DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 7 2003

David M. Fox, Esq.
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Washington, D.C. 20004

RE: Docket No. 03P-0140/CP1

Dear Mr. Fox:

This letter responds to your citizen petition (Petition) dated April 7, 2003, requesting that the Food and Drug Administration (FDA) refrain from approving abbreviated new drug applications (ANDAs) for topical mupirocin ointment products (mupirocin) where the applicant cannot support all elements of the labeling approved for the reference listed drug (RLD), GlaxoSmithKline's (GSK) Bactroban Ointment (Bactroban) (NDA 50-591). Specifically, you ask that FDA refrain from approving mupirocin ANDAs under section 505(j) of the of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355 (j)) where the applicant's bioequivalence data is substantially the same as that submitted in support of the approved Clay-Park Labs, Inc. (Clay-Park), 505(b)(2) (21 U.S.C. 355(b)(2)) new drug application (NDA) for mupirocin. If the data for any new topical mupirocin ointment product fails to support the full labeling of the RLD, you request that we require the submission of an NDA under section 505(b) of the Act. You also ask that FDA enforce a regulatory requirement that a showing of bioequivalence based on comparative clinical studies must include more than one independent, adequate and well-controlled study (21 CFR 320.24(b)(4)).[1]

In reaching its decision, FDA has considered all of the information in the Petition, comments from Heller, Ehrman, White & McAuliffe dated May 21, 2003, as well as other information available to the Agency. For the reasons set forth below, the Petition is denied.

## I. Background

The Agency approved GSK's NDA for Bactroban on December 31, 1987 (NDA 50-591). Bactroban is indicated for the topical treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*. In December 2002, we approved Clay-Park's NDA for mupirocin (NDA 50-788) under section 505(b)(2) of the Act. FDA allowed Clay-Park to duplicate certain sections of the approved labeling for Bactroban for use in treating impetigo. However, the Clay-Park labeling does not duplicate Bactroban's full Microbiology labeling. Clay-Park chose to delete the methicillin-resistant *Staphylococcus aureus* (MRSA) information rather than provide additional data requested by FDA.

[1] Your petition cites 21 CFR 320.24(b)(2), but we assume that this was a typographical error. 21 CFR 320.24(b)(2) refers to a urinary excretion study. 21 CFR 320.24(b)(4) refers to well-controlled clinical trials.

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PDN 1

## II. Discussion

### A. ANDAs Submitted Under 505(j) of the Act and NDAs Submitted Under 505(b)(2) of the Act

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Act, which established the current ANDA approval process. An ANDA applicant does not have to submit evidence of the safety and effectiveness of the drug product, because an ANDA relies on FDA's previous finding that the reference listed drug is safe and effective. Instead, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the reference listed drug as required by section 505(j)(2)(A)(iv) of the Act.[2] The scientific premise underlying the Hatch-Waxman Amendments is that, when other aspects of the drug products (e.g., active ingredient, strength, dosage form, labeling) are the same, bioequivalent drug products may be substituted for each other. A drug described in an ANDA is bioequivalent to the listed drug if:

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .[3]

The requirements for applications approved under section 505(b)(2) of the Act differ from the requirements for ANDA approval under section 505(j). An ANDA submitted under 505(j) must contain evidence that the proposed drug is bioequivalent to the reference listed drug (RLD) and that the proposed drug labeling is essentially the same as that of the approved listed drug. In contrast, an NDA submitted under section 505(b) is not required to be bioequivalent to the listed drug or to have the same labeling as the listed drug.[4] A 505(b)(2) application must contain information adequate to show that the drug is safe and effective.

### B. Bioequivalence

Approval of an ANDA for topical mupirocin ointment requires a showing that the proposed product is bioequivalent to Bactroban. You request that FDA follow certain bioequivalence requirements when it approves mupirocin ANDAs. You state that the bioequivalence requirement for ANDAs applies to both locally and systemically absorbed drug products. (Petition at 5) Because FDA has not published a guidance document on the demonstration of bioequivalence for topical

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[2] A drug that establishes bioequivalence as well as pharmaceutical equivalence is rated as therapeutically equivalent to the reference drug in FDA's *Approved Products with Therapeutic Equivalence Evaluations*, commonly referred to as the Orange Book.

[3] 21 U.S.C. 355(j)(8)(B)(i)); *see also* 21 CFR 320.1(e) and 320.23(b).

[4] A 505(b)(2) application is an NDA described in section 505(b)(2) of the Act. It is submitted under section 505(b)(1) of the Act and approved under section 505(c) of the Act.

drug products, and the scientific community has not accepted or validated any method, you claim that ANDA sponsors of topical drug products must demonstrate equivalence through "appropriately designed comparative trials" under 21 CFR 320.24(b)(4). (Petition at 6) You state that existing regulations require sponsors to conduct at least two independent trials to establish bioequivalence based on clinical endpoints (21 CFR 320.24(b)(4)). (Petition at 6)

FDA agrees that bioequivalence for topical mupirocin ointments may be established through the use of data from clinical trials. However, FDA disagrees that 21 CFR 320.24(b) requires that more than one clinical study be conducted to show bioequivalence. FDA interprets 21 CFR 320.24(b) to describe the types of studies ("approaches"), rather than the number of studies required.[5] The number of studies necessary for approval will depend on the specific product. For example, notwithstanding the fact that the regulation states that bioequivalence may be established by "[a]n in vivo test in humans . . ." (21 CFR 320.24 (b)(1)(i)), FDA has required more than one in vivo bioequivalence test for certain types of products (e.g., an in vivo study that measures the active moiety in the blood of fasting subjects and an in vivo study that measures the active moiety in the blood of fed subjects). See the guidance for industry on *Food-Effect Bioavailability and Fed Bioequivalence Studies* (December 2002).

FDA will determine what information is necessary to meet the statutory requirement for bioequivalence based upon the specific characteristics of the drug product under consideration. As the court in the *Schering* case recognized, "[a]lthough the Act mandates a showing of bioequivalence for generic drug approvals, there is no evidence that Congress intended to limit the discretion of FDA in determining when drugs were bioequivalent for purposes of ANDA approval." *Schering Corp. v. FDA*, 51 F.3d 390 at 399. The regulation at 21 CFR 314.94(a)(7) requires that an ANDA contain information showing that the drug product described in the ANDA is bioequivalent to the listed drug; 21 CFR 314.127(a)(6)(i) states that FDA will refuse to approve the ANDA if the information submitted is insufficient to show bioequivalence. In most cases, we require only one comparative clinical study to demonstrate bioequivalence for ANDAs for topical drug products.[6] Generally, we require only one clinical study for formulation changes for topical products of this type. For example, we approved the new polymer formulation for a topical tretinoin product (Avita cream 0.025%) submitted under (505(b)(2)) on one study. FDA therefore may decide what specific information is required to show that a mupirocin product described in an ANDA is bioequivalent to Bactroban.

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[5] This is similar to the Agency's interpretation of the language in section 505(j)(5)(D)((ii) and (iii) providing for 3 years of exclusivity if an NDA holder relies on new clinical studies for approval of an application or supplement. FDA interpreted the term "clinical studies" to describe the type of study necessary, not the number of studies, and will grant exclusivity on the basis of one required clinical study. 54 FR 28872, 28899 (July 10, 1989); 21 CFR 314.108.

[6] ANDAs for the following topical drug products were approved with only one bioequivalence study with a clinical endpoint: clotrimazole topical and vaginal cream, miconazole nitrate vaginal cream, and permethrin lotion.

FDA decides whether the amount of data and/or the number of studies submitted in an application are adequate to approve the application or to determine bioequivalence. If bioequivalence can be demonstrated with one appropriately designed bioequivalence study, we will not require additional studies. This is particularly important in light of one of the guiding principles for the conduct of an in vivo bioavailability study that no unnecessary human research should be conducted for such studies.[7] In addition, section 505(d) of the Act specifically recognizes that data from one adequate and well-controlled clinical study, together with confirmatory evidence, may be sufficient to show effectiveness. Therefore a single comparative clinical study, together with other supporting evidence, may be adequate to show comparative efficacy of mupirocin products to Bactroban.

Bioequivalence studies for generic mupirocin ointment 2% are generally designed as comparative clinical endpoint studies in patients 18 months of age or older with a clinical diagnosis of impetigo. Patients are randomized to receive the proposed ANDA product, the reference listed drug, or the vehicle (placebo). Typically, the randomization is 2:2:1, with equal numbers randomized to each active treatment arm and half as many to the placebo arm. These studies are double-blinded (which means that neither patients nor the medical staff evaluating the patients know which of the three study products is being used by the patient).

All patients enrolled are evaluated at baseline for signs and symptoms of impetigo on the Impetigo Skin Infection Rating Scale, and a bacterial culture of the lesion(s) is obtained. To qualify for analysis in the study, the culture for each patient must be positive for either *Streptococcus pyogenes* or *Staphylococcus aureus*. All patients whose cultures are not positive for one of these pathogens are discontinued and excluded from the analysis populations.

The conduct of the study is governed by specific study procedures. These procedures address the application of the assigned treatments, clinical evaluations and bacterial cultures, and follow-up evaluations.

The accepted primary endpoint for evaluation of bioequivalence of topical mupirocin products is the proportion of patients with clinical success. This is defined as sufficient resolution of signs and symptoms of infection, such that no additional antibiotic therapy is required to treat impetigo, as evidenced by assessment of certain clinical signs (e.g., blistering, inflammation, and itching) at the follow-up visit. Secondary endpoints include the proportion of patients with clinical success at the end of treatment, bacteriological success (defined as the absence of *Streptococcus pyogenes* or *Staphylococcus aureus* on culture) at the end of treatment, and bacteriological success at the follow-up visit.

To demonstrate bioequivalence, the 90% confidence interval of the difference between treatments in the proportion of patients with clinical success at the follow-up evaluation (i.e., the primary endpoint) must be within (-0.20, +0.20) in the population of compliant

[7] 21 CFR 320.25.

patients completing the study. Both active treatments should also be superior to placebo to show that the study design is adequately sensitive to show a difference between products.

We have decided that bioequivalence for topical mupirocin drug products can be demonstrated by an appropriately designed comparative clinical trial (i.e., a bioequivalence study with a clinical endpoint), such as that described above.[8] Only one such bioequivalence study with a clinical endpoint is necessary to support the approval of a mupirocin drug product under section 505(j). It is important to remember that the clinical study data submitted in an ANDA does not independently establish effectiveness, but demonstrates that the product can be expected to perform the same as the RLD.

All in vivo bioequivalence studies use one or more indicators of drug appearance at the site or sites of therapeutic activity. We review pharmacokinetic measures of bioavailability for a drug product intended to be absorbed into the systemic circulation and then delivered to the sites of activity by the blood. These measures reflect the rate and extent of absorption of the substance from the drug product and they are related to the drug availability at the sites of activity (21 CFR 320.24(b)(1)). For other drug products for which pharmacokinetic measures are not relevant or possible, pharmacodynamic measures are occasionally used as surrogate markers to signal the rate and extent of drug absorption and appearance at the site of activity (21 CFR 320.24(b)(3)). Even if a pharmacodynamic response is not directly related to the therapeutic response, it is still an effective measure that signals that the drug is at the site of therapeutic activity. In many cases where neither pharmacokinetic nor pharmacodynamic measures are possible, clinical endpoints in patients must be used as a signal of drug appearance at the site of activity. The drug must appear at the site or sites of activity to cause a clinical endpoint response. If clinical study data submitted in an ANDA demonstrate an equivalent clinical endpoint response to Bactroban and to the proposed mupirocin product, we are confident that the study provides an accurate demonstration of bioequivalence to Bactroban.

FDA has determined that data from a well-controlled comparative clinical trial can be used to establish bioequivalence for topical mupirocin ointment drug products. We disagree, therefore, with your analysis that 21 CFR 320.24(b)(4) requires at least two trials to ensure the validity of the results.

C. Labeling

In addition to the bioequivalence issue discussed above, you ask that we refrain from approving mupirocin ointment products under 505(j) of the Act when the applicant's bioequivalence data is substantially the same as the data supporting the Clay-Park 505(b)(2) application. (Petition at 2) In support of your request, you state that products approved under 505(j) must be for the same conditions of use and bear the same labeling

[8] See 21 CFR 320.24(b)(4).

as the RLD (21 U.S.C. 355(j)(2)(A)(i) and (v); 21 U.S.C. 355(j)(4); 21 CFR 314.92(a)(1)). (Petition at 4)

You also identify the differences between the Clay-Park labeling and the Bactroban labeling. (Petition at 7) FDA permitted the Clay-Park product submitted under 505(b)(2) to reference certain sections of the approved Bactroban labeling for use in treating impetigo, but did not permit the reference to Bactroban's full Microbiology section of the labeling. (Petition at 6) Specifically, the microbiology labeling for Bactroban states that mupirocin "is active against a wide range of gram-positive bacteria including methicillin-resistant Staphylococcus aureus (MRSA)." (Petition at 7) The Clay-Park labeling does not describe activity against MRSA. Clay-Park's labeling also includes a statement that "[m]ethicillin resistance and mupirocin resistance commonly occur together in Staphylococcus aureus and coagulase negative staphylocci," suggesting that the absence of activity against MRSA may be clinically significant. (Petition at 7) You argue that the limited use of the Bactroban labeling must be applied to all other similar mupirocin products that seek approval, either under 505(b)(2) or 505(j), based on a reference to Bactroban. (Petition at 7)

We agree that the mupirocin products approved under 505(j) of the Act generally must bear the same labeling as the RLD, Bactroban.[9] Section 505(j)(2)(A)(i) of the Act states that an ANDA must contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for [the listed drug]." If the proposed mupirocin product meets all the other requirements for approval under 505(j) and is bioequivalent to Bactroban, it is considered to be as effective as Bactroban in treating impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes* and, therefore, will bear the same indications as Bactroban.[10] The approved Bactroban labeling includes the statement "is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA)." Thus, any ANDA referencing Bactroban will also bear the same statement. If an ANDA meets all of the requirements of 505(j) and its implementing regulations at 21 CFR 314, FDA must approve the application.

The approval of the Clay-Park 505(b)(2) topical mupirocin product raises some unusual issues stemming from the differences between approvals under section 505(b) and (c) and those under section 505(j). Applications are approved under section 505(b) and (c) based upon the data available and standards for safety and effectiveness at the time of approval. In contrast, ANDA approvals generally are premised on the product in the ANDA duplicating a drug product that may have been approved many years before.

Differences between the labeling of the Clay-Park product and the labeling for Bactroban (and any ANDA referencing Bactroban) are based on the regulatory status of the Clay-

[9] Drug labeling for approved ANDAs can contain differences from the reference listed drug when the differences relate to different manufacturers for the drug product. See section 505(j)(2)(A)(v) of the Act (21 U.S.C. 355 (j)(2)(A)(v)); 21 CFR 314.94(a)(8)(iv); *Zeneca, Inc. v. Shalala*, 213 F.3d 161 (4th Cir. 2000).

[10] See section 505(j)(2)(A)(v) of the Act (21 U.S.C. 355 (j)(2)(A)(v)); 21 CFR 314.94(a)(8)(iv).

Park application as a 505(b)(2) NDA. FDA reviewed the Clay-Park 505(b)(2) for mupirocin ointment to determine whether it is safe and effective based on the Agency and sponsor's current medical and scientific knowledge. The Bactroban labeling states in the microbiology section that "Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. It is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA)." Because of recent information in the literature suggesting that resistance to mupirocin in MRSA is increasing,[11] FDA asked that Clay-Park provide evidence in its 505(b)(2) NDA that mupirocin is active against MRSA. Clay-Park elected not to provide such evidence and to delete the MRSA statement from the labeling. The Clay-Park NDA was approved without the statement regarding effectiveness against MRSA.

In contrast, an ANDA duplicates the listed drug, including the labeling for that product. Unless an approved product is withdrawn from the market for reasons of safety or effectiveness, it is a listed drug under section 505(j)(2)(A) and 21 CFR 314.3(b), and may serve as a basis for an ANDA approval. The statute requires, among other things, that an ANDA contain information to show "that the conditions of use prescribed, recommended, or suggested in the labeling . . . have been previously approved for [the listed drug]" (section 505(j)(2)(A)(i)). The statute further provides that FDA may not require information beyond that required in 505(j)(2)(A)(i) through (viii). Therefore, unlike in its review of a mupirocin 505(b)(2) NDA, FDA may not require an ANDA referencing Bactroban to contain additional data to support approval of labeling related to MRSA.

FDA also cannot refuse to approve ANDAs for mupirocin ointment on the grounds that information from the literature suggests that the labeling may need to be revised. FDA is required by statute to approve ANDAs referencing Bactroban that meet the requirements in section 505(j). Bactroban remains a listed drug approved by FDA and marketed by GSK with the MRSA labeling. FDA has not withdrawn or suspended the approval of the listed drug on any of the grounds set out in section 505(e), it has not issued a notice of opportunity for a hearing to withdraw approval of Bactroban, nor do any of the other bases for not approving an ANDA described in section 505(j)(4) apply. If and when the Bactroban labeling is revised to reflect reports of Bactroban resistance to MRSA, any ANDA referencing Bactroban must also be revised to duplicate the new approved Bactroban labeling. Until that time, the current Bactroban labeling is the labeling that must be referenced for purposes of ANDA approvals.

The approval of the Clay-Park NDA for a topical ointment raised the issue of what data is currently necessary to support a statement in the labeling of mupirocin products about effectiveness against MRSA. The same issue could have been raised in the review of any NDA for a new mupirocin product from GSK or another sponsor. It does not change the fact that Bactroban remains an approved product and thus may serve as a listed drug for ANDAs. Therefore, we deny your request to require that any mupirocin product

[11] See Barry D. Cookson, "The Emergence of Mupirocin Resistance: A Challenge to Infection Control and Antibiotic Prescribing Practice," *Journal of Antimicrobial Chemotherapy* (1998) 41; 11–18.

submitted as an ANDA under 505(j) carry the Clay-Park labeling, not the Bactroban labeling.

D. Q1, Q2, and Q3

You state that 21 CFR 314.94(a)(9)(v) generally requires that topical products submitted under section 505(j) contain the same inactive ingredients as the listed drug. (Petition at 8) You assert that topical products are formulated to contain the same inactive ingredients in essentially the same quantity or ratio as the listed product. (Petition at 8) The terms Q1 and Q2 are used to refer to whether such products are qualitatively (Ql) and quantitatively (Q2) the same as the listed product. You claim that a generic mupirocin product that is formulated to be Ql and Q2 the same as Bactroban will still be precluded from using an equivalence study in impetigo patients to support the full Microbiology labeling, including the MRSA labeling that has been approved for Bactroban. (Petition at 8) Q1 and Q2 are not sufficient measurements, you argue, because variables in supply and manufacturing may affect product viscosity and other characteristic of a topical product. (Petition at 10) For this reason, you request that the Agency use the structural or physical characteristic of a topical drug product (Q3), in addition to Q1 and Q2, to determine bioequivalence. (Petition at 10)

Your assertion on inactive ingredients in topical drug products is incorrect. Topical drug products may contain inactive ingredients different from the RLD as long as the product proposed in the ANDA is bioequivalent to the RLD and the inactive ingredients do not affect the safety or effectiveness of the drug product (21 CFR 314.94(a)(9)(v)). In general, the safety of the inactive ingredient may be demonstrated by reference to FDA-approved inactive ingredients contained in another approved drug product using the same route of administration.[12] Whether the inactive ingredient affects the effectiveness of the proposed drug product may be demonstrated in an ANDA through the bioequivalence study.[13]

In determining bioequivalence of topical products, the FDA does use the concepts of Q1, meaning qualitative similarity between generic and reference listed products, and Q2, representing quantitative similarity of composition. Although the Q1 and Q2 concepts are sufficient to ensure the same safety and effectiveness of a generic topical solution and an RLD, these in vitro analyses alone may not be sufficient to indicate that two topical semi-solid products are bioequivalent.

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[12] See the Inactive Ingredient Database at: http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

[13] Certain inactive ingredients that are added to a formulation of a topical drug product, such as propylene glycol, may affect the absorption of the drug through the topical route of administration. These inactive ingredients and their physico-chemical properties are known to the FDA. The effect that certain inactive ingredients have on the absorption of the active ingredient in a topical drug product is taken into consideration during the scientific review and is addressed during the review of the application. Additional information, in the form of a limited confirmatory study, may be required if an applicant uses an inactive ingredient that may affect the absorption of the active ingredient from the proposed drug product.

Q3, representing structural similarity of the product, is a newly proposed concept that refers to the physical attributes and state of aggregation of the drug product. Q3 captures differences that may be caused by manufacturing processes. Because Q3 is a newly defined concept and not fully developed for use, FDA currently recommends that bioequivalence for post-1962, non-solution, topical drug products be demonstrated by in vivo bioequivalence studies (505(j)(2)(a)(iv) of the Act; 21 CFR 314.94(a)(7); 21 CFR 320.21(b)(1) and (2)). Therefore, if an ANDA applicant can demonstrate through in vivo bioequivalence data that the product described in the ANDA is bioequivalent to the RLD and that it has facilities, methods, and controls in place for the manufacture, processing, or packaging of the drug that are adequate to ensure and preserve the identity, strength, quality, and purity of the proposed generic drug product, Q3 would not be necessary to ensure bioequivalence.

In vivo studies are required to demonstrate bioequivalence for topical ointments. Because an in vivo study provides the information necessary for comparative evaluation of the product described in the ANDA and RLD, any formulation differences that statistically affect the endpoints of the study would be evident in the results provided to the FDA. Because Q3 is not a developed concept and bioequivalence can be determined by in vivo studies, we deny your request to use Q3 to determine bioequivalence. We also deny your request to preclude the sponsor of an ANDA from using an equivalence study in impetigo patients to support the full Microbiology section of the labeling. As mentioned in II.C, if a generic version is bioequivalent to the RLD based on an appropriately designed comparative clinical trial and other information in the application, the drug product proposed in the ANDA will have the same labeling, including the MSRA labeling, as the RLD.

E. FDA Review of Mupirocin ANDAs

You have requested that mupirocin applications be reviewed by the Division of Anti-Infective Drug Products (DAIDP) because that particular division reviewed Clay-Park's 505(b)(2) application for mupirocin. (Petition at 11) In support of this request, you argue that because comparative clinical studies with efficacy endpoints will be required to demonstrate the bioequivalence of a mupirocin product submitted as an ANDA or an NDA under 505(b)(2), the division that reviewed the Clay-Park application would be best equipped to evaluate all applications for mupirocin products. (Petition at 11)

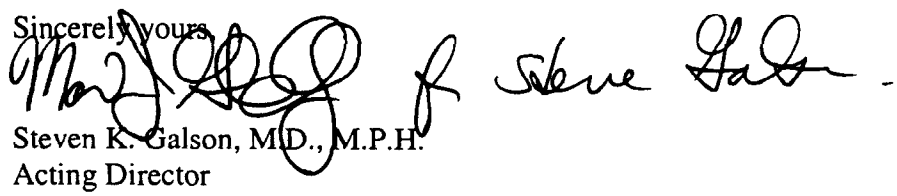
We disagree with your position that DAIDP should review all applications for mupirocin products, including ANDAs under 505(j) of the Act. The Center for Drug Evaluation and Research has ample expertise and resources to review bioequivalence studies with clinical endpoints (as recommended for topical mupirocin products), and has broad discretion to determine which components of the Center will undertake such a review.

## III. Conclusion

FDA has reviewed your petition, the submitted comments, and data and information available to the Agency. We do not agree that mupirocin ANDAs must demonstrate

bioequivalence to Bactroban by more than one independent, adequate and well-controlled clinical study. Bioequivalence for mupirocin ANDAs may be demonstrated by an appropriately designed comparative clinical trial (i.e., a bioequivalence study with a clinical endpoint). We also do not agree that mupirocin ANDAs must bear the same labeling as the Clay-Park 505(b)(2) NDA for mupirocin. Mupirocin products approved under 505(j) of the Act must bear the same labeling as the listed drug, Bactroban. Consequently, for the reasons described above, your petition is denied.

Sincerely yours,



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