

Johnson & Johnson

CONSUMER & PERSONAL PRODUCTS WORLDWIDE
Division of Johnson & Johnson Consumer Companies, Inc.

199 Grandview Road
Skillman, NJ 08558-9418

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February 14, 2006

Dockets Management Branch
Food and Drug Administration
Room 1061, 5630 Fishers Lane
Rockville, MD 20852

RE: Comments to Docket # 2005P-0417/CP1

Dear Sir/Madam:

Johnson & Johnson Consumer & Personal Products Worldwide (J&JCPPW) is the sponsor of the approved new drug applications (NDA's) for Retin-A® Cream 0.1%, 0.05% and 0.025% for topical application in the treatment of acne vulgaris. J&J CPPW is submitting these comments in opposition to the Suitability Petition of Triax Pharmaceuticals, Inc. filed by FDA on October 18, 2005 and the Suitability Petition Supplement filed by FDA on January 24, 2006 (Docket # 2005P-0417/CP1).

The petitioner, Triax Pharmaceuticals, Inc., has requested that the FDA approve intermediate strengths of Tretinoin Cream (0.0375% and 0.075%). The petitioner claims that approval of these intermediate strengths would provide increased ability to meet the specific needs of individual acne patients while presenting no new issues surrounding safety or effectiveness. Furthermore, the petitioner speculates that approval of these intermediate strengths should allow for improved patient compliance. J&JCPPW respectfully urges the FDA to deny the petition for the following reasons:

- The Petitioner has not addressed how they intend to demonstrate bioequivalence or efficacy of a new strength of Tretinoin Cream when there is no corresponding Reference Listed Drug (RLD).
- The Petitioner's assumption that intermediate strengths of currently marketed Tretinoin Cream would result in less irritation by significantly impacting the degree of tretinoin-induced irritation is not known and can only be shown by a direct comparison through clinical trials of the strengths in question.

I. Background

J&JCPPW is the sponsor (application holder) for the three approved NDA's for Retin-A® Cream 0.1%, 0.05% and 0.025% (NDA 17-340, 17-522 and 19-049, respectively). These topical drug products were first approved January 26, 1973 for sale and distribution in the United States.

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II. Unapproved New Strengths of generic Tretinoin Cream Requires Proof of Bioequivalence and Efficacy

As per 21 CFR 320.24 (b)(4), the approval of a generic version of a topical drug product is based on a well-controlled clinical trial for measuring bioavailability or demonstrating bioequivalence. This well-controlled clinical trial used to demonstrate bioequivalence usually consists of three treatment groups: test article, reference listed drug (RLD) and vehicle (test article). In order for the test article to be considered bioequivalent to the RLD, it has to show statistical superiority to the vehicle and statistical equivalence (results fall within 90% CI) to the RLD.

The Suitability Petition for the Intermediate Strengths of Tretinoin Cream does not address the method to prove superiority to a vehicle formulation or equivalency to the RLD. The Petitioner has claimed these products would be efficacious at these intermediate strengths by virtue of the fact that these concentrations are bracketed by currently approved strengths. We believe that these intermediate strengths are too close in concentration to the approved strengths to show any perceived or realized differences in efficacy, safety or patient compliance without benefit of clinical results and only serve to be a means of differentiation from the RLD drug products for marketing purposes.

Without the determinations of bioequivalence and efficacy, we believe the petitioner's product would not be a generic equivalent as per the definition of a topical generic product. Therefore, clinical investigations would be required to show the safety and effectiveness of these different strengths. Because these investigations would be required, the petition should be denied pursuant to 21 USC Section 355(j)(2)(C).

III. Intermediate strengths of currently marketed Tretinoin Cream would result in less irritation by significantly impacting the degree of tretinoin-induced irritation is not known and can only be shown by a direct comparison through clinical trials.

Irritation caused by topical application of a tretinoin product is a multifactorial process and is likely due to complex manifestations of anticipated pharmacologic actions such as the changes in cell turnover and compaction of the stratum corneum. The activity associated with tretinoin is presumed to be due to binding of intracellular receptors in the cytosol and nucleus, which ultimately results in the reduction of epithelial cell growth and differentiation. This mechanism of action does not support the assumption that a change in tretinoin delivery or formulation concentration would result in a proportional change in the irritation potential.

Substantiation of claims of less tretinoin- induced irritation between various strengths of Tretinoin Cream drug products can only be confirmed by direct clinical comparison between the products and not by inference alone. Adequate and well-designed trials would be required to prove this hypothesis. . Again, because clinical investigations would be required, the petition should be denied under 21 USC Section 355(j)(2)(C).

In addition, 21 USC Section 355(j)(2)(A)(iv) requires that generic applicants demonstrate that the ANDA drug can be "expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i). In this case, the petitioner has made clear that they intend the products to have a different therapeutic effect; that is, that the ANDA drug will have less irritation. Therefore, the ANDA should not be approved.

V. Conclusion

We feel there are several issues that would preclude the approval of intermediate strengths of Tretinoin Cream by the ANDA route and believe that the Petitioner has not adequately supported their argument set forth in Docket# 2005P-0417/CP1. The perceived benefits outlined by the Petitioner require data only obtainable through clinical trials. The Petitioner has not adequately addressed what method will be employed to demonstrate bioequivalence and efficacy to the RLD and have only theorized without benefit of clinical trials that these intermediate strengths would cause less irritation. For these significant reasons, this petition should be denied.

Thank you for your timely consideration of these comments. I would be happy to discuss further the issues raised in this submission. Please contact me at 908-874-2410.

Sincerely,



Stephanie J. Davis, RPh
Associate Director, Regulatory Affairs