTH(S) 1% 2.5%	
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 5,733,886		b. Issue Date of Patent 3/31/1998	c. Expiration Date of Patent 3/31/2015
d. Name of Patent Owner Gordon J. Dow Lloyd J. Baroody		Address (of Patent Owner) 1330 Redwood Way City/State Petaluma, California ZIP Code 94954-7121 Telephone Number 707-793-2600	
		FAX Number (if available) 707-793-0145	
		E-Mail Address (if available)	
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 Telephone Number	
		FAX Number (if available)	
		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 type="checkbox"/> Yes <input checked="" 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 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 type="checkbox"/> Yes <input checked="" 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 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 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) No. 17	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.) indicated for the topical treatment of acne vulgaris in patients 12 years or older
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 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.</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>12/20/07</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 checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Dow Pharmaceutical Sciences, Inc.</p>	
<p>Address 1330 Redwood Way</p>	<p>City/State Petaluma, California</p>
<p>ZIP Code 94954-7121</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>	

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 050819	
		NAME OF APPLICANT / NDA HOLDER Dow Pharmaceutical Sciences, Inc.	
<p><i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i></p>			
TRADE NAME (OR PROPOSED TRADE NAME) Clindaben Gel			
ACTIVE INGREDIENT(S) Clindamycin Phosphate, USP Benzoyl Peroxide, USP		STRENGTH(S) 1% 2.5%	
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 5,733,886		b. Issue Date of Patent 3/31/1998	c. Expiration Date of Patent 3/31/2015
d. Name of Patent Owner Gordon J. Dow Lloyd J. Baroody		Address (of Patent Owner) 1330 Redwood Way City/State Petaluma, California ZIP Code 94954-7121 Telephone Number 707-793-2600	
		FAX Number (if available) 707-793-0145	
		E-Mail Address (if available)	
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 Telephone Number	
		FAX Number (if available)	
		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 type="checkbox"/> Yes <input checked="" 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 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? Yes 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? Yes 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). Yes 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.) Yes No

2.6 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

3.2 Does the patent claim only an intermediate? Yes 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.) Yes No

4. Method of Use

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:

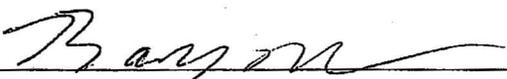
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) No. 41 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? Yes 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.) indicated for the topical treatment of acne vulgaris in patients 12 years or older

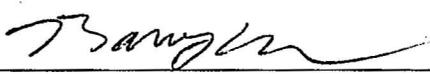
5. No Relevant Patents

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. Yes

6. Declaration/Certification	
<p>6.1 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.</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>12/20/10</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 checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Dow Pharmaceutical Sciences, Inc.</p>	
<p>Address 1330 Redwood Way</p>	<p>City/State Petaluma, California</p>
<p>ZIP Code 94954-7121</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>	

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		NDA NUMBER 050819	
		NAME OF APPLICANT / NDA HOLDER Dow Pharmaceutical Sciences, Inc.	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) Clindaben Gel			
ACTIVE INGREDIENT(S) Clindamycin Phosphate, USP Benzoyl Peroxide, USP		STRENGTH(S) 1% 2.5%	
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 6,117,843		b. Issue Date of Patent 9/12/2000	c. Expiration Date of Patent 2/18/2012
d. Name of Patent Owner Gordon J. Dow Lloyd J. Baroody		Address (of Patent Owner) 1330 Redwood Way	
		City/State Petaluma, California	
		ZIP Code 94954-7121	FAX Number (if available) 707-793-0145
		Telephone Number 707-793-2600	E-Mail Address (if available)
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 type="checkbox"/> Yes <input checked="" 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 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 type="checkbox"/> Yes <input checked="" 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 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 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 type="checkbox"/> Yes <input checked="" type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent)	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 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.)
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 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.</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>12/20/07</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 checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Dow Pharmaceutical Sciences, Inc.</p>	
<p>Address 1330 Redwood Way</p>	<p>City/State Petaluma, California</p>
<p>ZIP Code 94954-7121</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>	

EXCLUSIVITY SUMMARY

NDA # 50-819

SUPPL # N/A

HFD # 540

Trade Name: Acanya Gel

Generic Name: clindamycin phosphate 1.2% and benzoyl peroxide 2.5%

Applicant Name: Dow Pharmaceutical Sciences, Inc.

Approval Date, If Known

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?

3 years

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:

DPSI-06-22-2006-012

A Phase III, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 4-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of Clindaben (1/2.5) Gel, Clindaben Vehicle, Clindamycin (1%), and Benzoyl Peroxide (2.5%) Gels in the Treatment of Moderate to Severe Acne Vulgaris

DPSI-06-22-2006-017

A Phase III, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 4-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of Clindaben (1/2.5) Gel, Clindaben Vehicle, Clindamycin (1%), and Benzoyl Peroxide (2.5%) Gels in the Treatment of Moderate to Severe Acne Vulgaris

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"):

DPSI-06-22-2006-012 and DPSI-06-22-2006-017

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 # 41733

YES

!

!

! NO

! Explain:

Investigation #2

IND #

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?

Not Applicable

Investigation #1

!

YES

!

! NO

Explain:

! Explain:

Investigation #2

!

YES

!

! NO

Explain:

! 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: Tamika White
Title: Regulatory Project Manager
Date: September 29, 2008

Name of Office/Division Director signing form:
Title: Susan J. Walker, M.D., F.A.A.D.
Division Director, Division of Dermatology and Dental Products

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

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

/s/

Stanka Kukich
10/21/2008 03:40:06 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: NDA 50-819 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: Dermatology and Dental Products PDUFA Goal Date: 10/26/08 Stamp Date: 12/26/07

Proprietary Name: Acanya

Established/Generic Name: clindamycin phosphate 1.2%, benzoyl peroxide 2.5%

Dosage Form: Gel

Applicant/Sponsor: Dow Pharmaceutical Sciences, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: acne vulgaris

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

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

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 0 mo.	11 yr. 11 mo.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	12 yr. 0 mo.	16 yr. 11 mo.	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

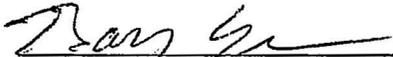
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tamika White
10/17/2008 02:51:44 PM

1.3.3 Debarment Certification

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

Date: 12/16/07

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 50-819 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Acanya Established/Proper Name: 1.2% clindamycin phosphate, 2.5% benzoyl peroxide Dosage Form: Gel		Applicant: Dow Pharmaceutical Sciences, Inc. Agent for Applicant (if applicable):
RPM: Tamika White		Division: Dermatology and Dental Products HFD-540
<p>NDA's: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s):</p> <p style="text-align: center;">BenzaClin b(4)</p> <hr style="width: 10%; margin: 0 auto;"/> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p style="text-align: center;"><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		October 26, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5 <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments:	
❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• If yes, exception for review granted (<i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i>)	<input type="checkbox"/> Yes
• If yes, OC clearance for approval (<i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <input type="checkbox"/>	9/24/08
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input checked="" type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, 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 the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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 section below (Summary Reviews).

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	
--	--

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/nonconsent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 10/23/08
---	-----------------------------------

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	10/22/08
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 5/29/08

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	10/22/08
❖ Original applicant-proposed labeling	12/21/07
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	10/22/08
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 3/6/08 <input checked="" type="checkbox"/> DMEDP 6/3/08; 9/26/08 <input checked="" type="checkbox"/> DRISK 9/16/08 <input checked="" type="checkbox"/> DDMAC 9/26/08 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	3/14/08
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If approval action, OC clearance for approval 	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) • Incoming submissions/communications 	<input checked="" type="checkbox"/> None
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) • Incoming submission documenting commitment 	<input type="checkbox"/> None 10/1/08 10/3/08
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	Letters: 7/30/08; 7/18/08; 3/5/08; 1/28/08 Faxes: 10/16/08; 9/26/08; 9/9/08; 8/13/08; 8/4/08; 7/1/08; 6/9/08; 4/24/08; 2/28/08; 2/13/08; 2/7/08
❖ Internal memoranda, telecons, etc.	Telecon 3/5/08
❖ Minutes of Meetings <ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) • Regulatory Briefing (<i>indicate date</i>) • Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not applicable <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> No mtg 11/27/07

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 5/29/08

• EOP2 meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg 9/18/06
• Other (e.g., EOP2a, CMC pilot programs)	Guidance 3/7/05
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/22/08
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/15/08
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	10/15/08
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	See page 76 of MO Review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See page 13 of MO Review
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ REMS • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	8/19/08; 8/21/08; 9/26/08
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/11/08
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/29/08; 10/7/08
Clinical Pharmacology <input type="checkbox"/> None	

⁵ Filing reviews should be filed with the discipline reviews.
Version: 5/29/08

❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 9/29/08; 10/22/08
❖ DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 10/7/08
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 9/25/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc 9/26/08
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 7/22/08 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/TeamLeader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 10/3/08
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	10/3/08
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)	Date completed: See page 71-79 of CMC Review <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs: ➤ TBP-EER	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
➤ Compliance Status Check (approvals only, both original and all	Date completed:

supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Appendix A to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

Tamika White
10/30/2008 10:39:45 AM



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

FACSIMILE TRANSMITTAL SHEET

DATE: October 16, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819	

Total no. of pages including cover: 4

Comments:

Please review and respond to the following information request.

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) 796-0310. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acanya™ (clindamycin phosphate and benzoyl peroxide) Gel 1.2% and 2.5%.

We have the following information request:

Based upon our assessment of the labels and labeling, we have identified the following area of needed improvement on the trade container label:

On the trade container label, delete or minimize the graphic of the face to increase readability of the established name and strength. If you choose to minimize the face graphic, you should ensure the graphic does not obscure the proprietary name, established name, and strength. An example of the latter alternative can be found on the trade container lid label (see Figure 2). Alternatively, you may also consider revising the font color of the text to provide a greater color contrast.

Figure 1: Trade Container Label

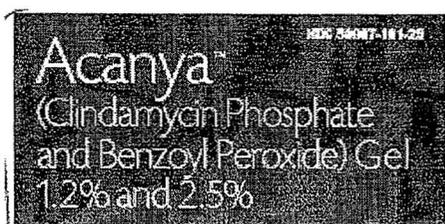


Figure 2: Trade Container Lid Label



Provide the color mock ups with indicated changes as soon as possible but no later than October 20, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-0310.

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

/s/

Tamika White
10/16/2008 06:33:45 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819	

Total no. of pages including cover: 3

Comments:

Please review and respond to the postmarketing request.

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) 796-0310. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acanya™ (clindamycin phosphate and benzoyl peroxide) Gel 1.2% and 2.5%.

The Agency has the following postmarketing request:

To conduct a 'maximum use systemic exposure (MUSE)' bioavailability study in the targeted patient population to determine the extent of systemic absorption of the active ingredients in Acanya™ Gel. Elements of the said study should include:

- a) Highest frequency of dosing in the proposed label for Acanya™ Gel
- b) Greatest duration of dosing in the above mentioned labels
- c) Use of to-be-marketed formulation
- d) Maximum total involved surface area to be treated at one time per labeling
- e) Amount applied per square centimeter to be documented
- f) Method of application/site preparation should be documented
- g) Sensitive and validated analytical method to measure active and potential metabolite(s).

Final study protocol submitted:	February 1, 2009
Patient accrual initiated:	May 1, 2009
Study completion:	August 1, 2009
Final report submission:	February 1, 2010

Send a letter stating the commitment as outlined above, and your agreement to the commitment and timetables. We request receipt of your written response no later than 3:00 p.m. on October 6, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-0310.

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

/s/

Tamika White
10/1/2008 03:38:27 PM
CSO



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

Via Federal Express

03 October 2008

Susan J. Walker, MD, Director
Division of Dermatological and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Subject: New Drug Application No. 050819 – Acanya™ Gel
SN0022 – Response to FDA Request for Information

Product: Acanya™ (Clindamycin Phosphate and Benzoyl Peroxide) Gel
1.2% and 2.5%

Indication: Acne Vulgaris

Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)

Dear Dr. Walker:

On 21 December 2007, pursuant to §505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and in accordance with Title 21 of the Code of Federal Regulations §314.50, Dow Pharmaceutical Sciences, Inc. (DPSI) submitted original New Drug Application (NDA) 050819 for Acanya™ (Clindamycin Phosphate and Benzoyl Peroxide) Gel, 1.2% and 2.5%, also known as Clindaben™ Gel or IDP-110 Gel.

Reference is made to the October 1, 2008 FDA e-mail request asking the Sponsor to review and respond to the postmarketing commitment contained in the communication. In the communication, the Agency requested that the Sponsor send a letter providing the commitment as outlined in the FDA correspondence and requested receipt of the written response no later than 3:00 p.m. (EDT) on October 6, 2008.

DPSI respectfully submits a written response to the Agency's postmarketing request as:

DPSI Response to FDA Request for Postmarketing Commitment Dated October 1, 2008

Susan J. Walker, MD
Page 2

This amendment is being submitted entirely electronically on one (1) CD. In addition, hard copy versions and original signatures are provided for the following documents for archival purposes:

- Cover letter
- Form FDA 356h
- Form FDA 3674

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have questions regarding the content of this submission, please contact me at 707-793-2600 or at bcalvarese@dowpharmsci.com.

Sincerely,



Barry M. Calvarese, MS
Vice President Regulatory and Clinical Affairs

Enclosures

**DPSI RESPONSE TO FDA POSTMARKETING COMMITMENT REQUEST
RECEIVED OCTOBER 1, 2008**

1.0 FDA REQUEST

The Agency has the following postmarketing request:

To conduct a 'maximum use systemic exposure (MUSE)' bioavailability study in the targeted patient population to determine the extent of systemic absorption of the active ingredients in Acanya™ Gel. Elements of the said study should include:

- a) Highest frequency of dosing in the proposed label for Acanya™ Gel
- b) Greatest duration of dosing in the above-mentioned labels
- c) Use of to-be-marketed formulation
- d) Maximum total involved surface area to be treated at one time per labeling
- e) Amount applied per square centimeter to be documented
- f) Method of application/site preparation should be documented
- g) Sensitive and validated analytical method to measure active and potential metabolite(s).

Final study protocol submitted:	February 1, 2009
Patient accrual initiated:	May 1, 2009
Study completion:	August 1, 2009
Final report submission:	February 1, 2010

Send a letter stating the commitment as outlined above, and your agreement to the commitment and timetables. We request receipt of your written response no later than 3:00 p.m. on October 6, 2008.

2.0 DPSI RESPONSE TO FDA REQUEST

The Sponsor accepts and affirms the commitment to conduct a Phase 4 maximum use systemic exposure (MUSE) bioavailability study in the targeted patient population to determine the extent of systemic absorption of the active ingredients in Acanya™ (Clindamycin Phosphate and Benzoyl Peroxide) Gel; to include the elements outlined above, and to be conducted according to the dates specified in the timetable paragraph preceding this paragraph in Section 1.0 – FDA Request.



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: September 26, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs.	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9894/9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819 Information Request	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 3:00 p.m. on September 30, 2008.

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) 796-0310. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acanya (clindamycin phosphate and benzoyl peroxide) Gel 1.2%/2.5%.

We have the following information requests:

1. Remove " ~~_____~~ gel" modifier from the trade name.
2. Amend the presentation of your trade name, established name, dosage form and strength in all container/closure systems as follows:

Acanya
(Clindamycin Phosphate and Benzoyl Peroxide) Gel
1.2% and 2.5%

3. Provide the color mock ups of the container/closures with indicated changes.

We request receipt of your written response as soon as possible but no later than 3:00 p.m. on September 30, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-0310.

b(4)

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

/s/

Tamika White
9/26/2008 04:27:00 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: September 9, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819 Information Requests	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 3:00 p.m. on
September 16, 2008.

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) 796-0310. Thank you.**

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME _____ Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide).

b(4)

We are reviewing your submission and have the following information requests.

1. Provide a table describing clinical study results from the two pivotal trials of the following:
TRADENAME Gel vs. Vehicle Gel – comparison at 12 weeks of
 - a. skin irritation (sum of itching, burning and stinging);
 - b. erythema; and
 - c. scaling

2. Provide the NDC # on the clindamycin phosphate solution container label.

We request receipt of your written response no later than 3:00 p.m. on September 16, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-0310.

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

/s/

Tamika White
9/9/2008 02:32:18 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: August 13, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819 Information Requests	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond as soon as possible but no later than 3:00 p.m. on August 20, 2008.

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) 796-0310. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME ~~_____~~, Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide).

b(4)

We are reviewing your submission and have the following CMC information requests.

1. The validation reports for methods STM 4-88 and 4-91 can not be located in your submission. Provide validation summaries for methods STM 4-88 and 4-91 per ICH Q2A and 2B. Validation information related to ~~_____~~ is not provided in Method STM 4-91; please provide.
2. Revise the expiration date instructions on the "Clindamycin Vial Label" from / months to 2 months (for post dispensed admixed drug product).
3. Per CFR 21 CFR 201.25, provide the bar code on all container/carton labels.
4. Include "Lot number and expiration date" on all container/carton labels.
5. Submit color mock-ups of all container/carton labels with the recommended changes.
6. All manufacturing sites should be included when the NDA is submitted. The new site identified in your submission dated July 23, 2008 is considered to be too late for consideration in this review cycle and should be submitted as a post-approval supplement.

b(4)

b(4)

We request receipt of your written response no later than 3:00 p.m. on August 20, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-0310.

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

/s/

Tamika White
8/13/2008 10:14:59 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 20, 2008

TO: Tamika White, Regulatory Project Manager
Brenda Vaughan, M.D., Medical Officer
Division of Dermatologic and Dental Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch 1
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 50-819

APPLICANT: Dow Pharmaceutical Sciences, Inc. **b(4)**

DRUG: _____

NME: No

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATION: Treatment of moderate to severe acne vulgaris

CONSULTATION
REQUEST DATE: April 8, 2008

DIVISION ACTION
GOAL DATE: August 22, 2008

PDUFA DATE: October 26, 2008

b(4)

I. BACKGROUND:

_____ is proposed for the treatment of acne vulgaris. _____ is a combination of clindamycin and benzoyl peroxide. The study was designed to determine the safety and efficacy of this combination of drugs as compared to the individual components and the drug vehicle.

b(4)

Dr. Mraz's site was selected for inspection because her financial disclosure form indicates a potential conflict of interest (she is an Associate Medical Director for Dow Pharmaceutical Sciences _____). Sites 40 and 72 had larger sample sizes and relatively large treatment effects.

b(6)

The protocols inspected included protocols # DPSI-06-22-2006-012 and DPSI-06-22-2006-017, both entitled "A Phase III, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 4-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of Clindabene (1/2.5) Gel, _____ Vehicle, Clindamycin (1%), and Benzoyl Peroxide (2.5%) Gels in the Treatment of Moderate to Severe Acne Vulgaris".

b(4)

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects	Inspection Date	Final Classification
Serena Mraz, M.D. Solano Clinical Research 127 Hospital Drive, #202 Vallejo, CA 94589	DPSI-06-22-2006-012: 65	30 Jun-6 Jul 08	Pending. (Interim classification is NAI)
Leonard Swinyer, M.D. Dermatology Research Center 3920 South 110 East, Suite 210 Salt Lake City, UT 84124	DPSI-06-22-2006-012: 79	23-26 Jun 08	NAI
Ronald Savin, M.D. The Savin Center, PC 134 Park Street New Haven, CT 06511	DPSI-06-22-2006-017: 47	18-27 Jun 08	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

b(4)

1. Serena Mraz, M.D.
Solano Clinical Research
127 Hospital Drive, #202
Vallejo, CA 94589

- a. **What was inspected:** Receipt and review of the endorsed inspection report is pending. Review of the preliminary report indicated that 72 subjects were screened, 67 subjects were randomized, and 54 subjects completed the study. Consent forms were reviewed for all 72 subjects. The records for 27 of the 54 subjects completing the study were reviewed, including, but not limited to, source documents, case report forms, medical records, inclusion/exclusion criteria, primary endpoint data, safety data, concomitant medications, adverse events, and drug accountability.
- b. **General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

2. Leonard Swinyer, M.D.
Dermatology Research Center
3920 South 110 East, Suite 210
Salt Lake City, UT 84124

- a. **What was inspected:** 79 subjects were enrolled in the study. The records for 34 subjects were reviewed including, but not limited to, source documents, case report forms, inclusion/exclusion criteria, concomitant medications, adverse event reporting, and drug accountability.
- b. **General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

3. Ronald Savin, M.D.
The Savin Center, PC
134 Park Street
New Haven, CT 06511

- a. **What was inspected:** 47 subjects were enrolled in the study. Consent forms for all subjects were reviewed. Source documents and case report forms were compared for 27 subjects. Primary efficacy endpoints were verified for inflammatory and non-inflammatory lesions. Inclusion/exclusion criteria, concomitant medications, adverse event reporting, and test article accountability were also reviewed.

- b. **General observations/commentary:** The protocol required that the same qualified individual assess the same subject at each visit to maintain consistency of evaluation. Review of source documents and case report forms revealed that lesion assessments for certain subjects (e.g., #s 008, 011, and 026) were done by two different evaluators at different visits. The case report forms stated that every effort should be made to use the same assessor. This discrepancy in evaluation procedures between the protocol and the CRF was noted in the letter to the investigator. The study coordinator (SC), who was not a trained and validated evaluator signed the "Evaluator Signature" line on the Tolerability Evaluation form for 12 subjects (#s 002, 006, 008, 009, 011, 021, 025, 026, 037, 041, 047, and 048). The SC's function to transcribe results was explained during the inspection and these evaluations were later countersigned by the investigator. Both observations in the letter to the investigator were noted as examples of lack of adherence to the investigational plan.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Receipt of the endorsed inspection report for Dr. Mraz is pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR(s).

The data generated by the sites of Drs. Mraz, Swinyer, and Savin appear acceptable in support of the respective application.

{See appended electronic signature page}

Roy Blay, Ph.D.
GCP Reviewer
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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

/s/

Roy Blay
8/21/2008 12:37:57 PM
CSO

Constance Lewin
8/21/2008 12:44:50 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-819

Dow Pharmaceutical Sciences, Inc.
Attention: Barry M. Calvarese, M.S.
Vice President, Regulatory & Clinical Affairs
1330 Redwood Way
Petaluma, CA 94954-7121

Dear Mr. Calvarese:

b(4)

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME _____, Gel (clindamycin phosphate 1.2%, benzoyl peroxide 2.5%).

We are in the process of reviewing your original NDA submission and have the following comments and recommendations.

1. Based on our review of the submitted information in your NDA 50-819, we have determined that you have not established a clinical bridge to an approved-listed drug. You have submitted a study report DPS 07-07-2005-001 to support a clinical bridge, however a clinical bridge cannot be established to an unapproved product / _____ (1% clindamycin, 5% benzoyl peroxide) gel (ANDA # 065443).

b(4)

You have submitted the in vitro percutaneous absorption data as an attempt to link this product to the currently unapproved ANDA product. In diseases where there is a disruption of the skin, in vitro studies are not accepted as a surrogate for in vivo bioavailability for the following reasons:

- a. The use of non-viable skin can alter the permeation properties of the skin (e.g. storage conditions).
- b. The use of normal skin instead of diseased skin, which due to the disrupted stratum corneum in diseased skin, can markedly affect drug penetration.
- c. The preparation of the skin samples usually requires the microtoming of the skin to a uniform layer, a situation that is neither physiologic nor relevant to diseased skin.
- d. In addition, there is no in vitro based clinical pharmacology class-labeling regarding topical benzoyl peroxide/clindamycin combination drug products as you have suggested.

2. If a sufficient clinical bridge is not established to an approved clindamycin/benzoyl peroxide product, additional nonclinical information would be needed to support an NDA [505(b)(2)] for the TRADENAME _____, Gel. The information needed would include an Ames test and an in vivo micronucleus assay for clindamycin phosphate. The information could be from the literature, but not referring to any marketed pharmaceutical.

b(4)

As soon as possible, please submit any additional information you may have relevant to these issues.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-2110.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Stanka Kukich
7/30/2008 10:41:35 AM

Executive CAC

Date of Meeting: July 22, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Barbara Hill, Ph.D., DDDP, Team Leader
Jiaqin Yao, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jiaqin Yao, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA: 50-819

Drug Name: Acanya _____ Gel (IDP-110 Gel)

Sponsor: Dow Pharmaceuticals

b(4)

Background:

The original IND (41,733) was submitted by Glaxo Dermatology and then was transferred to the current Sponsor. The Sponsor submitted an ANDA [65,443, _____ (1/5)] using the already marketed BenzaClin (clindamycin 1% - benzoyl peroxide 5%) Gel as the reference drug. The formulation for Acanya _____ Gel (1/2.5) is different from that for _____ (1/5), which was tested in the two carcinogenicity studies. In addition to the reduced concentration of benzoyl peroxide from 5% to 2.5% and the _____ concentration of propylene glycol from _____, Acanya _____ Gel has Carbomer 980 instead of _____ and Carbomer _____. The sponsor plans to rely on a clinical bridge with BenzaClin and _____ (1/5) and the safety data generated from the _____ (1/5) Gel to support this NDA filing [505(b)(2)] for the Acanya _____ Gel (1/2.5).

b(4)

Rat Oral Carcinogenicity Study:

Seven groups of 62 male and 62 female _____ CD(SD)IGS BR rats were treated via gavage with 0.3, 0.9, or 3.0 mL/kg/day Admixture Active Gel (_____, 0.9 or 3.0 mL/kg/day Benzoyl Peroxide 5% Gel, OR 0.9 or 3.0 mL/kg/day Clindamycin Phosphate 1% Gel for up to 97 weeks. Two additional control groups were treated with the Placebo Gel at 3.0 mL/kg/day as the test articles. The study was terminated at Week 97 due to mortality. No range finding data were available for this study and the adequacy of the study was discussed based on the toxicity.. A maximum tolerated dose appeared to have been achieved based on differences in body weights (i.e., decrease of approximately 10%) in males and females in groups treated with the high dose of Admixture Active Gel or Clindamycin Phosphate 1% Gel. Although there were some statistically significant differences in tumor incidence when control groups 1 and 2 were compared to the various treated groups, it appears that these differences were not biologically significant, due to either no trend with increasing dose or no difference from one of the placebo controls.

b(4)

Mouse Dermal Carcinogenicity Study:

Seven groups of 60 male and 60 female CD-1 mice were treated topically with 0.9, 2.7, or 15 mL/kg/day Admixture Active Gel (_____, 2.7 or 15 mL/kg/day Benzoyl Peroxide 5% Gel, or 2.7 or 15 mL/kg/day Clindamycin Phosphate 1% Gel for 2 years. Two additional control

b(4)

groups were treated with the Placebo Gel at 15 mL/kg/day as the test articles. No range finding data were available for this study and the adequacy of the study was based on dermal effects. A maximum tolerated dose appeared to have been achieved since animals in the high dose groups exhibited hyperkeratosis and epithelial hyperplasia at the treated site. Although there were some statistically significant differences in tumor incidence when control groups were compared to the various treated groups, it appears that these differences were not biologically significant, due to either no trend with increasing dose or no difference from one of the placebo controls.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agreed that the study was acceptable, although not optimal.
- The Committee concurred that there were no drug-related neoplasms in this study

Mouse:

- The Committee agreed that the study was acceptable, although not optimal.
- The Committee concurred that there were no drug-related neoplasms in this study
- The Committee noted that another formulation by another sponsor, using the same active ingredients, caused drug-related skin neoplasms in a 2-year rat dermal carcinogenicity study.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DDDP
Barbara Hill/HillB/Team leader, DDDP
Jiaqin Yao/YaoJ/Reviewer, DDDP
Tamika White/WhiteTA/CSO/PM, DDDP
Adele Seifried/ASeifried, OND IO

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

/s/

David Jacobson-Kram
7/23/2008 03:00:58 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-819

Dow Pharmaceutical Sciences, Inc.
Attention: Barry M. Calvarese, M.S.
Vice President, Regulatory & Clinical Affairs
1330 Redwood Way
Petaluma, CA 94954-7121

Dear Mr. Calvarese:

Please refer to your December 21, 2007 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME / ——— Gel (clindamycin phosphate 1.2%, benzoyl peroxide 2.5%).

b(4)

We have reviewed your request for proposed trade name “ ——— ” and have the following comments and information requests.

b(4)

We object to your proposed trade name “ ——— ” because it is vulnerable to name confusion that could lead to medication errors with Elocon, Cleocin T, and Ala-Quin.

b(4)

Your proposed second choice trade name “Acanya” is currently under review. We request that you submit at least one additional new trade name for consideration as soon as possible.

We have also reviewed your label, labeling and packaging for the product and have the following requests.

1. General Comment

Revise the active ingredients and corresponding product strengths to read as follows throughout the labels and labeling:

TRADENAME
(clindamycin phosphate and benzoyl peroxide gel)
1.2 %/ 2.5 %

or

TRADENAME

clindamycin phosphate 1.2 %
and
benzoyl peroxide 2.5 %

2. Trade Container Label and Carton Label

- a. Delete the graphic of the face to increase the available label area to increase the size of text and inclusion of other important information.
- b. Insert an area on the label and labeling that allows for inclusion of the 3 month expiration after pharmacist admixture of the product.

c.

b(4)

3. Professional Sample Container Label

Delete the graphic of the face from the container lid label to increase the available label area to increase the size of text and inclusion of other important information.

4. Clindamycin Vial Label

Increase the prominence of the statements "For external use only" and "Not for separate dispensing".

5. Package Insert

Delete all trailing zeros from numerical designations throughout the text as trailing zeros can often lead to confusion.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-0310.

Sincerely,

{See appended electronic signature page}

Bronwyn Collier
Acting Supervisor, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Bronwyn Collier
7/18/2008 09:22:11 AM



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

FACSIMILE TRANSMITTAL SHEET

DATE: July 1, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819 Information Requests	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 3:00 p.m. on July 9, 2008.

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) 796-0310. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for _____ gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide).

b(4)

We are reviewing your submission and have the following nonclinical and clinical information requests.

1. _____ major degradation products of clindamycin phosphate, _____ have been identified and may be a potential safety concern for the drug product. Provide the amount of the _____ degradants in test materials tested in nonclinical and clinical studies. In addition, provide any nonclinical information available for these degradants as well as an integrated safety summary for these degradants from the literature.
2. Provide the location in the NDA for the 1% clindamycin phosphate solution/5% benzoyl peroxide gel combination formulation and batch number(s) used in contact/sensitization study Protocol No. CLN-101, Besselaar Study #9145. If this information was not included in the NDA, please provide.
3. Is the 1% clindamycin phosphate/5% BP gel combination formulation referenced above the "final-to-be-marketed" formulation for the submitted ANDA?

b(4)

We request receipt of your written response no later than 3:00 p.m. on July 9, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-0310.

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

/s/

Tamika White
7/1/2008 03:01:08 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 9, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9895
Phone number: 707-793-2600 x601	Phone number: 301-796-0310
Subject: NDA 50-819 Chemistry Information Request	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 3:00 p.m. on June 23, 2008.

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) 796-0310. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for _____ Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide).

b(4)

We are reviewing your submission and have the following CMC information requests.

1. Upon the review of your Executed Batch Record, it is noted that _____ is used in the manufacture of benzoyl peroxide gel and clindamycin phosphate solution batches without a justification. Use of _____ is not appropriate. Provide justification.
2. Provide results of USP <661> testing on both the jar and bottle.
3. Provide a Letter of Authorization from _____ and their DMF number to review the CMC information pertaining to the _____.
4. Establish acceptance criterion for microbial limit testing USP <61> for the compounded gel product.
5. Tighten the acceptance criteria for benzoyl peroxide, total clindamycin content, and clindamycin phosphate content to _____. We recognize that your product may not be stable under room temperature storage conditions to meet the recommended tightened acceptance criteria; therefore, we recommend that the trade and physician's samples be stored at _____. In addition, limits for individual and total degradants for clindamycin should be tightened accordingly based on results of 5⁰C stability studies. Propose tightened acceptance criteria for these degradants.

b(4)

b(4)

b(4)

We request receipt of your written response no later than 3:00 p.m. on June 23, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-0310.

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

/s/

Tamika White
6/9/2008 09:43:17 AM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 24, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9894/9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819 Chemistry Information Request	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 3:00 p.m. on May 8, 2008.

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) 796-0310. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for _____ Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide).

b(4)

We are reviewing your submission and have the following CMC information requests.

1. As stated in meetings dated September 18, 2006 and November 27, 2007, provide a comparative in-vitro release testing of the two products (_____)

2. As stated in the September 18, 2006 meeting, provide the results of photostability testing of clindamycin phosphate solution, benzoyl peroxide gel, and the combination product.
3. Update the application with any additional stability data as soon as possible.
4. Provide the following:
 - a) Information on the type of samples _____ used in the clinical trial.
 - b) Ages of the drug product samples used in the clinical trials.
 - c) Storage conditions of samples prior to their use in the clinical trials.

We request receipt of your written response no later than 3:00 p.m. on May 8, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-2110.

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

/s/

Tamika White
4/24/2008 04:00:14 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 50-819

Dow Pharmaceutical Sciences
Attention: Barry M. Calvarese, MS
Vice President, Regulatory & Clinical Affairs
1330 Redwood Way
Petaluma, CA 94954-2600

Dear Mr. Calvarese:

Please refer to your new drug application (NDA) dated December 21, 2007, received December 26, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for _____, Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide). b(4)

We also refer to your submissions dated February 7, February 11, February 19, and February 29, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 26, 2008.

During our filing review of your application, we identified the following potential review issue:

The carcinogenicity data set you provided may require some modifications. Specific modifications to the carcinogenicity data set will be communicated to you after a thorough evaluation of the data set is complete.

We are providing the above comment to give you preliminary notice of the potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information: b(4)

- A. Letters of authorization for DMFs _____
- B. Registration stability data table 538-G BPO _____, Lot 1135 40 _____

- C. Representative samples with rheograms (_____)
_____) for Benzoyl peroxide _____ %, trade size admixture, and
physician sample. b(4)
- D. Supplier(s) of clindamycin phosphate drug substance for each clinical batch, and
clinical study number.
- E. The age of clindamycin phosphate _____, and benzoyl peroxide _____ at
time of dispensing to Phase 3 study subjects. b(4)
- F. Clarification on whether Lot #1918-123B that was used in the in vitro percutaneous
absorption study was ever used in a clinical trial or in the manufacturing of the
stability batches.

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.

We are reviewing the draft labeling, submitted in Physician's Labeling Rule (PLR) format, and have identified the following formatting issues:

Highlights of Prescribing Information

1. The trademark symbols in the HIGHLIGHTS OF PRESCRIBING INFORMATION should be removed because XML can not convert the symbol to Structured Product Labeling (SPL) format.
2. Major limitations of use should be briefly noted under the INDICATIONS AND USAGE heading [21 CFR 201.57 (a)(6); 21 CFR 201.57 (c)(2)].
3. 21 CFR 201.57(a)(6) requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug) is a (name of class) indicated for (indication(s)).”

You should propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or provide a rationale why pharmacologic class should be omitted from the Highlights.

4. The Initial U.S. Approval date should be revised to reflect the year in which FDA initially approved the new combination of active ingredients [21 CFR 201.57 (a)(3)].

Full Prescribing Information: Contents; Full Prescribing Information

5. The FULL PRESCRIBING INFORMATION section should begin on the next page.
6. Headings and subheadings must be named and numbered correctly as outlined under 21 CFR 201.56 (d)(1). Any required section, subsection, or specific information that is clearly inapplicable may be omitted from the Full Prescribing Information. However, the numbering should not change. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

We request that revised draft labeling addressing these issues be submitted by March 28, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a partial waiver of pediatric studies for this application for pediatric patients 0 to 11 years of age. Once review of your partial waiver request is complete, we will notify you whether the requested waiver has been granted. We note that you have submitted pediatric studies with this application for pediatric patients 12 to 17 years of age. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Tamika White, Regulatory Project Manager, at (301) 796-0310.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Stanka Kukich
3/5/2008 03:50:47 PM

MEMORANDUM OF TELECON

DATE: February 13, 2008

TIME: 12:00 p.m.

APPLICATION NUMBER: NDA 50-819

BETWEEN:

Name: Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs
Phone: (650) 517-5300
Representing: Dow Pharmaceutical Sciences, Inc.

AND

Name: Margo Owens, Acting Supervisory Project Manager
Tamika White, Regulatory Project Manger
Division of Dermatology and Dental Products (DDDP), HFD-540

SUBJECT: Information Needed Prior to Filing NDA 50-819

On February 13, 2008, the FDA informed the sponsor of two information requests that would be needed prior to filing the new drug application for _____ Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide) for the treatment of acne vulgaris. The two information requests were:

1. Provide the carcinogenicity data sets electronically.
2. Direct us to, or provide, the validation report for the analytical method used to measure clindamycin, benzoyl peroxide and benzoic acid in study #2104-047-051-053-056 entitled "In Vitro Percutaneous absorption of Clindamycin and Benzoyl peroxide from Benzaclin, Clindaben (1/2.5), _____ (1/5) and DUAC Topical Gel using Intact human skin from two healthy donors".

Provide the lot numbers of the investigational products and reference products used in the study listed above (i.e. # 2104-047-051-053-056).

The FDA advised the sponsor to submit this information no later than February 20, 2008 because the lack of these data affects the completeness of the application and could affect our ability to file the application.

The sponsor indicated that the request for clinical pharmacology information should be able to be submitted by the February 20, 2008 deadline. The sponsor expressed concern about submitting the carcinogenicity data electronically by February 20, 2008 since the studies were over ten years old.

b(4)

The sponsor indicated that if the lack of electronic data sets for carcinogenicity data was used as a reason for refusing to file the application, they would not accept that and would take the decision to a higher level.

The FDA reminded the sponsor that the discussion of these data was a topic at the Pre-NDA meeting held on November 27, 2007 where we advised them to submit these data with the NDA.

The call ended with a confirmation from FDA that the information requests would be sent via fax on February 13, 2008.

Tamika White
Regulatory Project Manager

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

/s/

Tamika White
3/4/2008 04:28:54 PM
CSO

Margo Owens
3/5/2008 03:53:59 PM
CSO

Tamika White
3/5/2008 03:56:06 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 28, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9894/9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819 Clinical Pharmacology Information Request	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 3:00 p.m. on March 4, 2008.

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) 796-0310. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for _____ Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide). **b(4)**

We also refer to your submissions dated February 7, 2008, February 11, 2008 and February 19, 2008.

We have reviewed your February 19, 2008, submission responding to our information request dated February 13, 2008. Based on the information you submitted, we have the following information request:

It appears that the Lot Number 1918-123B for Clindaben (1/2.5) Gel that was used in the in vitro skin permeation study No. 2104-047-051-053-056 is not in agreement with the Lot numbers (i.e. those used in the clinical studies or stability studies) currently provided in this NDA. Provide information on how Lot Number 1918-123B relates to the to-be-marketed formulation (e.g. provide a copy of the manufacturing batch record which contains a batch formula for this lot).

We request receipt of your written response no later than 3:00 p.m. on March 4, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-2110.

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

/s/

Tamika White
2/28/2008 12:57:40 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 13, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9894/9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819 Clinical Pharmacology/Nonclinical Information Request	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 3:00 p.m. on February 20, 2008.

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) 827-2020. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ~~_____~~ Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide).

b(4)

We are reviewing your submission and have the following comments and information requests.

1. Submit the data for the carcinogenicity studies in the appropriate format to permit statistical analysis.
2. Direct us to, or provide the validation report for the analytical method used to measure clindamycin, benzoyl peroxide and benzoic acid in study #2104-047-051-053-056 entitled "In Vitro Percutaneous absorption of Clindamycin and Benzoyl peroxide from Benzacilin, Clindaben (1/2.5), ~~_____~~ (1/5) and DUAC Topical Gel using Intact human skin from two healthy donors".

b(4)

Provide the lot numbers of the investigational products and reference products used in the study listed above (i.e. # 2104-047-051-053-056).

We request receipt of your written response no later than 3:00 p.m. on February 20, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-2110.

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

/s/

Tamika White
2/13/2008 04:15:11 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 7, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9894/9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819 Statistical Information Request	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 1:00 p.m. on February 12, 2008.

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) 827-2020. Thank you.

NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for _____, Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide).

b(4)

We are reviewing the Statistical section of your submission and have the following comments and information requests.

You submitted dataset titled "Analysis Dataset Subject Level" (ADSL.xpt) for both studies: DPSI-06-22-2006-012 and DPSI-06-22-2006-017. However, these datasets do not include a unique subjects ID number for each subject. It appears that the last digit in Variable USUBJID is missing. This is shown in the following example of the identification numbers that were included in ADSP.xpt (Study DPSI-06-22-2006-012).

Obs	INVID	SUBJID	USUBJID
1	11	2	01100
2	11	3	01100
3	11	5	01100
4	11	7	01100
5	11	11	01101
6	11	15	01101
7	11	16	01101
8	11	18	01101
9	11	19	01101
10	11	21	01102
11	11	22	01102

The Division requests that you provide datasets that include the full USUBJID variable.

We request a prompt written response no later than 1:00 p.m. on February 12, 2008 in order to continue our evaluation of your NDA.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-2110.

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

/s/

Tamika White
2/7/2008 02:36:47 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-819

NDA ACKNOWLEDGMENT

Dow Pharmaceutical Sciences, Inc.
Attention: Barry M. Calvarese
Vice President Regulatory & Clinical Affairs
1330 Redwood Way
Petaluma, CA 94954-7121

Dear Mr. Calvarese:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: _____ Gel (1% clindamycin phosphate – 2.5% benzoyl peroxide) **b(4)**

Date of Application: December 21, 2007

Date of Receipt: December 26, 2007

Our Reference Number: NDA 50-819

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 22, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(I)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above must be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 50-819

Page 2

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Tamika White, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Margo Owens
Acting Chief, Project Management Staff
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Margo Owens
1/29/2008 04:52:59 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 41,733

Dow Pharmaceutical Sciences, Inc.
Attention: Barry M. Calvarese, M.S.
Vice President, Regulatory and Clinical Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Calvarese:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5 %) Gel.

We also refer to the meeting between representatives of your firm and the FDA on November 27, 2007. The purpose of the meeting was to obtain input on the content and format of the planned NDA submission for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: November 27, 2007 **Time:** 1:00 P.M.
Location: WO 22 Room 1313 **Meeting ID:** 22665
Topic: IND 41,733 Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel for treatment of acne vulgaris
Subject: Pre-NDA meeting
Sponsor: Dow Pharmaceutical Sciences, Inc.
Meeting Chair: Susan J. Walker, M.D./Division Director, DDDP
Meeting Recorder: Margo Owens/Regulatory Project Manager, DDDP

FDA Attendees:

Susan J. Walker, M.D./Division Director, DDDP
Markham Luke, M.D., Ph.D./Team Leader, Clinical, DDDP
David Kettl, M.D./Clinical Reviewer, DDDP
Jane Liedtka, M.D./Clinical Reviewer, DDDP
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDP
Jiaqin Yao, M.D., Ph.D./Pharmacology Reviewer, DDDP
Rajiv Agarwal, Ph.D./ Chemistry Reviewer, ONDQA
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDQA
Abimola Adebowale, Ph.D./ Clinical Pharmacology/Biopharmaceutics Reviewer, DPEIII
Mohamed Alesh, Ph.D./Biostatistics Team Leader, DBIII
Clara Kim, Ph.D./Biostatistician, DBIII
Don Hare/Special Assistant to the Director, OGD
Nam Kim/Regulatory Counsel, ORP
Margo Owens/Regulatory Project Manager, DDDP

Sponsor Attendees:

Gordon J. Dow, Pharm.D./Founder and Chief Technical Officer, Dow
Barry M. Calvarese, M.S./Vice President, Regulatory and Clinical Affairs, Dow
A.J. Acker, RAC, Manager, Regulatory Affairs

b(4)

David Osborne, Ph.D./Vice President, Product Development
Diana Chen/Medical Affairs
Bhaskar Chaudhuri, Ph.D./President and CEO
Pramod Sarpotdar, Sr./Director, Formulation Product Development
Karen Yu, Ph.D./Project Manager (via teleconference)
Linda Mutter, Ph.D., DABT/Director, Preclinical, Regulatory Affairs (via teleconference)

Purpose:

The sponsor requests input from the Agency on the content and format of their planned NDA submission for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel. The pre-meeting briefing document (submitted October 22, 2007) provides background and questions for discussion.

Introductory Comments:

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Chemistry, Manufacturing and Controls:

Summary: IDP-110Gel (Clindaben Gel) is a combination product, containing 1% clindamycin (1.2 % clindamycin phosphate) and 2.5% benzoyl peroxide. IDP -110 Gel will be distributed as a kit containing two separate components that are to be mixed by the pharmacist prior to dispensing to the patient. _____ the physician samples. b(4)

Question:

IDP -110 Gel will be distributed as a kit containing two separate components that are to be mixed by the pharmacist prior to dispensing to the patient. _____ the physician samples. The _____ results in a product that conforms to the exact same specifications as the product produced when separate component formulations are admixed by the pharmacist. Provided the stability data is compelling, _____ physician samples concurrent with launch of the commercial kit using data submitted during the NDA review process. Is this acceptable to the agency? b(4)

Response:

This is a review issue. _____ physician samples are acceptable if the mechanically mixed (pre-mixed samples) are equivalent to the manually mixed product. To assess the equivalence, we will need to review and compare the following data: in-vitro drug release profile, impurity profile, homogeneity, batch analysis, and stability. We may raise other questions during the NDA review. b(4)

Additional comments:

1. _____

- _____ . Any method must be able to detect potential degradation products of both the active pharmaceutical ingredients.
2. Detailed information on the container/closure system and the manufacturing process, including in-process tests on _____ drug product for physician sample, must be provided in the submission.
 3. An expiration date will be established for the physician samples based on the real time stability data on three batches of the _____ drug product.
 4. Please clarify if the _____ is the only configuration proposed for the physician sample.
 5. Please address how the expiry dating of the physician sample package will be addressed, since no pharmacy controls would apply to this sample product once distributed. Given the typical use of office samples in a clinical setting, expired product could easily be administered to patients, presenting theoretical safety or lack of efficacy concerns. Labeling for the sample size product will also need to be addressed.
 6. We remind you that all issues from the previous Guidance meetings must be addressed in your submission.

b(4)

Pharmacology/Toxicology:

Question:

At the End of Phase 2 meeting with the Agency, DPSI proposed to support the 505(b)(2) NDA for IDP-110 Gel with clindamycin and BPO literature, nonclinical studies conducted with _____ (1/5) Gel, and a chromosome aberration study with clindamycin phosphate. FDA agreed that this strategy appeared to be acceptable if a clinical bridge to BenzaClin was established in the bioequivalence study with _____ (1/5) Gel and BenzaClin. The bioequivalence study has clearly established bioequivalence of _____ (1/5) Gel to the reference listed drug BenzaClin and a relatively better tolerability profile of IDP-110 Gel. The Clindamycin-Benzoyl Peroxide Gel ANDA is currently under review at the Office of Generic Drugs (ANDA #065443).

b(4)

Does the Agency agree that nonclinical commitments have been met for IDP-110?

Response:

The nonclinical database appears acceptable for the NDA filing. However, the final adequacy will be a review issue. Please provide the impurity profile of the _____ physician samples. If any new impurity exists at an unqualified level, sufficient nonclinical data on the new impurity should be submitted to support the safety of the drug product.

b(4)

In addition, the data for the carcinogenicity studies should be submitted in the appropriate format to permit statistical analysis. Information on providing electronic data can be found at <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>. The specific format (table) for submission of tumor data of two-year carcinogenicity studies can be found at <http://www.fda.gov/cder/regulatory/ersr/Studydata.pdf>. Guidance on statistical aspects of

carcinogenicity studies can be found in the draft guidance entitled Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals, which is available at <http://www.fda.gov/cder/guidance/815dft.htm>.

Clinical Pharmacology/Biopharmaceutics:

Question:

Does the Agency grant a waiver to Dow Pharmaceutical Sciences, Inc. for the absorption study?

Response:

No, we cannot grant the waiver for the absorption study at this time. Based on previous communications between the Agency and the sponsor, the following information would need to be provided for the waiver to be granted:

- Approval of ANDA # 065443 for _____ (1/5) Gel
- A full study report of the new in vitro skin permeation data conducted with IDP-110 Gel (Clindaben 1/2.5 Gel), _____ (1/5) Gel, Benzaclin, and Duac
- Comparative evaluation of the systemically related adverse events obtained with the Clindaben (1/2.5) Gel dosed QD, _____ (1/5) Gel dosed BID and Benzaclin® Topical Gel dosed BID obtained from clinical studies

b(4,

On August 2, 2007, the Agency sent a fax to the sponsor regarding their request for a waiver of the Phase 2 absorption study (submitted as SS 0079 and 0087 on 02/02/2007 and 05/16/2007). Please refer to those comments.

We acknowledge the inclusion of the summary of the bioequivalence study submitted in ANDA #065443, in this submission. However, we note that ANDA #065443 is still under review by the Office of Generic Drugs. In addition the comparative safety data with regards to the systemically related adverse events obtained with the Clindaben (1/2.5) Gel dosed QD, _____ (1/5) Gel dosed BID and Benzaclin® Topical Gel dosed BID obtained from the Phase 2 and 3 studies was not provided in this submission.

We acknowledge the inclusion of a summary of a recently completed in vitro skin absorption study with IDP-110 Gel (Clindaben 1/2.5 Gel), _____ (1/5) Gel, Benzaclin, and Duac provided in this submission. We note that this information was previously submitted in SN 0092: Response to FDA Facsimile of August 2nd, 2007 Regarding IND Serial Submissions 0079 and 0087 for _____[™] Gel IND 41733 and Request for Agency Reconsideration of absorption Waiver request Presented by Sponsor in SS0079. However, the sponsor did not provide the full study report that also includes the analytical method and validation report in both submissions. Therefore, we could not conduct a full review of the study report that would allow us to arrive at explicit conclusions.

Clinical/Biostatistics:

Question 1:

As discussed at the End of Phase 2 meeting with the Agency on September 18, 2006 (Appendix 4), the two phase 3 clinical studies will be successful if the following endpoints are demonstrated:

- 1) the sponsor's combination product is superior to vehicle in inflammatory and non-inflammatory lesion counts and the global severity score; and
- 2) the sponsor's combination product demonstrates superiority to both monads in global severity score and inflammatory lesion counts. Non-inflammatory lesion counts will be assessed for each of the arms, however, the dyad will not have to demonstrate superiority over the monads for this endpoint.

Does the Agency concur that if the above endpoints are demonstrated in the Phase 3 studies that an indication of Acne Vulgaris is achievable?

Response: As discussed at the End-of-Phase 2 meeting, the above endpoints will be considered as the primary endpoints for an indication for the treatment of acne vulgaris. However, whether the indication for the treatment of acne vulgaris will be achieved is a review issue.

Meeting Discussion:

The sponsor inquired whether formal analysis of non-inflammatory lesions including p-values should be conducted or whether descriptive analysis would be sufficient. In response, the Agency recommended that formal analysis of non-inflammatory and total lesion counts should be submitted in addition to the analysis of inflammatory lesion counts.

Question 2:

Is the Agency willing to reconsider this nested approach?

Response:

- 1) The proposed nested approach implies that the indication of this product may be for the treatment of inflammatory lesions of acne. Whether treatment of inflammatory lesions of acne can be considered as an indication is an issue to be discussed with the Division.
- 2) To control the type I error, the nested approach has to be pre-specified.
- 3) The endpoints agreed with the Agency were inflammatory and non-inflammatory lesion counts and not total lesion counts. The second stage of the proposed nested approach involves analyses of non-inflammatory and total lesion counts. The nested approach should evaluate the same efficacy variables as the method that does not include the nested approach.

Additional Clinical Comments:

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

All Case Report Forms (CRFs) should be submitted from the two phase 3 studies with electronic links for:

- a) all Serious AEs
- b) all Severe AEs
- c) all patients who discontinued for whatever the reason (not just because of adverse events).

Meeting Discussion:

The Agency requested that the sponsor submit all photographs taken during the conduct of these studies in an organized and reviewable manner.

A request for a waiver for pediatric studies with a suitable justification should be submitted with the NDA to ensure compliance with FDAAA of 2007.

A formal request for a waiver of further dermal safety studies for this product should be submitted with the application. This issue was previously reviewed in response to sponsor submission serial number 081 on February 9, 2007.

Additional Statistical Comments

The sponsor should provide the Agency with SAS transport files in electronic form. The data sets should include demographic and baseline data as well as efficacy and safety data. Data Sets should include:

- a. The database for the Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses.
- b. Each data set should include the treatment assignments. For each of the primary and secondary endpoints, an indicator variable that denotes whether measurements are actual or imputed should be included.
- c. The submission should include adequate documentation for the data sets including definitions of each variable in the data set, formulas for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation.
- d. In addition to the electronic data sets, the NDA submission should include the following items:
 - o Study protocols including the statistical analysis plan, protocol amendments and their dates, and a copy of the Case Report Form.
 - o The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

Project Management:

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. Based on the repeal of section 507 of the Food, Drug and Cosmetic Act, you are advised that clindamycin would not be eligible for marketing exclusivity. The Sponsor may refer to the guidance document issued by the Agency in May 1998, *Guidance for Industry and Reviewers: Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. This guidance document defines the administrative actions required by the agency for reviewing and

approving antibiotic drug applications that were submitted after November 21, 1997. You may also refer to the *Federal Register* notice 99N-3088, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs* issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507.

4. We remind you of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain and assessment of the safety and effectiveness of the pediatric patients unless this requirement is waived or deferred.
5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
6. You are reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

ACTION ITEM:

The Agency will ask our Office of Biostatistics about whether carcinogenicity data sets are required from the older studies that the sponsor intends to submit in the NDA.

- A response to this issue was sent via facsimile to the sponsor on December 7, 2007.

Minutes Preparer: _____
Margo Owens/Regulatory Project Manager DDDP

Chair Concurrence: _____
Susan J. Walker, M.D./Division Director, DDDP

b(4)

Linked Applications

Sponsor Name

Drug Name

IND 41733

DOW
PHARMACEUTICAL
SCIENCES

BENZOYL PEROXIDE ~~and~~/CLINDAMYCIN
PHOSPHAT

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

/s/

SUSAN J WALKER
12/19/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 41,733

Dow Pharmaceutical Sciences, Inc.
Attention: Barry M. Calvarese
Vice President, Regulatory and Clinical Affairs
350 Corporate Boulevard
Robbinsville, NJ 08691

Dear Mr. Calvarese:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5 %) Gel.

We also refer to the meeting between representatives of your firm and the FDA on September 18, 2006. The purpose of the meeting was to obtain input on the development plan for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Susan Walker, M.D.
Division Director
Division of Dermatologic and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: September 18, 2006 **Time:** 9:00 A.M.
Location: WO 1417 **Meeting ID:** 19663
Topic: IND 41,733 Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel for treatment of acne vulgaris
Subject: End of Phase 2 meeting
Sponsor: Dow Pharmaceutical Sciences, Inc.
Meeting Chair: Susan Walker, M.D./Division Director, DDDP
Meeting Recorder: Margo Owens/Regulatory Project Manager, DDDP

FDA Attendees:

Susan Walker, M.D./Division Director, DDDP
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDP, HFD-540
Jiaqin Yao, M.D., Ph.D./Pharmacology Reviewer, DDDP, HFD-540
Jane Chang, Ph.D./ Chemistry Reviewer, ONDQA
Abimola Adebowale, Ph.D./ Pharmacokinetics Reviewer, DPEIII, HFD-880
Tien-Mein Chen, Ph.D./ Pharmacokinetics Reviewer, DPEIII, HFD-880
Markham Luke, M.D., Ph.D./Team Leader, Clinical, DDDP, HFD-540
David Kettl, M.D./Clinical Reviewer, DDDP, HFD-540
Kathleen Fritsch, Ph.D./Biostatistician, DBIII, HFD-725
Clara Kim, Ph.D./Biostatistician, DBIII, HFD-725
Fred Marsik, Ph.D./Microbiologist, DAIDP, HFD-520
Margo Owens/Regulatory Project Manager, DDDP, HFD-540

Sponsor Attendees:

Dow Pharmaceutical Sciences, Inc.
Gordon J. Dow, Pharm.D./Founder and Chief Technical Officer
Barry M. Calvarese, M.S./Vice President, Regulatory and Clinical Affairs

David Osborne, Ph.D./Vice President, Product Development (via teleconference)
Karen Yu, Ph.D./Project Manager (via teleconference)
A.J. Acker, RAC, Manager, Regulatory Affairs (via teleconference)
Robert N. Decker, MS, Associate Manager, Clinical Affairs (via teleconference)
Charles Chavdarian, Ph.D., Senior Director, Analytical Sciences (via teleconference)
Simon Yeh, Ph.D. Manager, Methods Development, Analytical Sciences (via teleconference)

Purpose:

The sponsor requests input from the Agency on their proposed CMC and clinical development plans for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel. The pre-meeting briefing document (submitted July 24, 2006) provides background and questions (pg. 10) for discussion.

The sponsor is reminded to refer to and address any pending issues conveyed during the November 13, 2003, March 7, 2005, and June 27, 2006, Guidance meetings.

Chemistry, Manufacturing and Controls (CMC):

From the FDA draft reviewer's comments dated June 21, 2006, the FDA stated that "a more comprehensive in-use admixture stability study should be performed on three registration batches to support an NDA filing". In response to this comment DPSI has generated a stability protocol for two upcoming registration batches of Clindaben (1/2.5) Gel. In addition, one registration batch of Clindaben (1/2.5) Gel is currently on stability.

Sponsor's CMC Question 1:

Does the Agency agree that the stability protocol as included in this Briefing Book will support an NDA filing?

Agency's Response:

No, the stability protocol provided in the Briefing Book is not adequate to support the NDA. The following issues should be addressed:

- 1) Add testing on the individual components _____ admixing for admixture stability. This is to ensure the quality, potency, and purity of each component is acceptable prior to admixing.

Sponsor: Agree. Testing of the individual components is done under a separate protocol.

- 2) The stability protocol for the current stability batch should be amended to include testing for benzoyl peroxide particle size distribution and homogeneity for all remaining time points if DPSI choose to pursue the proposed plan of _____ stability batch plus _____ registration batches of Clindaben (1/2.5) Gel. This approach is not a filing issue. However, it may carry some risk pending on the outcome of the stability data as particle size data at the early time points will not be available for the current stability batch.

Sponsor: Agree. The stability protocol of the current stability batch will be amended to include testing for benzoyl peroxide particle size distribution and homogeneity for all remaining time points starting at _____

- 3) Samples for admixture stability study should be prepared using validated admixing procedure. That is, each admixture sample should be individually prepared in the to-be-marketed container closure system following the validated admixing procedure. The procedure proposed on page 39 of the Briefing Book, _____, is not acceptable as it is not the procedure intended to be used by pharmacists.

Agency: Type of mixing, i.e. hand mixing vs. _____, used for preparation of admixture could affect the physical stability of the admixture. Admixture samples prepared by the proposed _____ mixer do not represent actual samples dispensed

by pharmacists. Therefore, the physical stability is not monitored adequately with the proposed protocol.

Sponsor: The sponsor acknowledged that they had not thought about the impact of mixing on the physical stability of the admixture. The sponsor stated that variability in the assays was observed with admixture prepared by hand mixing procedure. b(4)

The sponsor will submit a clarifying statement on this issue for the Agency's review.

- 4) The organisms tested in the microbial limit test (Table 3.1.1) should be described and their acceptance criteria should be provided.

Sponsor: Agee. Information will be provided.

- 5) We reiterate the recommendation made in the November 12, 2003 and June 27, 2006 Guidance Meetings for the necessity of a photostability study on the admixture. The Briefing Book does not include this study.

Sponsor: Agee. Information will be provided.

- 6) Numerical limits for clindamycin phosphate, clindamycin, and clindamycin phosphate degradation products should be proposed in the tentative regulatory specification of Clindaben (1/2.5) Gel (Table 3.1.1). Similar comment, i.e. numerical limits for clindamycin phosphate and clindamycin, was conveyed to you in the June 27, 2006 Guidance Meeting.

Sponsor: Agee. Information will be provided.

DPSI has developed a protocol to validate the admixing instructions (e.g. mixing time) for Clindaben (1/2.5) Gel to ascertain that sufficient mixing is achieved.

Sponsor's CMC Question 2:

Does the Agency agree that this protocol as included in this Briefing Book is sufficient to validate the mixing time for Clindaben (1/2.5) Gel?

Agency's Response:

No, it is not adequate to validate the mixing time. The criteria for selecting the mixing time should include a total clindamycin content of _____ of label claim. Validated regulatory analytical methods should be used for the assay. The clindamycin phosphate analytical method (STM-04-91) described on page 27 of the Briefing Book is not consistent with the methods (STM 04-95 for clindamycin phosphate and STM 04-113 for clindamycin) listed in the Clindaben (1/2.5) Gel Regulatory Specification (Table 3.1.1). Please clarify. b(4)

Sponsor: Agree. An error in the analytical method was in the Briefing book. The correct information will be provided.

Pending Issues from Previous Guidance Meetings

The following items were conveyed to you in the November 12, 2003 and June 27, 2006 Guidance Meetings and have not yet been addressed:

- Please discuss the issue of clindamycin precipitation referred to in the November 20, 1995, amendment. Also, justify the absence of a test for precipitate formation with either clindamycin solution or the combination product. (A verbal response was given in the June 27, 2006 Guidance Meeting. But a written response has not been given.)
- Perform photostability studies on clindamycin phosphate concentrate, benzoyl peroxide gel, and the combination product _____ gel.

Clindamycin _____ Specification:

- Numerical limits for clindamycin phosphate and clindamycin should be proposed. "Report", as shown in Table 3.5.2 (SN:068) is not an acceptable entry.
- Add "total clindamycin content" and its acceptance criterion
- The organisms tested in the microbial limit test should be described and their acceptance criteria should be provided.

Benzoyl Peroxide _____ Specification:

- Add particle size test and its proposed acceptance criterion
- Add homogeneity and its acceptance criterion
- The organisms tested in the microbial limit test should be described and their acceptance criteria should be provided.

Pharmacology/Toxicology:

The Agency understands that the sponsor is establishing a clinical bridge to Benzaclin by conducting a bioequivalence study with the 1/5 _____ formulation and Benzaclin. If, after review of this study, the Agency determines that this bridge is adequate then the existing nonclinical information and an in vitro chromosome aberration study with clindamycin phosphate appear to be adequate in principal to support a 505(b)(2) NDA. Please include copies of all references and English translations if necessary.

b(4)

If a sufficient clinical bridge is not established to an approved clindamycin/benzoyl peroxide product, additional nonclinical information would be needed to support an NDA [505(b)(2)] including a chronic topical toxicity study in a nonrodent model, three genotoxicity studies for clindamycin phosphate, besides the literature information outlined by the sponsor previously. Information from the labeling of an approved drug product can not be referred to unless a sufficient clinical bridge has been established to the approved drug product.

It is recommended that the sponsor provide information on the levels of the degradation products in the drug product/substances used in the nonclinical and clinical studies so that it can be determined if they are adequately qualified or the sponsor otherwise qualify the levels of the degradation products.

It should be emphasized that because complete data are not currently available, the perceived nonclinical data requirement may change during review of the IND/NDA.

Clinical Pharmacology/Biopharmaceutics:

There were no clinical pharmacology or biopharmaceutics questions identified in this briefing package. We summarize the previous discussions in the meetings and have a comment for the sponsor:

- In the 11/12/03 meeting, the Agency indicated that pharmacokinetic studies to assess the degree of and/or potential for systemic absorption would be needed.
- In the 03/07/05 meeting, you indicated that a Phase 2 systemic absorption study would be proposed to be conducted and submitted in the NDA. However, the Agency did not agree with the overall design of the protocol.
- In the 06/27/06 meeting package, you indicated “In the sponsor’s opinion, the presence of a large safety data base for the two actives (BPO and clindamycin), the establishment of a safety bridge via the comparison of (1/5) gel to Benzacilin and the ability to cross-reference the Clindagel absorption study support the rationale not to conduct an absorption study on Clindaben (1/2.5) Gel. The supporting information and rationale is provided in Sections 4, 5, and 6 of this briefing package. DPSI proposes not to conduct a phase 2 absorption study at this time.”

b(4)

The Agency responded in the meeting “the information provided in the briefing document appears insufficient for a waiver of phase 2 absorption studies to be granted. The Clindagel data is not sufficient to satisfy the recommended elements of the phase 2 maximal use study which would use a formulation identical to the clinically studied/to-be-marketed formulation. Clindamycin gel product absorption data in place of the combination product would require justification, since there might be differences in absorption due to a vehicle effect. Please submit your rationale to demonstrate why data from the clindamycin only product is sufficient.”

However, you reiterated in the meeting that adequate safety data would be presented to justify the decision not to perform the absorption study. You would present bioequivalence data and supporting safety data (including use of their product under maximal use conditions) to the reference listed drug, Benzacilin, in a written waiver request.

To date, we are still awaiting your written waiver request with your rationale to demonstrate why an in vivo bioavailability study of your product under maximal use conditions will not be conducted at this time.

The sponsor stated they will submit the waiver request within the next 2-3 weeks.

Clinical and Biostatistics:

Sponsor’s Clinical Question 1:

The sponsor seeks approval for moderate to severe inflammatory acne. Is this labeling indication agreeable to the Agency?

b(4)

Agency’s Response:

Labeling is a review issue and depends on the information submitted to the NDA. Acne vulgaris is an evolving indication and the contributions of inflammatory versus non-inflammatory lesions

are the focus of ongoing discussions. Labeling decision for specific acne lesions may be referred to an advisory committee for resolution. In general, patients seek treatment for, and clinicians treat, "acne vulgaris" and sponsors are encouraged to consider this broader indication.

However, an indication for "~~_____~~" has precedent, given demonstrable efficacy and safety in at least two adequate and well-controlled studies.

b(4)

Patients with acne characterized as "severe" are likely to have significant non-facial acne, and this is not addressed in the protocol. Please clarify how this issue will be addressed.

Sponsor's Clinical Question 2:

Is the phase 3 protocol in Appendix 5.3 acceptable?

Agency's Response:

Review of the phase 3 protocols submitted in serial number 71 is ongoing and comments regarding the protocol will be conveyed to the sponsor when complete. The sponsor is encouraged to submit the phase 3 protocol as a Special Protocol Assessment.

The sponsor stated that they plan to begin the study in two weeks and will not submit an SPA to the Agency for review.

In brief, the primary endpoints of absolute change in inflammatory lesion counts, and percent of subjects who achieve a two point reduction at week 12 in the Evaluator's Global Severity Score seem acceptable for an indication for inflammatory lesions of acne. As previously recommended at the June 27, 2006 guidance meeting, efficacy would be demonstrated if:

1. The sponsor's combination product is superior to vehicle in inflammatory and non-inflammatory lesions and the global severity score, and
2. The sponsor's combination product is superior to both monads in two of three lesion counts (inflammatory, non-inflammatory, and total) and the global severity score.

The Agency stated that while approval of subsets of acne has some regulatory precedent, clinicians do not generally evaluate patients as "inflammatory", or "non-inflammatory". It was recommended that the indication sought should be acne vulgaris, as opposed to "~~_____~~". This is especially true given that this is a combination product.

b(5)

The sponsor pointed out that the proposed indication was developed because of the language of the draft guidance for acne. The Agency responded that as long as all the appropriate endpoints were measured, this would be a review issue to determine approval for the treatment of acne vulgaris indication.

After extensive discussion regarding proposed endpoints and review of the sponsor's phase 2 study results, agreement was reached on the following endpoints:

Success would be demonstrated if:

1. The sponsor's combination product is superior to vehicle in inflammatory and non-inflammatory lesion counts and the global severity score, and
2. The sponsor's combination product demonstrates superiority to both monads in global severity score and inflammatory lesion counts. Non-inflammatory lesion counts will be assessed for each of the arms, however, the dyad will not have to demonstrate superiority over the monads for this endpoint.

For phase 3 protocols, the Agency does not recommend the use of a visual analog scale (VAS). Rather, the static, global integer scale is recommended to be used. The VAS can be measured as an exploratory secondary endpoint but would have little regulatory utility.

Please refer to additional endpoints from biostatistics concerning the proposed evaluation criteria.

Sponsor's Clinical Question 3:

Dow Pharmaceutical Sciences, Inc. (DPSI) is proposing a nested statistical analysis approach that would allow for an initial labeling claim of ' _____ ' followed by analysis of the noninflammatory lesions which, if successful, would allow for an acne vulgaris claim. Is the attached Statistical Analysis Plan (SAP) in Appendix 5.4 acceptable to the Agency? (Note: this approach was suggested prior to the agreement on the above success criteria)

b(4)

Agency's Response:

The sponsor's proposed nested approach is novel and the Agency cannot agree to it at this time. The SAP does not clearly state how the set of hypothesis test results would be collated into claims. In addition, especially for combination products, the Agency is interested in evaluating overall acne and not limiting to a subset of acne lesion types. The Agency's thinking on the most appropriate way to evaluate combination products for acne continues to evolve as new information becomes available. It may be possible to reduce the number of comparisons needed to establish efficacy for the full indication and fulfill the combination policy. The Agency is open to further discussion on this issue.

After extensive discussion, the sponsor proposed to evaluate the following comparisons to achieve a successful clinical study:

- Combination product vs. vehicle
 - Evaluator's Global Severity Score (EGSS)
 - Inflammatory lesions count
 - Non-inflammatory lesion count
- Combination product vs. each monad
 - Inflammatory lesion count
 - EGSS

Following comments are in response to the SAP.

1. The Division reiterates previous comments from the March 7, 2005 meeting that the Evaluator's Global Severity Score should be on a 5-grade scale instead of a 6-grade scale.
2. The sponsor proposed to stratify subjects by Baseline Evaluator's Global Severity Score (EGSS) (moderate vs. severe) and by two skin phototype groups (I, II, III vs. IV, V, VI), therefore by 4 strata. The sponsor should provide the reasoning for using such stratification factors. Stratification should be limited to factors that are expected to be highly correlated to the efficacy results. Each stratum should have sufficient number of subjects to avoid empty cells and their impact on the analysis.
3. If the sponsor chooses to stratify subjects at randomization, the stratification factors should be included in the analysis model. This should be applied in both the lesion count and EGSS analyses.

The sponsor agreed to include the stratification factors in the analysis model for lesion counts. However, they stated that it would be infeasible to include the factors in the Cochran-Mantel-Haenszel (CMH) model to analyze EGSS. The sponsor suggested that they could use Generalized Linear Interactive Modeling (GLIM) instead of CMH. The Agency responded that GLIM could be used as a supportive analysis.

4. If the treatment by center interaction is significant, the protocol should pre-specify a sensitivity analysis to ensure that the efficacy results are not driven by extreme centers (e.g. evaluating efficacy after deleting extreme centers).
5. The sponsor proposed two sensitivity analyses to investigate the impact of data imputation on the EGSS. The protocol should include a sensitivity analysis to investigate the impact of the imputation method on lesion counts as well to ensure that the efficacy results are not driven by the imputation method.
6. The protocol states to use an ANOVA model with treatment, center, center by treatment interaction as factors, and baseline lesion count as covariate to analyze the lesion counts. The reviewer assumes that the sponsor plans to use an ANCOVA model, not an ANOVA model for the analysis.

Clinical Microbiology:

There were no clinical microbiology questions identified in this briefing package. We have the following comment for the sponsor:

Agency:

1. The Sponsor needs to be aware that because no microbiology data is being gathered during the Phase 3 clinical studies the "Microbiology" section of the package insert will be limited in what is said about Clindaben™ from a microbiology perspective.
2. Please provide information on the in vitro activity of clindamycin and benzoyl peroxide individually against *P. acnes*. Information on the in vitro activity of the combination of clindamycin and benzoyl peroxide required to inhibit the growth of *P. acnes* should also be submitted to the Agency. This information can be from recent laboratory studies (within the last 3 years) or from the recent literature (within the last 3 years).

The Sponsor asked for the number of bacterial isolates for which clindamycin, benzoyl peroxide, and the combination of benzoyl peroxide in vitro susceptibility data had to be provided. The Agency indicated that data for at least 100 isolates of *Propionibacterium acnes* needs to be provided. Included in the 100 isolates should be isolates with different mechanisms of antimicrobial resistance. The Sponsor indicated that they are in the process of obtaining the information and in the mean time they will submit the data they have to date to the IND for review and comment by the Agency. The Agency indicated that this is acceptable.

Project Management:

Agency:

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. 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 information requests.
3. Based on the repeal of section 507 of the Food, Drug and Cosmetic Act, the sponsor is advised that Clindaben Gel (clindamycin, 1% - benzoyl peroxide, 2.5%) would not be eligible for marketing exclusivity. The sponsor may refer to the guidance document issued by the Agency in May 1998, *Guidance for Industry and Reviewers Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. This guidance document defines the administrative actions required by the agency for reviewing and approving antibiotic drug applications that were submitted after November 21, 1997. The sponsor may also refer to the *Federal Register* notice 99N-3088, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs* issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507.
4. The sponsor is encouraged to submit its revised protocols as Special protocols through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review, comment and agreement, prior to study initiation.
5. The sponsor is encouraged to request a Pre-NDA Meeting at the appropriate time.
6. The sponsor is reminded that all new NDAs/BLAs and efficacy supplements submitted on or after June 30, 2006 must include content and format of prescribing information based on the new Physicians Labeling Rule at the time of submission (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

Minutes Preparer: _____
Margo Owens/Regulatory Project Manager DDDP

Chair Concurrence: _____
Susan Walker, M.D./Division Director, DDDP

**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/

Susan Walker
10/13/2006 01:27:34 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 41,733

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

Please refer to your Investigational New Drug Application (IND) file for Clindabene Gel (1% clindamycin phosphate, 2.5% benzoyl peroxide).

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2005. The purpose of the meeting was to discuss your drug development plans.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

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

Enclosure

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

Meeting Date: March 7, 2005
Meeting ID# 14738

Time: 10:30 a.m.

Location: N225

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel

Indication: Treatment of Acne vulgaris

Sponsor: Dow Pharmaceutical Sciences

Guidance Meeting

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Jonca Bull, M.D., Office Director, ODEV, HFD-105
Shaw T. Chen, M.D., Ph.D., Associate Director for Special Product Review-Botanical Drug Products, HFD-105
Ramesh Sood, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Saleh Turujman, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Paul Brown, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Abi Adebawale, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer, DPEIII, HFD-880
Fred Marsik, Ph.D., Clinical Microbiology Team Leader, DAIDP, HFD-520
Markham Luke, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540
Phyllis Huene, M.D., Medical Officer, DDDDP, HFD-540
Mohamed Alesh, Ph.D., Biostatistics Team Leader, DBEIII, HFD-725
Steve Thomson, Biostatistics Reviewer, DBEIII, HFD-725
James Morton, Pharmacist Intern, FDA Experiential Program
Frank H. Cross, M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Barry M. Calvarese, Vice President, Regulatory Affairs and Clinical Affairs
David Osborne, Ph.D., Vice President, Product Development
Gordon Dow, Ph.D., Founder and Chief Technical Officer
Karl Beutner, MD, Ph.D., Vice President and Chief Medical Officer

b(4)

A.J. Acker, RAC, Associate Manager, Regulatory Affairs
Karen Yu, Ph.D., Senior Product Manager

With reference to the February 4, 2005, briefing package, the following discussion took place:

Chemistry, Manufacturing and Controls:

Sponsor's CMC Question 1 of February 4, 2005, Briefing Package: "DPS has updated the CMC section with new information taking into account previous questions by the Agency from the December 12, 2003 (*sic*) guidance meeting. The new information contains updated specifications and directions to the pharmacist for preparing the combination product. Does the Agency agree with the proposed CMC plan?"

Agency:

No. The sponsor did not adequately address the CMC issues raised at the Guidance Meeting of November 12, 2003. The sponsor is requested to respond to all the issues raised by the chemistry reviewer during the guidance meeting of November 12, 2003. If some of these issues were addressed in a previous IND amendment, the sponsor is requested to please cite the number and date. The deficiencies in the current briefing package are listed below.

The sponsor was requested at the guidance meeting of November 12, 2003, to provide a compilation table of the batches/lots used in the studies to date, clearly indicating in addition to the site and date of manufacture, the batch/lot size, the formulation (with or without preservatives, _____, etc.), which batches were used in which studies i.e., clinical, toxicology, stability, studies (including protocol number), etc. The information provided in Table 2.3 in the current briefing package is inadequate. For example, it does not provide information on the site and date of manufacture of the batches listed, and how the batches were used (clinical, toxicological, biopharmaceutical, etc.).

b(4)

1. Quantitative Composition

In Table 2.4, the _____ of benzoyl peroxide should be justified. The _____ of clindamycin phosphate in Table 2.5 should be justified.

b(4)

The amount of water in the combination product (Table 2.6) should be specified. Qs. is not acceptable as the sole entry for such a large amount. Minor adjustments to the specified amount may be made to take into account the variation in the amount of potassium hydroxide added to _____

b(4)

2. Specifications

- a. The sponsor is reminded that according to the ICH Q6A, a specification is defined as a list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described. In the tables of proposed specifications for the drug products, the column heading entry should be "acceptance criterion", instead of the current "regulatory specifications".
- b. The identification test for benzoyl peroxide and for clindamycin phosphate should be specific. Simple matching of sample and standard retention times alone is not considered to be specific. However, HPLC coupled with UV or MS is considered specific.

IND 41,733, Clindabene™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

The sponsor is requested to clarify what is meant by the entry "positive for" in the identification test for benzoyl peroxide and for clindamycin phosphate in the tentative specification tables.

- c. The proposed impurity levels are too high. Have batches with this level of impurities been qualified? Each acceptance criterion should be set no higher than the qualified level of the given degradation product. Furthermore, the acceptance criteria for specified impurities and for total impurities should be based on the actual results of stability studies of manufactured batches (clinical and registration). While it is understood that the impurity profiles for the two drug substances will be defined as a result of the stability study, and that the impurities will be evaluated as required by the Phase 3 stability protocol, the following deficiencies are noted in the proposed specifications of the intermediate and final drug products.

3. Tentative Specification for Benzoyl Peroxide Gel

There are several deficiencies in the proposed tentative regulatory specification of Benzoyl Peroxide Gel (Table 2.7).

Table 2.7 Tentative Product Specifications of Benzoyl Peroxide Gel

Test	Regulatory Specification
Appearance	Opaque white to off-white smooth gel
Identification Test	Positive for Benzoyl Peroxide
pH	
Benzoyl Peroxide Content	
Degradation Products:	
Homogeneity	
Viscosity	
Microscopic Examination	
Microbial Limit Test	

NMT - Not More Than

b(4)

- a. Although the appropriateness of the proposed values for acceptance criteria are review issues, the proposed acceptance criteria of the degradation products seem too high. For example, the acceptance criterion of _____ for _____ is too high without adequate justification. As stated above, justification should be provided for all the proposed acceptance criteria.
- b. The sponsor states on page 11 in the CMC section of the briefing jacket (CMC Tab) that no _____ was detected in early stability studies (7% benzoyl peroxide formulation), yet an acceptance criterion of _____ is set for _____. The sponsor also states that "_____".

b(4)

b(4)

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

If oxidation were to occur, the final oxidation products are likely to be the natural products _____, yet no acceptance criterion is set for either "likely" decomposition product. If no acceptance criterion is set for either of these compounds, the sponsor has to demonstrate that these "likely" compounds are absent from the drug product through its shelf life.

b(4)

- c. "Report", as shown in the above table, is not an acceptable entry for an acceptance criterion. The homogeneity and microscopic examination attributes should be specified.
- d. The proposed limit of _____, for unknown degradation impurities is too high. The sponsor is referred to the recommended values under ICH Q3B, and to the additional comments below.
- e. The sponsor is requested to justify the upper limit of the benzoyl peroxide content (_____).

b(4)

b(4)

4. Tentative Specification for Clindamycin Phosphate Concentrate

There are several deficiencies in the proposed tentative regulatory specification of Clindamycin Phosphate Concentrate (Table 2.8).

Table 2.8 Tentative Product Specifications of Clindamycin Phosphate Concentrate

Test	Regulatory Specification
Appearance	Colorless to pale yellow clear solution with a distinctive odor
Identification Test (HPLC)	Positive for Clindamycin Phosphate
pH	
Clindamycin Content (Clindamycin Phosphate and Clindamycin)	
Degradation products	
Stability	

NMT - Not More Than

b(4)

- a. The sponsor is asked to explain the source of the "pale yellow" color and the "distinctive odor". An odor test is not recommended.
- b. An acceptance criterion is not provided for "free" clindamycin. Instead, clindamycin is listed together with the parent drug substance, clindamycin phosphate. This is not acceptable. The sponsor is requested to list clindamycin separately from the parent drug substance, clindamycin phosphate, and to provide an acceptance criterion for "free" clindamycin. The sponsor should also be requested to provide properly labeled HPLC chromatograms (LCs) where the two compounds are resolved (separated).
- c. The sponsor is requested to justify the upper limit of the clindamycin content (_____). The sponsor is reminded that _____ are not permitted.
- d. The only specified degradation product of clindamycin is _____ for which an acceptance criterion of _____ is proposed.

b(4)

b(4)

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

Justification for such a high acceptance criterion should be provided. No other known degradation products of clindamycin phosphate, such as _____, are listed in the proposed regulatory specification. The sponsor is requested to provide justification (evidence) that these related degradation products do not increase on storage or are absent over the requested shelf life of the product. (Representative chromatograms recorded under analytical conditions which can detect these degradation products at the expected ICH levels in the drug product should be provided in the NDA.)

b(4)

- e. The proposed limit of $\frac{1}{10}$ for unknown degradation impurities is too high. The proposed acceptance limit for individual degradation products should be justified based on the actual accrued data. Although ICH Q3B guidance does not apply to products containing fermentation and semi-synthetic drug substances, the sponsor can use the general principles described in this guidance to set appropriate acceptance criteria for impurities. The recurring impurities should be classified as specified unknown impurities with their individual acceptance criteria. More restrictive acceptance criteria should be proposed for unspecified unknown individual impurities.

b(4)

5. Tentative Specification for Clindaben (clindamycin phosphate 1%, benzoyl peroxide 2.5%) Gel

There are several deficiencies in the proposed tentative regulatory specification of Clindaben (clindamycin phosphate 1%, benzoyl peroxide 2.5%) Gel (Table 2.9).

**Table 2.9 Tentative Regulatory Specifications of Clindaben (1/2.5)
(clindamycin/benzoyl peroxide) Gel to Access Shelf Life of Admixed Product**

Test	Regulatory Specification
Appearance	Opaque white to off-white smooth gel
Microbial Limit Test*	Pass
pH	_____
Benzoyl Peroxide Content	_____ label claim
Degradation Products**	Report as % of label claim
_____	_____
_____	_____
Clindamycin Content (Clindamycin Phosphate and Clindamycin)	_____ label claim
Degradation Products***	Report as % of label claim
_____	_____

b(4)

* On initial
 ** Expressed as percentage of benzoyl peroxide label claim.
 *** Expressed as percentage of Clindamycin label claim.
 NMT - Not More Than

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

- a. An acceptance criterion is not provided for "free" clindamycin. Instead, clindamycin is listed together with the parent drug substance, clindamycin phosphate. This is not acceptable. The sponsor is requested to list clindamycin separately from the parent drug substance, clindamycin phosphate, and to provide an acceptance criterion for "free" clindamycin. The sponsor should also provide properly labeled HPLC chromatograms (LCs) where the two compounds are resolved (separated).
- b. The sponsor is requested to provide justification for the upper limit of the clindamycin content (——— similarly, for the upper limit of the benzoyl peroxide content ——— **b(4)**
- c. The above (deficiency) comments concerning the known degradation products of benzoyl peroxide in the Benzoyl Peroxide Gel and the known degradation products of clindamycin phosphate in the Clindamycin Phosphate Concentrate apply also to the Clindaben Gel.
- d. The proposed limits for unknown degradation impurities related to benzoyl peroxide exceed the recommended values under ICH Q3B. The limits under ICH Q3B are calculated on the basis of the maximum daily use of the drug product. According to the absorption evaluation of Clindaben (Maximum topical exposures in Appendix 2 of the briefing jacket), 4 g of the drug product was applied to the face, back, neck and chest. The ICH Q3B limits are calculated below on the basis of a 4 gm daily dose. Please see our comment 5 above under clindamycin phosphate concentrate regarding setting acceptance criterion for individual impurities related to clindamycin phosphate.
- e. According to ICH Q3B (Attachment 1), when the maximum daily dose of a drug substance is >100 mg but less than 2 g, as it is for benzoyl peroxide (1.2 g) in this drug product, the respective identification and qualification thresholds for impurities would be 0.2% or 2 mg TDI and 0.2% or 3 mg total daily dose, whichever is lower. The proposed acceptance criterion for each unknown related degradant of benzoyl peroxide is also ——— which is — times the ICH Q3B threshold. **b(4)**

The sponsor is requested to provide a justification for the acceptance criteria of NMT — for any unknown substances related to benzoyl peroxide in the regulatory specification of the benzoyl peroxide gel drug product (Table 2.7). **b(4)**

6. Manufacturing, Controls

- a. Although a general step-by-step description of the manufacturing method for Benzoyl Peroxide Gel is provided (on page 14), the in-process controls required to monitor the step in question are not provided. For example, in one of the ———, the instructions call for the ——— without stating how the operator determines the proper ———. Similarly, ——— calls for the [benzoyl peroxide] ——— without providing how proper ——— and even ——— is ascertained. **b(4)**
- b. Similar deficiencies are found in the manufacturing controls provided in the general step-by-step description of the manufacturing method of the Clindamycin Phosphate Solution.

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

- c. A brief description of the packaging and labeling process for clinical supplies should be also provided. Reprocessing procedures and pertinent controls should be described, if applicable.

7. Container Closure System

The sponsor is reminded that any changes in the container closure system (also referred to as the packaging system) should be reported. The sponsor is also reminded to ascertain that their vehicle does not cause extractables to contaminate the drug product, by including qualitative and quantitative extraction profiles of the container closure using the particular vehicle or an appropriate solvent. Please refer to Attachment C of the CDER Guidance for Industry "*Container Closure Systems for Packaging Human Drugs and Biologics*", which is available on the CDER website.

8. Stability

- a. The sponsor states that they plan to manufacture additional batches at the commercial site, and that the batches will be used in the proposed clinical studies. The sponsor also states that stability studies will be performed on these batches, and the data will be provided to the Agency. However, a stability protocol was not provided.
- b. The sponsor is reminded of the following:
 - i. To provide the stability protocol that will be used in the primary stability studies. The stability protocol should include a description of the drug product under investigation in the stability program, a description of the packaging, a list of the tests, sampling time points for each of the tests, temperature and humidity conditions to be studied, expected duration of the stability program, and the proposed bracketing/matrixing protocol, if applicable.
 - ii. The following information should be included in an NDA (needed information to bear in mind for an NDA submission)\
 - A detailed data table that includes the lot number, manufacturing site, the date of manufacture of the drug product, and the drug substance used to manufacture the lot should be provided. Each table should contain data from only one storage condition. Individual data points for each test should be reported. Representative chromatograms should be provided, if applicable.
 - A short description should be provided for each of the parameters being investigated in the stability program (i.e., stress, long-term, and accelerated) demonstrating that the appropriate controls and storage conditions are in place to ensure the quality of the product used in clinical trials. Tests unique to the stability program should be adequately defined.

- The shelf life (expiration date) that will be granted will be based on a review of stability data provided under ICH conditions. For planning purposes, it is recommended that the stability protocol be extended through the proposed expiration data. It is recommended that the NDA submission contain stability information from accelerated and long-term testing on three batches of the same formulation of the dosage form in the container closure proposed for marketing. Two of the three batches should be at least pilot scale. The third batch may be smaller.

Pharmacology/Toxicology:

Sponsor's question 2 of February 4, 2005, Briefing Package: "DPS believes that the nonclinical studies completed for ~~1/5~~ (1/5) Gel fully supports Clindaben (1/2.5) Gel. In addition to the studies already completed, DPS will complete genotoxicity studies prior to filing of the NDA. Does the Agency agree?"

Agency:

1. As previously noted, the nonclinical studies already conducted for Clindaben appear to be adequate in principal to support a 505(b)(2) NDA provided that the sponsor establishes a sufficient clinical bridge to an approved clindamycin/benzoyl peroxide product. If the sponsor does not establish a clinical bridge to an approved clindamycin/benzoyl peroxide product (whether 505(b)(1) or 505(b)(2)) then additional nonclinical information would be needed to support an NDA including a chronic topical toxicity study in a nonrodent model, genotoxicity and developmental and reproductive toxicity. Studies conducted with the 1/5 formulation would likely be adequate to support the 1/2.5 formulation. Note that other changes such as increased levels of active or inactive ingredients may not be supported by the existing studies.
2. It is noted that the sponsor plans to complete genotoxicity studies to support the NDA. It is recommended that this information be consistent with the appropriate ICH guidances (S2A, S2B). In general, genotoxicity studies are conducted with individual compounds. Reproductive and developmental toxicity information for each active ingredient was also previously noted as absent. It is recommended that reproductive and developmental toxicity studies consistent with ICH guidances be included in an NDA (See ICH M3, S5A, S5B).
3. It is also noted that the tentative product specifications have relatively high levels of degradation products. The sponsor should provide information on the levels of these degradation products in the materials used in the nonclinical and clinical studies so that it can be determined if they are adequately qualified or the sponsor should otherwise qualify these levels.

Clinical Microbiology:

1. In the Phase 3 study protocol (#7002-EIHP-01-05), please include a provision to collect specimens from inflammatory and non-inflammatory lesions of subjects who do not respond to treatment with Clindaben for culture of *Propionibacterium acnes*. All isolates of *P. acnes* need to be tested against clindamycin and benzoyl peroxide to determine the concentrations of these antimicrobials individually and combined required to inhibit the growth of the *P. acnes* isolates.

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

The sponsor agreed to test isolates of *P. acnes* obtained from a subset of acne patients who fail therapy by clinical criteria. The isolates would be tested against clindamycin and if possible against benzoyl peroxide. The sponsor raised the issue that benzoyl peroxide is not soluble in water and therefore it may not be possible to test it against the isolates. The sponsor agreed to investigate this further and to let the Agency know if it is or is not possible to test benzoyl peroxide against the isolates. The sponsor will submit their proposal for determining what acne patients will be cultured, how specimens will be obtained, and what method will be used to determine the isolates susceptibility to clindamycin and if possible, benzoyl peroxide, to the Agency for review. The Agency agreed that the sponsor's proposal was a satisfactory way to proceed.

2. Please provide information on the in vitro activity of clindamycin and benzoyl peroxide against *P. acnes*. If data is available on the concentration of the combination of clindamycin and benzoyl peroxide required to inhibit the growth of *P. acnes* that information should be submitted to the Agency. This information can be from recent laboratory studies (within the last 3 years) or from the recent literature (within the last 3 years).
3. The sponsor needs to be aware that because there will be no microbiology data being gathered during the Phase 3 clinical study the "Microbiology" section of the package insert will be limited in what is said about Clindaben from a microbiology perspective.

Clinical Pharmacology/Biopharmaceutics:

Sponsor's question 3 of February 4, 2005, Briefing Package: "A Phase 2 systemic absorption study is proposed to be conducted and submitted in the NDA. Does the Agency agree with the overall design of the protocol provided in Appendix 2?"

Agency:

No we do not agree. Please see comments below:

1. Frequency of dosing:

Please clarify the proposed once a day application for this study, particularly in light of the proposed Phase 3 Protocol 7002-E1HP-01-05 which has a twice a day frequency of dosing.

2. Duration of dosing:

Please provide a rationale for the proposed 14-day duration of dosing.

3. Use of the highest proposed strength:

Please provide a rationale for the application of the proposed 4 gram weighed dose of Clindaben (1/2.5) gel face, neck, back and chest. Comments are also needed to explain the protocols claim that this daily dose represents a four-fold increase over the anticipated typical upper clinical dose.

b(4)

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

4. PK Sampling and Analytical methods:

Please clarify why the absorption by the skin of benzoyl peroxide is not being measured.

The sponsor acknowledged the above comments.

The sponsor stated that they do not intend to measure benzoyl peroxide in plasma because it is challenging in terms of assay development so they would like a waiver of this requirement. The Agency asked the sponsor to put together their rationale and request for a waiver in writing, which we would look at and provide them with the appropriate response.

The sponsor was also asked to remove the ceiling of \angle as the maximum daily dose because clinically the patient may use more than \angle .

b(4)

Clinical

Sponsor's question 4 of February 4, 2005, Briefing Package: "Based on recent prior experience with large scale combination product acne trials, questions can be raised regarding the sensitivity of the static global acne scale to changes in non-inflammatory lesions and to its bearing on clinically meaningful improvement. The sponsor understands the Agency's rationale and agrees with the utilization of the static global acne scale as the primary endpoint when comparing the combination product to the vehicle. However, the sponsor proposes that the static global acne scale is a secondary endpoint when comparing the combination product to the monads due to the limited sensitivity and correlation to clinically meaningful outcomes. Does the Agency concur?"

Agency:

1. The Agency does not concur. The static global scale provides a clinically and regulatory useful evaluation of the subject as a whole with regard to severity of acne. The Agency continues to recommend that this be used as a co-primary endpoint along with the lesion counts for any evaluation of this acne product including for a superiority comparison of the dyad combination product to the monads. Achieving success in this manner is a clinically meaningful outcome.
2. The basis for the sponsor's assertion does not appear to be well-grounded. The sponsor is invited to provide evidence to support this assertion, to enable further discussion in this regard.

Sponsor's question 5 of February 4, 2005, Briefing Package: "The sponsor believes that, when comparing a combination acne product to its monads, the insensitivity of the static global acne scale results in unreasonable sample size requirements.

The sponsor would like to propose an approach to address this with a meta-analysis or integrated summary of efficacy method by combining the static global acne scale efficacy data from both Phase 3 studies and then apply inferential statistics to compare the combination product to the monads. Please comment on this approach."

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

Agency:

The static global assessment provides useful information on the acne subject for the investigator and the Agency and should be retained. As information regarding this endpoint from two studies is needed for a single-ingredient product for approval, this is also needed for the dyad vs. each of the monad comparators. Dosing and power calculations should be based on Phase 2 studies. Please also see Biostatistics comments below.

The sponsor stated that the global has only 50% of the power as compared to lesion counts and needs more patients to allow for success.

Sponsor's question 6 of February 4, 2005, Briefing Package: "The sponsor would like to consider pursuing an indication for both 'acne' and '_____ ', depending on the outcome of the Phase 3 clinical studies. If the combination drug product beats both monads and vehicle in two out of three lesion counts, then an 'acne' claim would be possible. If the combination drug product beats both monads and vehicle in the inflammatory lesion count, then an ' _____ ' claim would be possible. Please comment on this approach."

b(4)

Agency:

1. Either an indication for 'acne' or ' _____ ' may be sought so long as the indication being sought is pre-specified and depending on the outcome of the clinical trials. Multiple analysis plans may result in an adjustment to preserve alpha (see Biostatistics comments below). The investigator's static global evaluation should be a part of the primary efficacy variable.
2. The sponsor is taking a risk as Phase 2 studies were not done with the proposed formulation. The sponsor is welcome to propose for discussion with the Agency an alternative statistical plan that would involve a nesting approach to evaluate "acne" and " _____ ". Please note the indication for ' _____ ' alone will likely be worded differently from that currently in the Duac label.

b(4)

Additional Agency Comments

1. For a 505(b)(2) application, the sponsor should conduct comparisons to the reference listed product(s) to provide clinical information on comparative bioavailability (i.e., 21 CFR 320.24(b)(4)). See guidance meeting minutes from November 12, 2003. With regard to a 505(b)(2), the sponsor should specify the informational pieces that are sought from the reference listed drug product with regard to the Agency's findings of safety and efficacy for that listed drug product.
2. Further, this is a fixed combination product as per 21 CFR 300.50. The sponsor should adequately demonstrate that the combination dyad product is superior to each of the monads in product vehicle and the vehicle alone for each of the primary endpoints. This could be accomplished via two adequate and well-controlled clinical studies that incorporate each of the needed arms.

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

3. The Agency also commented on 2 point improvement on a 5 point acne global (0 to 4) as a potential evaluation of success. It was discussed that 2 point improvement could be taken as a measure of global success if the studies prespecified this endpoint as a win. Subjects who start the study as "severe" or 4 would need to improve to "mild" or 2. Subjects who start the study as "mild" would need to improve to "clear" or 0. Labeling in the Clinical Studies section would reflect the prespecified endpoints. If subjects who enter as "severe" do not "clear" or "almost clear" (0 or 1) then the Indications and Usage section would indicate that the drug product would not be indicated for severe acne.
4. With regard to resistance concerns, the Sponsor should demonstrate whether lack of efficacy can be correlated with drug resistance.
5. The sponsor should conduct dermal safety studies using the final to-be-marketed drug products. Generally, the required topical safety studies are cumulative irritancy (not less than 30 evaluable subjects), contact sensitization (not less than 200 evaluable subjects), photoallergenicity (not less than 50 evaluable subjects), and phototoxicity (not less than 30 evaluable subjects). These studies should be conducted with the final to-be-marketed formulation and is usually conducted in parallel with phase 3 studies. However, if Phase 1/2 studies should reveal an irritancy signal, and the product is to be labeled as an irritant, cumulative irritancy testing may not be needed. Phototoxicity and photoallergenicity studies may be waived by the Agency if there is no absorption in the 290 to 700 nm range.
6. The sponsor should address ICH E1A regarding long term safety assessment of their drug product for the chronic indication of acne vulgaris. The sponsor queried whether with a 505(b)(2) application, where the Agency used the findings of safety and efficacy for a reference listed product, the need for long term safety could be waived. The Agency replied that if the excipients and the active ingredients do not indicate potential serious concern regarding long-term safety, then potentially, the sponsor could put together an argument as to why such a study could be conducted as a Phase 4 study rather than as required pre-approval.
7. The sponsor should study an acne population that is relevant to that seen in the United States. The demographics with regard to race and gender of studies conducted should adequately address this need.

Biostatistics:

Sponsor's question 4 of February 4, 2005, Briefing Package: "Based on recent prior experience with large scale combination product acne trials, questions can be raised regarding the sensitivity of the static global acne scale to changes in non-inflammatory lesions and to its bearing on clinically meaningful improvement. The Sponsor understands the Agency's rationale and agrees with the utilization of the static global acne scale as the primary endpoint when comparing the combination product to the vehicle. However, the Sponsor proposes that the static global acne scale is a secondary endpoint when comparing the combination product to the monads due to the limited sensitivity and correlation to clinically meaningful outcomes. Does the Agency concur?"

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

Agency:

The Agency disagrees with the sponsor proposal to use the static global acne scale as a secondary endpoint when comparing the combination product to the monads. The global acne scale takes into account both inflammatory and non-inflammatory lesions, yet it places more weights on inflammatory lesions compared to non-inflammatory lesions. Estimates of lesion counts (inflammatory or non-inflammatory) tend to be inaccurate especially when lesions counts are large.

Sponsor's question 5 of February 4, 2005, Briefing Package: "The sponsor believes that, when comparing a combination acne product to its monads, the insensitivity of the static global acne scale results in unreasonable sample size requirements. The sponsor would like to propose an approach to address this with a meta-analysis or integrated summary of efficacy method by combining the static global acne scale efficacy data from both Phase 3 studies and then apply inferential statistics to compare the combination product to the monads. Please comment on this approach."

Agency:

For replication of study findings efficacy results for each of the co-primary endpoints should be established for each study independently. A possible approach for reducing the sample size is to use unequal treatment allocation for the different treatment arms based on the sponsor's experience with the efficacy for the various treatment arms. Other approaches for reducing the sample size include seeking a specific acne type indication or disease severity based on efficacy results from sponsor's previous studies.

Sponsor's question 6 of February 4, 2005, Briefing Package: "The sponsor would like to consider pursuing an indication for both 'acne' and '_____', depending on the outcome of the Phase 3 clinical studies. If the combination drug product beats both monads and vehicle in two out of three lesion counts, then an 'acne' claim would be possible. If the combination drug product beats both monads and vehicle in the inflammatory lesion count, then an '_____' claim would be possible. Please comment on this approach." b(4)

Agency:

Efficacy results from the sponsor's previous trials might be utilized in forming the statistical hypotheses to be tested so that the sponsor achieve their objective above and Type I error rate remains controlled. However, for the validity of this approach a pre-specification of the statistical hypotheses to be tested is required.

Additional Biostatistics comments:

1. The protocol indicated that "a sensitivity analysis will be conducted to investigate the impact of data imputation on the dichotomized global severity", however, no method is specified. The protocol should pre-specify the planned method to be used in the sensitivity analysis, as selection of the method after the data collected does not ensure efficacy results are not driven by the method of data imputation.

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

2. The protocol stated that "an overall treatment test (using the data from all treatment groups under consideration) will be presented, and then to carry pairwise comparison only when the overall test is significant." The goal of this overall comparison is not clear. Furthermore, the proposed approach might not control Type I error rate.
3. The protocol indicated that pooling will be carried out to achieve a minimum of 8 subjects in each active treatment arm. The Agency recommends the study be planned to have minimum of 5 subjects in the vehicle arm (i.e., 10 subjects per active arm) to avoid problems in the analysis of cell with 0 frequency. The protocol might pre-specify an approach for pooling small centers if actual enrollment did not meet the above criteria for some centers.

The sponsor is referred also to the Agency comments made at the Guidance meeting conducted November 12, 2003.

Project Management:

1. Comments shared with you today 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.
2. For applications submitted after February 2, 1999, you are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
4. You are encouraged to request and attend an End of Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Comments on Phase 1 and Phase 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.

The meeting ended amicably.

Minutes preparer: Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Project Manager

Concurrence Chair (or designated signatory): Jonathan K. Wilkin, M.D., Division Director

**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
4/1/05 05:24:07 PM