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Dockets Management Branch
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

**Docket No. 03P-0140 – Comments In Response To Citizen Petition**
**Regarding Approval Of Generic Mupirocin Topical Ointment Products**

On behalf of a client, the undersigned respectfully submits these comments in response to the Citizen Petition filed April 7, 2003 on behalf of GlaxoSmithKline ("GSK"), in which GSK requests that FDA "refrain from approving abbreviated new drug applications (ANDAs) for generic topical mupirocin ointment products where the applicant cannot support all elements of the labeling approved for the reference listed drug (RLD)." As demonstrated herein, GSK's Petition proceeds from a faulty premise, ignores crucial facts, and relies upon non-existent policy. The Petition, accordingly, should be denied.

The Faulty Premise. GSK notes that Clay-Park Labs recently received approval of a topical mupirocin ointment product under a 505(b)(2) NDA, and that Clay-Park's labeling omits certain microbiology information that appears in GSK's Bactroban brand topical mupirocin ointment product labeling. GSK also notes that Clay-Park's product is not "AB" rated to Bactroban. From these observations GSK argues that Clay-Park's clinical testing methodology must be inadequate to support the use of such microbiology information in the labeling of any ANDA-approved mupirocin product, i.e., if the ANDA approval was "based on data similar to that submitted by Clay-Park."

The Overlooked Facts. The Petition ignores the fact that Clay-Park's product formulation uses a carrier (Softisan, or hard fat) that has never previously been used in a topical drug product, and that this formulation difference is what forced Clay-Park to seek approval under a 505(b)(2) NDA instead of an ANDA. Moreover, GSK ignores the fact that the Clay-Park product exhibits substantially greater systemic absorption than the RLD product, apparently as a result of the formulation difference. These crucial factual distinctions, and not any infirmity in Clay-Park's testing methodology, would explain Clay-Park's failure to obtain approval of labeling that is identical to GSK's Bactroban labeling.

GSK's Reliance On Non-Existent FDA Policies. The Petition goes further astray by asserting that the technical limitations posed by Clay-Park's unique and problematic mupirocin formulation would also be inherent in a generic formulation that is qualitatively (Q1) and quantitatively (Q2) identical to GSK's Bactroban ointment, and also by relying on informal speeches by an FDA employee for the proposition that topical drug products must specifically demonstrate "Q3" sameness in order to be deemed bioequivalent to the RLD. No such policy exists.

03P-0140 C1

In addition, GSK argues that if a topical mupirocin product is eligible for ANDA approval, "such product must be supported by two independent clinical trials to establish bioequivalence to Bactroban Ointment." As the Petition itself points out, FDA's long-established and recently confirmed policy is to approve ANDAs for topical drug products based upon a single comparative clinical trial to show bioequivalence, even when such study only examines one of several approved indications for the RLD. GSK offers no persuasive basis, nor legally supportable mechanism, for its request that FDA suddenly abandon this policy in connection with mupirocin topical ointment ANDAs.

Because GSK's Petition is wholly without merit, it should be promptly denied.

## I. THE APPROVAL OF THE CLAY-PARK MUPIROCIN PRODUCT DOES NOT GOVERN APPROVAL OF MUPIROCIN ANDAs BECAUSE THE CLAY-PARK PRODUCT IS QUALITATIVELY AND CLINICALLY DIFFERENT THAN BACTROBAN

### A. GSK Relies On The Faulty Premise That Clay-Park's Testing *Methodology* Precluded A Finding of Bioequivalence For Clay-Park's Product, And Would Preclude A Bioequivalence Finding For A True Generic Mupirocin Ointment Product

In its petition GSK exerts considerable effort to turn the absence of certain microbiology information in the labeling of Clay-Park's 505(b)(2) mupirocin product into an affirmative bar to the inclusion of such information in a bioequivalent ANDA mupirocin product. As GSK incorrectly hypothesizes,

> In short, the agency apparently determined that a showing of equivalence in patients with impetigo could only support the same labeling for that indication; the data could not be extended to labeling for other conditions of use, including the discussion of other pathogens identified in the Microbiology section of the approved labeling. This limitation on the use of the primary showing of bioequivalence must be applied to all other similar mupirocin ointment drug products that seek approval, either under 505(b)(2) or 505(j), based on a reference to Bactroban Ointment.

GSK Petition at 7. Not only is GSK's speculation nonsensical in the abstract, it is contradicted by the facts of the Clay-Park product approval, and the law and policy governing FDA's review and approval of this type of product.

In particular, GSK seeks to explain the "BX" rating of Clay-Park's product as resulting from the omission of certain in-vitro antimicrobial activity information from the Clay-Park

labeling, but then makes an unsupported leap in logic by arguing that this omission reflects a fatal infirmity in the use of the FDA-accepted methodology for purposes of demonstrating bioequivalence of topical drug products. GSK's hypothesized explanation, that the Clay-Park labeling differences were due to the *type* of comparative bioequivalence study used, is a complete non-sequitur because it ignores crucial facts about the Clay-Park product and the results of its study. When these facts are properly considered, it becomes obvious that the Clay-Park product approval was based on the unique characteristics of that product and that mupirocin products submitted and accepted for review under an ANDA are not bound by the labeling restrictions placed on the Clay-Park product. The following table illustrates the defect of GSK's approach:

| **GSK's Incomplete Analysis** | **Appropriate Regulatory Analysis** |
|---|---|
| | Significant Formulation Difference (Q1/Q2) in Clay-Park Product: Unprecedented Carrier<br>↓<br>Difference Requires Clinical Safety Data, Making Product Ineligible For ANDA; Clay-Park Must Use 505(b)(2) NDA<br>↓<br>Pharmacokinetic Differences Observed (Substantially Increased Systemic Absorption Compared to Brand Product)<br>↓<br>***Comparative Clinical Biostudy Does not Support Bioequivalence or Microbiology Information for Clay-Park's Product due to Significant Pharmacokinetic and Formulation Differences*** |
| Clay-Park's Omission of Microbiology Information<br>↓<br>BX Rating<br>↓<br>***No* Comparative Clinical Biostudy Can Support Bioequivalence or Microbiology Information For *Any* Generic Formulation That is Q1/Q2-Same As Bactroban** | ↓<br>Microbiology Labeling Information Must Be Based On Data Specific To Clay-Park's Product<br>↓<br>Clay-Park's Omission of Microbiology Information<br>↓<br>BX Rating |

**B. GSK Overlooks The Crucial Facts That Actually Required Clay-Park's Product Labeling To Omit Certain Information And Receive a "BX" Rating**

GSK glosses over the fact that Clay-Park's product uses an inactive ingredient in its formulation (Softisan 378®, or hard fat) that is not used in GSK's Bactroban, and which apparently had never previously been approved in *any* drug product for topical administration. This difference in inactive ingredients, at a minimum, would have required Clay-Park to identify and characterize the differences between Softisan and GSK's carrier (PEG-400/PEG-3350) and to demonstrate, via "limited confirmatory studies," "that the differences do not affect the safety of the proposed product" if it wanted to obtain approval under an ANDA. 21 C.F.R. § 314.94(a)(9)(v). However, as GSK admits in a passing footnote, Petition at 7, note 6, the difference in inactive ingredient in this case actually necessitated that Clay-Park use the 505(b)(2) NDA approval route instead of an ANDA. *See* FDA, Guidance for Industry: *Applications Covered by Section 505(b)(2)* (Oct. 1999) at 5 (noting that 505(b)(2) NDAs are appropriate for changes in formulation, i.e., "for a proposed drug product that contains a different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application.").

However, GSK fails to adequately comprehend and acknowledge the legal ramification that once a product is required to be approved through the 505(b)(2) NDA pathway, as opposed to the ANDA pathway, there is no requirement for the 505(b)(2) product to have the "same" labeling as the reference listed product. In fact, any microbiology, safety and efficacy labeling which is derived from clinical studies on the 505(b)(2) product will have to be included in the 505(b)(2) product's labeling if it differs from the RLD's labeling. *See* 21 C.F.R. § 314.50(d)(4)(ii), 314.50(d)(5).

In this respect, the first fallacy of the Petition is GSK's failure to acknowledge that it must have been the *results* of Clay-Park's clinical and other studies of its Softisan 378-based product that led to the variations in the Clay-Park labeling . This is because Clay-Park's studies revealed important clinical differences that precluded approval of Clay-Park's Softisan 378-based product with identical labeling as Bactroban. Of particular significance, Clay-Park's product results in substantial systemic absorption of mupirocin (reflected by up to 3.0% urinary excretion of monic acid), *see* Clay-Park Mupirocin Ointment 2% Approved Labeling (Clinical Pharmacology section)[1], whereas Bactroban "showed no measurable systemic absorption" of mupirocin. Bactroban Ointment Approved Labeling (Clinical Pharmacology section).[2] The increased absorption of Clay-Park's mupirocin ointment is not necessarily surprising, given that the manufacturer of Softisan 378 promotes the product by noting that it "allows for rapid melting

[1] Attached hereto at Tab A.

[2] Attached hereto at Tab B.

of the product on the skin, and active ingredients are therefore quickly released," and further promotes the product's "absorption-promoting properties."[3]

Thus, with respect to Clay-Park's labeling, GSK's clinical pharmacology and microbiology data on its PEG-based Bactroban Ointment product obviously are not scientifically or legally relevant to the Clay-Park Softisan-based product, and as a result, the findings from studies of the Clay-Park's product took precedence over labeling derived from GSK's product. *See* 21 C.F.R. § 314.50(d)(4)(ii), 314.50(d)(5). The differences in formulation, and the resultant clinical differences, ultimately precluded the use of identical labeling that would be necessary for an AB rating. None of this, however, is relevant to the approvability of an ANDA for a mupirocin ointment product that uses the same PEG-based carrier formulation as Bactroban, based on comparative clinical bioequivalence data. As shown below, the sponsor of such a product would be able to demonstrate bioequivalence using a comparative clinical trial, and based on that demonstrated equivalence, utilize the "same labeling" as Bactroban. *See* 21 C.F.R. §§ 314.94(a)(7), 320.24(b)(4). Thus, GSK's contention that a mupirocin ointment ANDA cannot be approved "where the applicant's bioequivalence data is substantially the same as that submitted in support of Clay-Park's [505(b)(2) NDA]," Petition at 2, 14, is a red herring because it ignores the crucial scientific and legal distinctions that mandated the differences in Clay-Park's labeling. GSK's effort to sweep these distinctions under the rug should be rejected.

## II. GSK RELIES ON NON-EXISTENT FDA POLICY BY ARGUING THAT A Q1/Q2 MUPIROCIN OINTMENT PRODUCT IS NOT ELIGIBLE FOR ANDA APPROVAL AND AN "AB" RATING BASED ON A SINGLE COMPARATIVE BIOEQUIVALENCE STUDY

### A. FDA's Topical Bioequivalence Policy Unequivocally Does *Not* Require A Showing Of "Q3" Sameness

The next fatal flaw in GSK's petition is the contention that "a proposed generic mupirocin ointment product that is formulated to be Q1 and Q2 the same as Bactroban Ointment will still be subject to the same limitations" as Clay-Park's non-Q1/Q2 505(b)(2)-approved mupirocin ointment product. Petition at 8. As discussed above, Clay-Park's mupirocin product required independent safety and pharmacokinetic data, reviewed under a 505(b)(2) NDA, due to its unprecedented formulation using Softisan 378. This new formulation, with its distinctly different in vivo behavior, led to the regulatory requirement of different labeling, i.e., labeling specifically derived from data from the Clay-Park product. Thus, if anything is clear, it is that the "limitations" inherent in the Clay-Park approval are not relevant to a Q1/Q2 ANDA mupirocin product, which is eligible for approval under an ANDA using FDA's long-established bioequivalence criteria for topical drug products. 21 C.F.R. § 320.24(b)(4).

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[3] *See* SASOL Germany GmbH, *Product Information SOFTISAN® 378*, attached hereto at Tab C.

As GSK would have it, a generic product would also be required to demonstrate not only Q1 (quality) and Q2 (quantity) sameness, but also "Q3" sameness (structural and physical characteristics). This approach is inconsistent with binding FDA policy and recent precedent. *See infra*. In support of its position, GSK seriously misuses and misrepresents informal comments of a single FDA employee, Dr. Jonathan Wilkin, in a recent Pharmaceutical Sciences Advisory Committee presentation with respect to the potential relevance of structural and physical characteristics (Q3) of a topical drug product. First, Dr. Wilkin's comments upon which GSK relies, reflect at most his personal views on a dynamic technical subject that must be governed by established FDA regulations, guidance (if any), and precedents. FDA officials, at the urging of management, have made clear in recent years that Agency policy is not and cannot be made or announced on an ad-hoc basis in speeches by individual employees. This rejection of "podium policy" is crucial for FDA to maintain a reputation as an Agency governed by law derived from scientific consensus. FDA should not base its decision here on GSK's self-serving interpretation of Dr. Wilkin's unofficial comments, especially when those comments were taken out of context by GSK for anticompetitive purposes.

More to the point, Dr. Wilkin's comments make clear that FDA's current policy is not to demand Q3 type data from sponsors of generic topical drug products: [T]raditionally the focus has been limited to what everyone calls Q1 and Q2. Qualitative sameness. It's the list of ingredients. Quantitative sameness, those ingredients are there in the same amounts as found in the innovator." ACPS transcript at 206-207. Moreover, as Acting Director Helen Winkle made clear in her introductory memorandum to the March 12 advisory committee meeting at which Dr. Wilkin spoke, the Committee discussion was not in any way meant to reflect a change in FDA's traditional topical bioequivalence standards, and the panel on which Dr. Wilkin spoke was presented solely "as an 'awareness' topic for the advisory committee in preparation for more in depth discussion at future meetings." Memorandum From Helen Winkle to Members, Advisory Committee for Pharmaceutical Sciences, Feb. 11, 2003.[4] Even Dr. Wilkin made clear in his presentation that alternative methodologies beyond Q1/Q2 sameness "*may*" be an option in the future to supplement new technologies that will replace clinical trials and thereby decrease the development time and costs of bringing generic topical products to market. *See* Wilkin Slide 20.

Thus, despite Dr. Wilkin's and GSK's personal views of what the future may hold, FDA must currently adhere to its established policy and precedents that Q1/Q2 sameness is sufficient to support a bioequivalence determination for a topical product. As FDA ruled just a year ago,

> A demonstration of bioequivalence in the treatment of [one indication] will confer approval for the [related indication] provided that the test and reference formulations are qualitatively [Q1] and quantitatively [Q2] the

[4] Copy attached at Tab D, available at http://www.fda.gov/ohrms/dockets/ac/03/briefing/3926B1_01_A-FDA-Winkel%20Cover%20Letter.pdf

> same. It is generally the current practice for locally acting drugs that have more than one related indication to demonstrate bioequivalence by conducting the bioequivalence study in a single indication....

Letter From Janet Woodcock, M.D. to Westwood Squibb Pharmaceuticals, Inc., Docket No. 95P-0379 (May 22, 2002) at 2 (emphasis added) (the "Westwood Squibb Petition Ruling").

Thus, although GSK grudgingly admits that FDA's policy was, and remains, to allow bioequivalence findings for Q1/Q2 same generic products without a showing of Q3 sameness, Petition at 10, it now asks that this policy – so recently reaffirmed – be abandoned based on a misrepresentation of the forward-looking comments of a single FDA official. Because FDA is still far from adopting any official changes to topical bioequivalence standards, unless and until such changes are adopted by FDA using formal means GSK's request for a more stringent (and here, wholly unnecessary) bioequivalence standard must be rejected, and FDA must timely approve any pending ANDAs for mupirocin ointment products that demonstrate Q1 and Q2 sameness, and are supported by an adequate bioequivalence study.

### B. FDA Recently Reaffirmed Its Longstanding Policy That A Single Clinical Bioequivalence Study Is Sufficient To Support Approval Of AB-Rated Topical Generic Drug Products

GSK's Petition also relies upon non-existent FDA policy by arguing that more than one comparative clinical bioequivalence study would be required in support of an ANDA for a topical mupirocin ointment product. Petition at 12-13. GSK's entire argument in this respect hinges on an isolated and inappropriately narrow reading of the "plain language" of 21 C.F.R. § 320.24(b)(4). Although that provision does use the plural term "trials" as one permissible basis for topical drug bioequivalence determinations, FDA's regulations also clearly permit the Agency to accept "any other approach deemed adequate by FDA to establish bioavailability or bioequivalence." 21 C.F.R. § 320.24(b)(6) (emphasis added). As at least one court has held, "the intent behind Section 355(j)(7)(B) [the statutory definition of "bioequivalence"] is clear from the language, structure, and legislative history of the 1984 amendments to the FDCA, all of which suggest that Congress permitted the FDA to retain its historically wide discretion in defining showings of 'bioequivalence.'" *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 648 (D.D.C. 1992), *vacated as moot sub nom Schering v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993). Thus, not only is FDA's current policy correct, it will survive any judicial challenge by GSK.

Of particular relevance to this Petition, FDA's longstanding policy to make topical bioequivalence determinations based on a single comparative clinical biostudy was recently re-affirmed in very similar circumstances in the Westwood Squibb Petition Ruling, *supra*. FDA's Westwood Squibb Ruling involved a Petition request for FDA to impose similarly burdensome and unnecessary bioequivalence standards for another topically administered generic drug product, and the Agency clearly rejected GSK's position that multiple clinical studies are necessary to show bioequivalence for a generic topical product:

> Generally, bioequivalence testing for topical products using clinical studies with clinical endpoints relies on a single study in one indication, usually the one that is most difficult to treat. If the generic drug product is shown to be bioequivalent for one indication, it is expected to be bioequivalent for all related indications with the same site of action.

Westwood Squibb Petition Ruling at 4 (emphasis added).

GSK also argues that a bioequivalence finding may only be used to support labeling for the treatment of impetigo, but not labeling discussing antibacterial activity against specific bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). Petition at 10. This position is also without merit, in part because of the inapplicability of the previously discussed reasons for the limitations on Clay-Park's mupirocin labeling. Moreover, GSK's position is also contradicted by FDA's Westwood Squibb Petition Ruling, in which the Agency reiterated the policy that allows generic labeling for an approved *indication* even if that indication was not the subject of a comparative clinical study:

> Neither the statute nor the regulations require an applicant to submit comparative clinical trial data for each separate disease indication before FDA may approve an ANDA. It is well-accepted that FDA has wide discretion to determine how the bioequivalence requirement is met; FDA's discretion need only be based on a "'reasonable and scientifically supported criterion, whether the [agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs.'" Thus, a comparative clinical trial to establish bioequivalence with the RLD in each labeled indication is not required by the Act or its implementing regulations.[5]

Westwood Squibb Petition Ruling at 4-5 (emphasis added). Thus, even if MRSA infection was approved as a specific indication (which it is not), FDA policy would properly allow approval of labeling for such an indication based on a single study involving a different indication. For mupirocin ointment products, however, there is only a single approved indication – topical treatment of impetigo – and a showing of bioequivalence in that indication is fully sufficient to support labeling that is the same as the RLD product in that, and all other, respects, including activity against specific bacteria such as MRSA.[6]

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[5] In support of this position, FDA cites to *Bristol-Myers Squibb v. Shalala*, 923 F. Supp. 212, 218 (D.D.C. 1996) (quoting *Schering, supra*, 782 F. Supp. at 651).

[6] Indeed, it would be a perverse result to protect GSK's current MRSA microbiology labeling when GSK has not provided substantial evidence to support MRSA treatment as a separate indication, since if such an indication were approved it would not be subject to protection under FDA's established policy.

The fact that GSK's commercial interests are not well served by FDA's policy to allow topical bioequivalence findings based on Q1/Q2 sameness, and a single study, in no way undermines the reasonableness of this longstanding approach, even if another approach may ultimately be adopted in the future. Because GSK's Petition is based on FDA bioequivalence policies that are currently non-existent, its Petition must be denied, and any pending ANDAs that meet FDA's traditional bioequivalence standards must be approved with labeling that is the same in all relevant respects to GSK's Bactroban Ointment.

* * *

Finally, it is noteworthy, and more than a little troubling, that GSK's petition was submitted just three days after FDA withdrew its proposed rule "Citizen Petitions: Actions That Can Be Requested by Petition; Denials, Withdrawals, and Referrals for Other Administrative Action," *see* 68 Fed. Reg. 16461 (April 4, 2003), and only weeks before its formulation patent for Bactroban Ointment will expire. The FDA's proposed rule would have required the inclusion of a certification that GSK's petition:

- Includes all information and views on which the petition relies;
- Is well grounded in fact and is warranted by existing laws or regulations;
- Is not submitted for any improper purpose, such as to harass or to cause unnecessary delay; and
- Includes representative data and information known to the petitioner which are unfavorable to the petition.

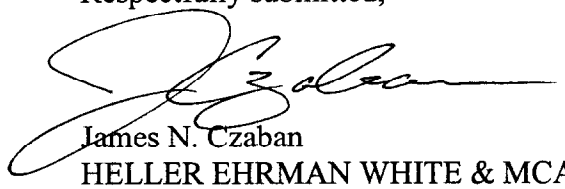
64 Fed. Reg. 66822 (Nov. 30, 1999). GSK's petition clearly could not truthfully include such a certification since it is not well grounded in fact, it ignores information that is unfavorable, twists tangentially relevant information to make it appear favorable to its petition when it is not, and is clearly filed for an improper purpose – to impede the timely approval of competing generic mupirocin ointment applications.

## CONCLUSION

The GSK Petition is based on nothing more than faulty premises, faulty logic, and non-existent bioequivalence standards. Specifically, the scientific and legal facts underlying the approval of Clay-Park's Q1/Q2 *different* mupirocin topical ointment are irrelevant to the approval standards for an ANDA for a Q1/Q2-same mupirocin topical ointment product. Moreover, FDA's consistent and longstanding policy, as reaffirmed in the Westwood Squibb Petition Ruling, is to permit ANDA approval of a Q1/Q2 same topical product based on a single clinical bioequivalence study. And finally, the true intent of GSK's petition, evidenced by its timing and lack of foundation, is clearly motivated by anticompetitive intent and is not well

grounded in law, science, or policy. For the reasons set forth herein, the Petition should be denied and denied swiftly.

Respectfully submitted,



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