GlaxoSmithKline
U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929
Tel. 215 751 3868
Fax. 215 751 4926

October 19, 2004

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned, on behalf of GlaxoSmithKline (GSK), submits this petition under 21 CFR 10.30 to request that the Commissioner of Food and Drugs (the Commissioner) take the actions described below with respect to Abbreviated New Drug Applications (ANDAs) that reference Bactroban Nasal® (mupirocin calcium ointment, 2%), where the proposed drug product contains the amorphous form of the active pharmaceutical ingredient.

ACTIONS REQUESTED

The undersigned respectfully requests that the Commissioner refrain from receiving, reviewing, and approving any ANDA for a nasal mupirocin calcium product that contains the amorphous form of the active pharmaceutical ingredient. Rather, the Commissioner should require the submission of a New Drug Application under section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA) to support the proposed marketing of any such product.

STATEMENT OF GROUNDS

On July 7, 2004, GSK submitted a citizen petition requesting that the Commissioner refrain from approving any ANDA that references Bactroban Cream®, where the proposed product contains the amorphous form of mupirocin calcium. *See* Tab 1, Docket No. 2004P-0290/CP1 (July 7, 2004) (the Bactroban Cream® Petition). The Bactroban Cream® Petition is pending before the agency and we hereby incorporate by reference the arguments and evidence included therein. For the same reasons presented in the Bactroban Cream® Petition, the agency is prohibited from considering any ANDA for nasal

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mupirocin calcium products that are based on the amorphous form of the active pharmaceutical ingredient.

There are specific scientific reasons why an ANDA for a nasal mupirocin calcium product, based on the amorphous form of mupirocin calcium, cannot be received, reviewed, or approved by the agency. First, according to patent information surveyed in the Bactroban Cream® Petition, the amorphous form of the active ingredient purports to have distinct physical, chemical, and biopharmaceutical properties. *See* Tab 1 at 3-5, 7-8. Based on these differences, the amorphous form of the active pharmaceutical ingredient cannot be considered "the same as" the crystalline form, and head-to-head testing cannot establish the bioequivalence of the two ingredients.

Second, there is no consensus standard of identity, such as a USP standard, that recognizes both the amorphous and crystalline forms of mupirocin calcium as acceptable alternative forms of the active pharmaceutical ingredient. *Id.* at 11-12. Third, the amorphous form of the active pharmaceutical ingredient may crystallize over time, rendering a product that purports to contain the amorphous form of mupirocin calcium "adulterated" or "misbranded" under sections 501 and 502 of the FDCA. *Id.* at 9-10, 13-14. Fourth, in view of the purported differences between the amorphous and crystalline forms of mupirocin calcium, the formulation of a product that relies on amorphous mupirocin calcium will require new *in vitro* and *in vivo* studies to characterize the safety and effectiveness of the product in humans; such studies must be submitted under section 505(b)(2) rather than section 505(j) of the FDCA. *Id.* at 18-19. The legal and evidentiary basis for these arguments are set forth in full in the Bactroban Cream® Petition.1/ *Id.* at 5-6.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

1/ The only issues raised in the Bactroban Cream® Petition that may not be applicable here are those relating to the dosage form and composition of the product, as discussed in section III.B of the Bactroban Cream® Petition. *See* Tab 1.

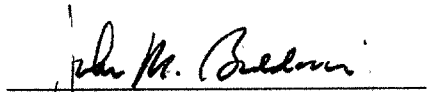
ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

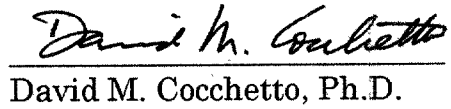
CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



John M. Baldoni, Ph.D.
Senior Vice President
Pharmaceutical Development
R&D Worldwide



David M. Cocchetto, Ph.D.
Vice President
Antiviral/Antibacterial Regulatory Affairs

Encl.

cc: David M. Fox
Hogan & Hartson LLP

GlaxoSmithKline

GlaxoSmithKline
Research & Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Tel. 919 483 2100
www.gsk.com

July 7, 2004

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned, on behalf of GlaxoSmithKline (GSK), submits this petition under 21 CFR 10.30 to request that the Commissioner of Food and Drugs (the Commissioner) take the actions described below with respect to abbreviated new drug applications (ANDAs) for topical mupirocin calcium products containing the amorphous form of the active ingredient.

GSK markets Bactroban Cream®, which contains the crystalline form of mupirocin calcium. It appears that one or more generic drug sponsors may have submitted to the Food and Drug Administration (FDA) ANDAs for topical products containing the amorphous form of mupirocin calcium. As discussed below, these different physical forms of mupirocin calcium cannot be considered the "same" active ingredient for purposes of premarket approval. Furthermore, use of the amorphous form of mupirocin calcium raises numerous issues regarding the identity of the active ingredient over time, the nature of the dosage form, and the effect of inactive ingredients on the safety and effectiveness of the product.

Because mupirocin calcium is a "pre-1997" antibiotic under section 125 of the Food and Drug Administration Modernization Act, Bactroban Cream® is not subject to the Food, Drug, and Cosmetic Act's (FDCA's) patent listing and certification procedures. *See* Pub. L. No. 105-115, 111 Stat. 2296 (1997). Therefore, GSK is left to speculate regarding the existence of these ANDAs. Rather than wait until the approval of any such ANDAs, however, GSK is submitting this petition now, when it will be significantly less burdensome for FDA to consider these issues.

I. ACTIONS REQUESTED

(1) The undersigned respectfully requests that the Commissioner refrain from approving any ANDA for a topical mupirocin calcium product containing the amorphous form of the active ingredient. Rather, the Commissioner should require for any such product a new drug application (NDA) under section 505(b) of the FDCA, because of the changes to the active and inactive ingredients and the dosage form of the reference listed drug (RLD), Bactroban Cream®.

(2) In the alternative, the Commissioner should take the following actions before approving any ANDA for a topical mupirocin calcium product containing the amorphous form of the active ingredient:

(a) Prescribe a standard of identity for mupirocin calcium that takes into account the different forms of the active ingredient;

(b) Require the submission of a suitability petition for a change in dosage form, to the extent that the amorphous form of mupirocin calcium cannot be maintained in a cream base; and

(c) Determine whether the inactive ingredients of such a product raise issues of safety or effectiveness that require additional *in vitro* or *in vivo* studies, and whether such studies must be submitted under section 505(b) of the FDCA.

II. STATEMENT OF GROUNDS

A. Factual Background

1. *Approved and Pending Applications*

Bactroban Cream® (mupirocin calcium) 2% (NDA 50-746) was first approved on December 12, 1997. The product is indicated for use in the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* or *Streptococcus pyogenes*. The active ingredient in Bactroban Cream® is described

in the labeling as "the dihydrate crystalline calcium hemi-salt of the antibiotic mupirocin." Tab 1 at 1.

The crystalline form of mupirocin calcium is protected by patent. *See, e.g.*, United States Patent No. 5,436,266. Based on this fact, on a recently issued patent and several patent applications, and on drug master files (DMFs), GSK believes that one or more sponsors may have submitted to FDA ANDAs for topical mupirocin calcium products containing the amorphous form of the active ingredient.

For example, on December 3, 2002, the Patent and Trademark Office issued United States Patent No. 6,489,358 (the '358 patent) to Ilana Lavon *et al.*, assigned to Agis Industries. This patent claims "[a] stable pharmaceutical preparation for topical and nasal uses, comprising *Mupirocin calcium amorphous* as an anti-microbial active agent therein, in combination with a pharmaceutically acceptable solvent providing stability therefor." Tab 2 at 2 (emphasis added). This patent also claims "a cream preparation . . . ." *Id.* at 3.

Similarly, on August 14, 2003, the World Intellectual Property Organization published under the Patent Cooperation Treaty (PCT) international application No. PCT/US02/35585 (the PCT application). This patent application, submitted by Teva Pharmaceuticals USA, Inc., seeks to claim various processes for preparing crystalline and amorphous mupirocin calcium and pharmaceutical compositions comprising amorphous mupirocin calcium. *See* Tab 3 at 35-41.

Finally, GSK considers the existence of one or more ANDAs likely, based on the existence of several DMFs. In addition to GSK's own, FDA's database currently lists three other files for mupirocin: "Mupirocin as Manufactured in Debrecen, Hungary," held by Teva Group and submitted March 11, 1999; "Mupirocin as Manufactured in Zagreb, Croatia," held by Pliva DD and submitted February 12, 2001; and "Mupirocin Calcium (Amorphous) as Manufactured in Beer Sheva, Israel," held by Chemagis Ltd. and submitted April 15, 2003. *See Drug Master Files*, at www.fda.gov/cder/dmf/xls/1q2004ALLEXCEL.xls.

2. *Different Polymorphic Forms of the Same Active Ingredient*

Many pharmaceutical ingredients can exist in different physical forms, a phenomenon known generally as "polymorphism." In broad terms, an

active ingredient is said to be in a crystalline form when its molecules exist in one or more crystal lattice arrangements. *See* David. J. W. Grant, "Theory and Origin of Polymorphism," in *Polymorphism in Pharmaceutical Solids: Drugs and the Pharmaceutical Sciences*, Vol. 95, at 1-2 (Marcel Dekker, Inc., 1999) (*Polymorphism in Pharmaceutical Solids*). By contrast, amorphous forms "consist of disordered arrangements of molecules and therefore possess no distinguishable crystal lattice nor unit cell and consequently have zero crystallinity." *Id.* at 8.

These different forms can possess significantly different physical properties. For example, amorphous forms generally exhibit lower thermodynamic stability and faster dissolution than crystalline forms. *See* J. Keith Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in *Polymorphism in Pharmaceutical Solids*, at 208. The melting points and total solubility of the forms can be different as well. *See infra* at section III.A.1.

These different forms are related, however, and the amorphous form of an active ingredient will crystallize over time. This is because the amorphous form possesses higher free energy than the crystalline form. It therefore "represents a metastable state, so thermodynamics *requires* that crystallization eventually occur." Michael J. Pikal, "Impact of Polymorphism on the Quality of Lyophilized Products," in *Polymorphism in Pharmaceutical Solids*, at 408 (emphasis added).

This tendency of the amorphous form to crystallize is particularly true in the presence of moisture, which has a "profound influence" on crystallization:

> As the moisture content increases, the glass transition temperature decreases sharply, and particularly for accelerated stability testing, it is not unusual for the glass transition temperature at modest levels of residual moisture to be less than the storage temperature. In such cases, increased molecular mobility in the amorphous material allows crystallization to take place on the timescale of the experiment (i.e., during storage).

Id. Finally, "one often finds that the water content increases significantly upon storage. This can facilitate crystallization of one or more of the formulation components." *Id.* at 409. As discussed below, the likelihood that water will lead

to the crystallization of amorphous mupirocin calcium has critical implications for any topical mupirocin calcium product.

B. Statutory and Regulatory Background

The FDCA requires that an ANDA describe a product with the identical active ingredient, dosage form, strength, conditions of use, and labeling as a reference listed drug. *See* 21 USC 355(j)(2)(A). A generic drug also must be bioequivalent to its RLD. *See id.* Two drugs are bioequivalent if there is no significant difference in the rate and extent to which the active ingredient in the drugs becomes available at the site of action. *See* 21 USC 355(j)(8); 21 CFR 320.1(e).

The Medicare Prescription Drug, Improvement, and Modernization Act recently amended the FDCA to provide that FDA may assess the bioavailability of non-systemically absorbed drugs, by using "scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action." Pub. L. No. 108-173, 117 Stat. 2066 (2003) (codified at 21 USC 355(j)(8)(A)(ii)). It also provided that FDA may establish "alternative, scientifically valid methods" for bioequivalence, if those methods can detect "a significant difference between the drug and the listed drug in safety and therapeutic effect." *Id.* (codified at 21 USC 355(j)(8)(C)).

For a generic drug to be considered fully interchangeable with its RLD, the two must be both "pharmaceutically equivalent" and "therapeutically equivalent." Drugs are pharmaceutically equivalent if they contain identical amounts of the identical active ingredient, in the identical strength and dosage form, and meet the identical compendial or other applicable "standards of identity." 21 CFR 320.1(c). Such drugs may then be therapeutically equivalent if they are bioequivalent, adequately labeled, and manufactured in accordance with good manufacturing practice regulations. *See Approved Drug Products with Therapeutic Equivalence Evaluations* (24th ed. 2004), at Preface 1.2 (the *Orange Book*).

A generic drug sponsor who wishes to make a change to an RLD, such as a change in dosage form, must first submit a "suitability petition." *See* 21 USC 355(j)(2)(C). If FDA determines that clinical investigations are not needed to show the safety and effectiveness of the product, as changed, the petition will be granted and the sponsor may submit an ANDA. *See id.*; 21 CFR

314.93. Such an altered product generally will be considered a "pharmaceutical alternative," however, and will not be therapeutically equivalent to the RLD. *See* 21 CFR 320.1(d).

In contrast to ANDAs, NDAs submitted under section 505(b)(2) of the FDCA are intended to be used when a sponsor wishes to make a change to an existing product, and the change is one for which clinical investigations are needed to ensure the safety and effectiveness of the product. *See* 21 USC 355(b)(2); 21 CFR 314.54. For example, sponsors have used section 505(b)(2) to gain approval of products with different, but related, active ingredients, and products with different formulations. The agency's position is that FDA may rely on its prior finding of safety and effectiveness for the reference product, and that only the incremental data needed to support the change must be submitted. *See* 21 CFR 314.54(a).[1]

III. ARGUMENT

A. Crystalline and Amorphous Mupirocin Calcium Are Not the "Same" Active Ingredient

Whether the crystalline and amorphous forms of an active ingredient may be considered the "same" for purposes of premarket approval is a controversial issue. The leading precedent in the area is FDA's response to a citizen petition regarding GSK's antibiotic drug product, Ceftin® (cefuroxime axetil) tablets. There, FDA stated that the agency would:

> [C]onsider an active ingredient in a generic drug product to be the same as an active ingredient in the reference listed drug if it meets the same standards for identity. . . . [I]n most cases, the standards for identity are described in the [United States Pharmacopeia (USP)], although the Agency might prescribe additional standards that are material to the ingredient's sameness.

Citizen Petition Response, Docket Nos. 00P-1550, 01P-0428 (Feb. 15, 2002), at 8 (Ceftin® Response) (footnote removed); *see also* 57 FR 17950, 17959 (Apr. 28,

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1 This position is controversial. It has been challenged in at least three citizen petitions (Docket Nos. 03P-0176, 02P-0447, and 01P-0323) and in a lawsuit filed after FDA approved a product under this policy. (This approval was recently stayed after FDA discovered that an agency official relied upon some category of "inappropriate data" in approving the product. *See* Tab 4.)

1992) ("For example, for some drug products, standards for crystalline structure or stereoisomeric mixture may be required.").

In the case of Ceftin®, the RLD contained the amorphous form of cefuroxime axetil, while the generic products contained the active ingredient in a wholly or partially crystalline form. *See* Ceftin® Response at 2. Ultimately, because the applicable USP monograph for Ceftin® was revised to recognize both the amorphous and crystalline forms of cefuroxime axetil, FDA determined that both were the "same" for purposes of premarket approval. *See id.* at 9.

Where there is no USP monograph, a proposed generic product must meet a prescribed standard of identity, to be considered the "same" as, and "pharmaceutically equivalent" to, the RLD. *See* Ceftin® Response at 8; 21 CFR 320.1(c) (describing "pharmaceutical equivalents" as drug products that "meet the identical compendial or other applicable standard of identity"); *see also* 57 FR at 17959 ("FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity."). The agency has yet to prescribe such a standard for mupirocin calcium. *See infra* at section III.A.4.

Frank O. Holcombe, Jr., Ph.D., has stated for FDA that where there is no USP monograph, there may still be constraints on the use of other forms of the drug substance. "In such cases, identity or sameness arguments might be based on differences in physical characteristics of the drug substance forms, leading to potential differences in drug product performance." *Issues of Polymorphism and Abbreviated New Drug Applications*, Advisory Committee for Pharmaceutical Science (ACPS) (May 8, 2002). As described below, the crystalline and amorphous forms of mupirocin calcium possess such different physical characteristics.

1. The Different Polymorphic Forms of Mupirocin Calcium Possess Significantly Different Physical Characteristics

To the extent that the USP has issued standards of identity for mupirocin, it has required the crystalline form of the active ingredient. *See Mupirocin*, USP 27/NF 22 (2004) (referring to <695> *Crystallinity*, which provides a test "to determine compliance with the crystallinity requirement where stated in the individual monograph . . . ."). There currently is no monograph for the calcium salt of mupirocin, although USP is soliciting monographs for both the drug substance and drug product. *See Call for High Priority Monographs*, at www.usp.org/standards/monographnames.html.

More importantly, there are significant differences in the physical characteristics of the crystalline and amorphous forms of mupirocin calcium, which can lead to differences in drug product performance. Many of these differences are disclosed in a recently published patent and several patent applications, which claim pharmaceutical preparations containing amorphous mupirocin calcium and methods for producing both the crystalline and amorphous forms.2

For example, the '358 patent (assigned to Agis Industries) asserts that amorphous mupirocin calcium is more soluble than the crystalline form in water and in hexylene and propylene glycol: "The results show clearly the different behavior of the amorphous compound, compared with the crystalline one. The amorphous form is much more soluble in hydrophilic solvents." Tab 2 at 5. Also, the PCT application characterizes amorphous mupirocin calcium as having a significantly lower melting point than the crystalline form (70-76 °C *versus* 125-137 °C), as well as lower purity, initially and after storage. Tab 3 at 8.3

As discussed in the '358 patent, these differences between the crystalline and amorphous forms, the patentees claim, go directly to the different performance of the resulting drug products. After describing the perceived "poor solubility" of the crystalline form in water and hydrophilic solvents, and how this "*may reduce its bioavailability*," the patentees assert that "we . . . shorten the time it takes the active [ingredient] to reach the target area. In other words, keeping the active substance in a soluble state *might increase the bioavailability*." Tab 2 at 3 (emphases added).

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2 We take no position as to the validity of these claims, or to the ability of the claimed processes to produce stable amorphous mupirocin calcium. GSK also has no specific information on any applications that may have been submitted to FDA. Rather, we accept these claims at face value for purposes of this petition, as assertions by the patentees as to the differences between the crystalline and amorphous forms of mupirocin calcium.

3 GSK understands that statements made in the course of patent prosecution or litigation may not be relevant to FDA's determination of the "sameness" of two active ingredients. *See* Ceftin® Response at 16. However, these statements are factual assertions regarding differences in the physical properties of the polymorphic forms of mupirocin calcium. To that extent, they are directly relevant to FDA's determination.

2. *When Solubility, Stability, and Absorption are Different, the Different Polymorphic Forms Must be Controlled*

The purported differences, as discussed above, in the solubility, melting point, and purity of the different polymorphic forms of mupirocin calcium bear directly on the identity of the active ingredient for purposes of premarket approval. As FDA stated a decade before its Ceftin® Response, in a petition response regarding the identity of a different active ingredient, "FDA considers differences in waters of hydration resulting in polymorphic crystal forms of the same active moiety (i.e., different forms the same active ingredient) to be the same *when dissolution, solubility, and absorption are shown to be equivalent*." Citizen Petition Response, Docket No. 90P-0240 (Apr. 6, 1992), at 4 (emphasis added). When they are not, as with mupirocin calcium, the different polymorphic forms cannot be considered the "same" active ingredient.

FDA reiterated this view more recently, at an October 2002 ACPS meeting on polymorphism in ANDAs. Lawrence X. Yu, Ph.D., presented for FDA a series of decision trees on "when and how polymorphs in a drug substance in ANDAs should be monitored and controlled." ACPS Transcript (Oct. 21, 2002), at 161.[4] The first decision tree asks whether there are known polymorphs with different apparent solubilities. *See Scientific Considerations of Polymorphism in Pharmaceutical Solids: Abbreviated New Drug Applications*, ACPS (Oct. 21, 2002). If so, and if any of the known polymorphs are not both highly soluble and sufficiently stable, the second tree instructs FDA to set a polymorphic acceptance criterion for the drug substance. *See id.* Finally, the third decision tree instructs FDA to set an acceptance criterion for the drug product, if there is "sufficient concern that polymorphic acceptance criterion for drug product [sic] should be established." *Id.*

During his presentation, Dr. Yu said that, in general, there would not be a sufficient concern "if the most stable polymorphic form is used or the

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4 These decision trees were based in part on the International Conference on Harmonization Guidance on Q6A Specifications: *Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, which itself contains a series of decision trees on controlling the forms of an active ingredient, "where differences exist that have been shown to affect drug product performance, bioavailability, or stability . . . ." 65 FR 83041, 83046 (Dec. 29, 2000).

form is used in a previously commercialized product." ACPS Transcript (Oct. 21, 2002), at 174. "However," as Dr. Yu explained, "if we know that a crystal form exists and we know the reference listed drug uses the amorphous form there is a potential for this amorphous form to convert into a crystal and under this scenario there is a concern." *Id.* at 175. Likewise, if the RLD uses a crystalline form and the proposed product uses the amorphous form, there must also be a concern.

Each of the tests outlined by Dr. Yu – for purposes of determining whether specific control and acceptance criteria are required – is satisfied with respect to mupirocin calcium. As disclosed in the '358 patent and the PCT application, crystalline and amorphous mupirocin calcium are not both highly soluble and sufficiently stable. The crystalline form is known to be more stable than the amorphous form. The patentees also assert that the amorphous form is more soluble, and that this greater solubility may impact the bioavailability of the product. *See, e.g.*, Tab 2 at 3,5. Finally, as discussed below, there is a significant risk that amorphous mupirocin calcium will crystallize over time.

3. FDA's Bioequivalence Methodology for Topical Dosage Forms is Inadequate to Detect Such Differences

As a general matter, and particularly with solid oral dosage forms, significant differences in the solubility and bioavailability of products containing different polymorphic forms may be detected in bioequivalence studies. FDA relied upon this fact in its Ceftin® petition response, which concerned a tablet dosage form. There, the agency acknowledged that different polymorphic forms can affect the dissolution and bioavailability of products. "Thus, it is possible that a difference in physical form of the active ingredients might prevent a proposed generic drug from being bioequivalent to the reference listed drug (thus barring approval of the ANDA)." Ceftin® Response at 12.

In this case, however, the "bioequivalence" methodology for topical dosage forms is a comparative clinical study in patients, using a subjective outcome measure. *See* ACPS Transcript (Apr. 14, 2004), at 226 (stating that such a study must show that the 90 percent confidence interval around the ratio of the cure rates of the test and reference products is between 80 and 120 percent). According to FDA, this "is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence." 21 CFR 320.24(b)(4). With Ceftin®, by contrast, the solubility and bioavailability of the different physical forms could be

compared directly through the rate and extent of systemic absorption of the solid oral drug products. *See id.* at 320.24(b)(1)(i).5

Given the lack of sensitivity of *in vivo* bioequivalence methodologies for topical dosage forms, and the assertions (discussed above) regarding differences in the solubility, stability, and bioavailability of the crystalline and amorphous forms of mupirocin calcium, the only alternative is to require an original showing of safety and effectiveness for the amorphous form. That is, the crystalline and amorphous forms should be considered different active ingredients for purposes of premarket approval. *See* 21 USC 355(j)(2)(A); 21 CFR 314.92(a)(1). Sponsors seeking to use the amorphous form of mupirocin calcium in topical products should proceed under section 505(b) of the FDCA, where the safety and effectiveness of the products may be fully evaluated.

4. *Pharmaceutical Equivalence Requires That Products Meet an Identical Compendial or Other Applicable Standard of Identity*

An ANDA applicant must show that the active ingredient in its proposed product is the "same" as the active ingredient in the RLD. 21 USC 355(j)(2)(A)(ii)(I); *see* 21 CFR 314.92(a)(1) (stating that a proposed generic drug must be "identical in active ingredient(s)" as the listed drug). The active ingredient in a proposed generic is considered by FDA to be the same as that contained in the listed drug if both meet the same "standards for identity." 57 FR at 17959. In the Ceftin® Response, FDA explained that reliance on a standard of identity represents a "more flexible approach" than the alternative of requiring complete identity of physico-chemical characteristics. Ceftin® Response at 8-9. Such standards of identity would, in most cases, be described in the USP, with the understanding that FDA may prescribe additional standards to ensure "sameness." *Id.* at 8.

The USP standards of identity are contained within "official monographs" that are a developed using a process akin to notice and comment rulemaking.6 These are "public quality standards"; they are recognized in

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5 Section 505(j) of the FDCA requires that generic drugs contain the same active ingredients, *and* possess the same bioavailability, as their reference products. These are separate statutory requirements, and should not be conflated. *See* 21 USC 355(j)(2)(A)(ii), 355(j)(2)(A)(iv). For example, even where they are bioequivalent, FDA considers different salts of the same active moiety to be different active ingredients.

6 Under the USP process, any person may submit to the USP a proposal for a new standard of identity. Proposals are reviewed by the appropriate Expert Committee, which may

numerous statutes and rules and can often have the force and effect of law.[7] The USP has not, however, set forth a standard of identity for the calcium salt of mupirocin. The only applicable USP standard at this time is for mupirocin, which sets forth a test for crystallinity. *See* Mupirocin,USP 27/NF 22.

In the absence of a USP standard, and based on the reasoning in the Ceftin® Response, the agency must prescribe a standard of identity for mupirocin calcium. Moreover, it must do so before reviewing any proposed mupirocin calcium products under section 505(j) of the FDCA that do not purport to contain the crystalline form. At this time, the crystalline form of mupirocin calcium is the only form of the drug that FDA has approved for marketing. The crystalline form also is specified in the approved labeling of the listed drug, Bactroban Cream®. Finally, as shown above, the sponsors of the amorphous form of the drug have themselves posited that the amorphous form has distinct physico-chemical characteristics from that of the crystalline form.

In short, while FDA may recommend a specification for a product within the context of an individual NDA or ANDA, it cannot prescribe a "standard of identity" – for purposes of determining "sameness" under section 505(j) or "pharmaceutical equivalence" under 21 CFR 320.1 – without a public process that allows for comment by all interested persons (including the sponsor of the RLD). The standard prescribed by the agency will serve the same purpose as a USP monograph and, likewise, must be adopted through a public process.

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publish them for public review and comment. All comments are then reviewed and incorporated into the proposal by the Expert Committee, which then approves the proposal or revises it for additional review and comment. *See Standards Development Process*, at www.usp.org/aboutUSP/p4/p4_g03.html; *compare* 21 CFR 10.40.

7 For example, a drug may be deemed adulterated under section 501 of the FDCA if it does not conform to an applicable USP standard. *See* 21 USC 351(a) and (b). In addition, FDA requires that a drug that bears a "compendial name" must "[comply] in identity with the identity prescribed in an official compendium under such recognized name." 21 CFR 299.5(a); *see* 21 USC 321(j) (defining the term "official compendium" to mean, among others, the USP).

B. Use of Amorphous Mupirocin Calcium Raises Issues Regarding the Identity of the Active Ingredient and the Nature of the Dosage Form

Even if the crystalline and amorphous forms of mupirocin calcium are determined to be the "same" active ingredient, use of the amorphous form raises a host of issues regarding the identity of that ingredient over time, and regarding the dosage form that will be needed to maintain it in the amorphous form. For example, if amorphous mupirocin calcium is placed in a cream dosage form, the presence of water in the cream is likely to promote crystallization. This will raise issues as to how the product should be labeled and whether it will be rendered adulterated or misbranded over time. *See* 21 USC 351(c), 352(a). At the same time, if the active ingredient is placed in a non-aqueous (non-cream) dosage form to prevent crystallization, the product must be regarded as a pharmaceutical alternative to Bactroban Cream®, rather than as a pharmaceutical equivalent. *See* 21 CFR 320.1.

1. *With Water, Amorphous Mupirocin Calcium Will Crystallize Over Time*

As shown above, the crystallization of amorphous active ingredients is well recognized. The agency itself has written that, "[o]ne polymorph may convert to another during manufacturing and storage, particularly when a metastable form is used. Since an amorphous form is thermodynamically less stable than any crystalline form, inadvertent crystallization from an amorphous drug substance may occur." *Scientific Considerations of Polymorphism in Pharmaceutical Solids: Abbreviated New Drug Applications*, ACPS (Oct. 21, 2002).

The crystallization of an amorphous active ingredient is particularly likely when that ingredient is exposed to moisture, as when placed in an aqueous dosage form. As the water content in a drug substance increases, the amorphous form becomes more fluid, with greater molecular mobility and greater reactivity. *See* Michael J. Pikal, "Freeze Drying," in *Encyclopedia of Pharmaceutical Technology*, Vol. 2, at 1310 (James S. Swarbrick & James C. Boylan, eds. 2002) (*Encyclopedia of Pharmaceutical Technology*). This lowers the "glass transition temperature," or the temperature at which stability failure and crystallization are likely to occur. *See id.*

This increase in water content can occur during creation or storage of the amorphous form, during its formulation, or during use and storage of the

product. The moisture may be absorbed from reagents or solvents used during manufacture, from humidity in the environment, or from product packaging. In any case, even small amounts of water can have a dramatic impact, decreasing the glass transition temperature to below the storage temperature. "Moreover, because the glass transition temperature often changes dramatically in a narrow range of water content, the onset of instability could be quite sudden." *Id.* at 1312.

The placement of amorphous mupirocin calcium in a cream dosage form would expose that active ingredient to a significant amount of moisture, leading to its inevitable crystallization.8 As described further below, creams, by definition, contain significant aqueous components. The European Pharmacopoeia, for example, defines creams as "multiphase preparations consisting of a lipophilic phase and *an aqueous phase*." *Semi-solid Preparations for Cutaneous Application*, European Pharmacopoeia (2002), at 560 (emphasis added) (Ph. Eur.).9

In short, and based on GSK's experience, amorphous mupirocin calcium will readily crystallize in the presence of an aqueous-based formulation. As a result, a mupirocin calcium cream product that is described in the approved labeling as containing the amorphous form of the active ingredient is likely to be rendered misbranded over time. *See* 21 USC 352(a). In addition, such a product will no longer have the purity or quality it purports to have, and will be rendered adulterated within the meaning of the FDCA. *See id.* at 351(c) (stating that a drug will be deemed adulterated if, among other things, "its purity or quality falls below . . . that which it purports or is represented to possess").10

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8 The PCT application acknowledges this tendency of the amorphous form: "[A]morphous mupirocin calcium prepared by the [claimed] process can be dissolved in an ethanol/water mixture, followed by removal of the ethanol, and *crystallization from water to recover the dihydrate*." Tab 3 at 15 (emphasis added); *see also id.* at 12, 15, 19, 26, 28.

9 Recognizing the impact that such an aqueous environment may have on an amorphous active ingredient, one member of the ACPS made the following statement at a recent meeting on the bioequivalence of topical products: "Over the shelf life of a lot of creams you will get crystal growth and the efficacy of that cream will change because the crystals start to grow and they don't have the same transport property that they did." ACPS Transcript (Apr. 14, 2004), at 248. In reply, FDA's Robert A. Lionberger, Ph.D., stated that the agency controls for such crystal growth by ensuring, through *in vitro* testing, the stability of the product over its shelf life. *See id.*

10 The labeling of Bactroban Cream® describes the crystalline form of mupirocin calcium. *See* Tab 1 at 1. Sponsors seeking to use the amorphous form of mupirocin calcium are likely to

2. *Without Water, Amorphous Mupirocin Calcium Cannot Be in the Same Dosage Form as Bactroban Cream®*

Alternatively, a sponsor seeking to use the amorphous form of mupirocin calcium may seek to maintain the active ingredient in a non-aqueous environment, in an attempt to prevent its crystallization over time. Even if possible, however, such a non-aqueous product could not be considered to be a cream dosage form. As such, it would be regarded as a pharmaceutical alternative to Bactroban Cream®, rather than as a pharmaceutical equivalent. *See* 21 CFR 320.1.

The FDCA generally requires that any product submitted under section 505(j) be in the same dosage form as its RLD. *See* 21 USC 355(j)(2)(A)(iii). The agency has interpreted this to mean that such products must be in the "identical" dosage form. 21 CFR 314.92(a)(1).11 In the alternative, where a proposed product is not in the same dosage form as its RLD, the FDCA requires that the product be the subject of an approved suitability petition, before submission of the ANDA. *See* 21 USC 355(j)(2)(C); 21 CFR 314.93.

The statute does not define the term "dosage form." The agency has long maintained, however, a list of dosage forms in the Uniform Terms Appendix to the *Orange Book*. *See* Citizen Petition Response, Docket No. 93P-0421 (Aug. 12, 1997) (affirming the *Orange Book* as FDA's source for dosage form classifications). Therefore, in order for products to be considered to be in the same dosage form, they must fall within the identical dosage form category, as set forth in the *Orange Book*. *See id.* at 3.12

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seek a change in the labeling, to remove the reference to crystallinity. Such a change in the description of the active ingredient is contrary to the FDCA and should not be permitted. *See* 21 USC 355(j)(2)(A)(v). Rather, to obtain original labeling, sponsors must seek approval under section 505(b) of the FDCA. Moreover, it would be false and misleading to remove the reference to crystallinity if, in fact, the product crystallizes during usage or shelf life.

11 According to the *Orange Book*, the precise dosage form for Bactroban Cream® is "cream, augmented."

12 The agency's maintenance of these separate dosage form classifications is important to the overall statutory scheme. It would undermine the intent of 21 USC 355(j)(2)(C), for example, to allow a sponsor to avoid the suitability petition process simply by describing a proposed ointment product as a so-called "waterless cream."

The *Orange Book* currently recognizes numerous topical dosage forms – including creams, emulsions, ointments, and others – in separate and distinct classifications. These distinct terms are based upon, and are consistent with, the dosage forms defined in the USP for use in its official monographs. *See* <1151> *Pharmaceutical Dosage Forms*, USP 27/NF 22; *see also* Citizen Petition Response, Docket No. 93P-0421 (Aug. 12, 1997), at 4.

The General Chapters of the USP defines a cream dosage form as containing a significant aqueous component:

> Creams are semisolid dosage forms containing one or more drug substances dissolved or dispersed in a suitable base. This term has traditionally been applied to semisolids that possess a *relatively fluid consistency* formulated as either *water-in-oil . . . or oil-in-water . . . emulsions*. However, more recently the term has been restricted to products consisting of *oil-in-water emulsions* or *aqueous microcrystalline dispersions* of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable.

<1151> *Pharmaceutical Dosage Forms*, USP 27/NF 22 (emphases added); *accord Center for Drug Evaluation and Research (CDER) Data Standards Manual: Dosage Form* (2000). As noted above, the Ph. Eur. likewise defines a cream as consisting of a lipophilic phase and an aqueous phase. *See Semi-solid Preparations for Cutaneous Application*, Ph. Eur., at 560.

An amorphous mupirocin calcium product held in a non-aqueous environment will not meet this definition. Agis Industries' '358 patent, for example, describes a so-called "waterless cream formulation" containing: White petrolatum, mineral oil, lanoline alcohol, cetostearyl alcohol, aluminum stearate, polyethylene glycol 400, titanium dioxide, and hexylene glycol. Tab 2 at 6. This formulation does not contain the aqueous component required by the USP and the Ph. Eur.

Rather, the '358 patent formulation appears to fit more closely the definition of an "ointment," defined in the USP as "semisolid preparations intended for external application to the skin or mucous membranes." More specifically, "hydrocarbon base" ointments are defined in the USP as follows:

> These bases, which are known also as "oleaginous ointment bases," are represented by *White Petrolatum* and *White Ointment*. Only

> small amounts of an aqueous component can be incorporated into them. They serve to keep medicaments in prolonged contact with the skin and act as occlusive dressings. Hydrocarbon bases are used chiefly for their emollient effects, and are difficult to wash off. They do not "dry out" or change noticeably on aging.

<1151> *Pharmaceutical Dosage Forms*, USP 27/NF 22 (emphasis original); *accord CDER Data Standards Manual: Dosage Form*.

Both the Ph. Eur. and the British Pharmacopoeia also cite petrolatum (also known as paraffin) and lanolin (also known as wool fat) as typical components of ointments. *See Semi-solid Preparations for Cutaneous Application*, Ph. Eur., at 559; *Topical Semi-Solid Preparations of the British Pharmacopoeia*, British Pharmacopoeia (2002), at 1905; *see also* Guru Betageri and Sunil Prabhu, "Semisolid Preparations," in *Encyclopedia of Pharmaceutical Technology*, at 2438-39 (describing the addition of lanolin to create an "absorption base" ointment).

The notable presence of white petrolatum and lanoline alcohol in the '358 patent formulation suggests that it is a hydrocarbon base or absorption base ointment. The '358 patent further suggests such an ointment by claiming a "cream preparation according to claim 6, where the hydrophobic phase comprises *an oleaginous base* selected from the group consisting of *petrolatum and hard fat* . . . ." Tab 2 at 3 (emphasis added). In either case, the lack of a significant aqueous component indicates that the formulation cannot be regarded as a cream.

Finally, the physical characteristics of the product described in the '358 patent would be significantly different than those of Bactroban Cream®. Instead of being "relatively fluid" and "more cosmetically and aesthetically acceptable," as called for by the USP's definition of a cream, the '358 patent formulation appears likely to be more occlusive. As the agency has recognized, such differences in the properties of products, and their significance to consumers, are reasons to maintain the distinctions between dosage forms. *See* Citizen Petition Response, Docket Nos. 95P-0262, 96P-0317 (Dec. 1, 2000) (upholding the distinction between tablets and capsules in part on patient and physician preference); *see also Orange Book* at Appendix: Uniform Terms (distinguishing between, among other dosage forms, creams and ointments).

As an ointment, an amorphous mupirocin calcium product would be a pharmaceutical alternative to Bactroban Cream®, not a pharmaceutical

equivalent, and thus must be the subject of an approved suitability petition. *See* 21 USC 355(j)(2)(C); *see also* ACPS Transcript (Apr. 14, 2004), at 240 ("[P]roducts that are pharmaceutically equivalent . . . means they have the same active ingredient in the same dosage form so we are comparing a cream versus a cream, not a cream versus an ointment or versus a solution . . . .").

C. Use of Amorphous Mupirocin Calcium Will Likely Require a Novel Composition of Inactive Ingredients

FDA generally requires that generic products intended for topical administration contain the same active and inactive ingredients as their reference products. *See* 21 CFR 314.94(a)(9)(v). A sponsor may seek approval of a product with different inactive ingredients, provided the sponsor "identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product." *Id.* FDA will refuse to approve an ANDA if "there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy." *Id.* at 314.127(a)(8)(ii)(A).

For example, FDA will refuse to approve an ANDA if the proposed product includes a significantly greater content of one or more inactive ingredients than previously used in the drug product. *See id.* at 314.127(a)(8)(ii)(A)(*6*). Likewise, FDA will refuse to approve an ANDA if the proposed product is intended for topical administration and there has been:

> [A] change in the properties of the vehicle or base that might increase absorption of certain potentially toxic active ingredients thereby affecting the safety of the drug product, or a change in the lipophilic properties of a vehicle or base, e.g., a change from an oleaginous to a water soluble vehicle or base.

Id. at 314.127(a)(8)(ii)(A)(7). Such products may be approved under section 505(b), where the safety and efficacy of the novel inactive ingredients can be characterized.

FDA previously has enforced these regulations with regard to mupirocin itself. Clay-Park's application for mupirocin ointment was deemed ineligible for submission as an ANDA because, in the agency's words, "the reference listed drug utilized a bland water miscible ointment base and [the Office of Generic Drugs] could not approve an ANDA that involved a change in

the lipophilic properties of the vehicle or base." Chemistry Review of NDA 50-788 (Dec. 3, 2002), at 8; *see* 21 CFR 314.127(a)(8)(ii)(A). Clay-Park thus submitted an NDA under section 505(b)(2). Other 505(b)(2) NDAs for topical products containing different formulations than the innovators' products include Avita™ (tretinoin gel and cream) 0.025%, Clindagel® (clindamycin phosphate gel) 1%, and Testim™ (testosterone gel) 1%.

In the case of mupirocin calcium, a comparison between Bactroban Cream® and the "waterless cream" described in the '358 patent reveals completely different formulations. For example, Bactroban Cream®'s approved labeling states that it contains benzyl alcohol, cetomacrogol 1000, cetyl alcohol, mineral oil, phenoxyethanol, purified water, stearyl alcohol, and xanthum gum. *See* Tab 1 at 1. Other than mineral oil, the '358 patent formulation contains completely different inactive ingredients, such as white petrolatum, lanoline alcohol, cetostearyl alcohol, polyethylene glycol 400, and hexylene glycol. *See* Tab 2 at 6.[13] Also, the lipophilic properties of this base appear to be different than that of Bactroban Cream®. *See* 21 CFR 314.127(a)(8)(ii)(A).

Such completely different inactive ingredients may have significant effects on the safety, tolerability, and efficacy of any mupirocin calcium product. *See* ACPS Transcript (Apr. 14, 2004), at 233, 256 (recognizing the impact excipients may have on the safety and efficacy of topical products); *see also* 21 CFR 314.127(a)(8)(ii)(A). A sponsor seeking approval of such a product should therefore be required to proceed under section 505(b), where these differences may be appropriately characterized.

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13 Several of the inactive ingredients disclosed in the '358 patent (*e.g.*, lanoline alcohol, cetostearyl alcohol, and polyethylene glycol 400) exceed the values listed in FDA's inactive ingredient database for cream dosage forms, or are not listed at all. *See Inactive Ingredients in FDA Approved Drugs*, at www.accessdata.fda.gov/scripts/cder/iig/index.cfm; *see also* 21 CFR 314.127(a)(8)(ii)(A).

IV. CONCLUSION

FDA should refrain from considering any ANDA for a topical mupirocin calcium product that contains the amorphous form of the active ingredient. The agency at this time lacks a prescribed "standard of identity" for purposes of determining the "sameness" of the amorphous and crystalline forms of mupirocin calcium. Statements made by leading generic sponsors in patent applications suggest that the two forms exhibit different physico-chemical characteristics that are material to a finding of sameness. Moreover, the formulation needed to hold the active ingredient in an amorphous form is likely to differ markedly from that used in the RLD, Bactroban Cream®.

For these reasons, we respectfully request that the Commissioner determine that all topical mupirocin calcium products that purport to contain the amorphous form of the active ingredient shall be filed only under section 505(b) of the FDCA.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

John M. Baldoni, Ph.D.
Senior Vice President
Pharmaceutical Development
R&D Worldwide

David M. Cocchetto, Ph.D.
Vice President
US Regulatory Affairs
(antiviral/antibacterial products)

Encls.

cc: David M. Fox
Brian R. McCormick
Hogan & Hartson L.L.P.