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APPLICATION NUMBER:

203567Orig1s000

<u>OTHER ACTION LETTERS</u>

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NDA 203567

COMPLETE RESPONSE

Dow Pharmaceutical Sciences
Attention: Sean Humphrey, MS
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your New Drug Application (NDA) dated July 25, 2012, received July 26, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (efinaconazole) Topical Solution, 10%.

We acknowledge receipt of your amendments dated August 6, 10, and 20, September 26, October 17, and 22, December 6, 7, 14, 19, and 20, 2012; and January 9 and 17, March 18 and 29, 2013.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The quality of the product can not be assured due to:

1. Inadequate manufacturing process and control information of the filling/capping ^(b) (4) operation.

    Per 21 CFR 314.50 (d)(1)(ii)(c), the application shall contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product. The description is expected to be included in Section 3.2.P.3 of the application.

    The application did not describe the filling/capping ^(b) (4) process in the Section P.3 as well as in the Master Batch Record with sufficient details and specifics to ensure the process is robust and can produce batches with acceptable leakage rate.

2. Inadequate specification for the drug product.

Stability study results on weight loss for the [(b) (4)] fill stored at 25ºC confirms a significant loss of formulation ingredient(s) in multiple units (referred to as true leakers in this letter) which eventually showed residues on the outside of the bottles. For a product with a volatile organic formulation and a known history of leakage, the use of a sensitive and specific method for leak detection is critical to ensure the quality of the product. Multiple technologies with different leak-detection principles such as pressure or voltage differentiation are available for evaluation.

3. Inadequate integrity of the container closure system.

Batch release and stability data submitted in the application show unacceptable number of failure incidences for package integrity. Additionally, the presence of a significant number of true leakers has been confirmed through the weight loss study. These observations indicate that the proposed container closure system does not provide adequate protection for the drug product.

- True leakers and latent leakers have been detected for multiple batches in the weight loss study.

- The greater failure incidence in package integrity test for later time points indicates that [(b) (4)] is not the only cause responsible for the failure.

- The non-specific [(b) (4)] method employed for leakage detection can not discern the cause of exterior residue (i.e. filling line dripping/vibration or true leakage), and can not detect non-residue-producing leaks.

4. Inadequate stability data to assure the expiration dating period.

The stability data presented in Section 3.2.P.8 (stability) of the application were generated from batches manufactured using a manufacturing process which is not representative of commercial production process.

INFORMATION NEEDED TO RESOLVE DEFICIENCIES

1. Regarding manufacturing process and control information:

- Update Section P.3 and Master Batch Record with a description for the optimized commercial process, including details of the filling/capping [(b) (4)] operation with all in-process controls and operation ranges of process parameters.

- Produce three production batches using the optimized processes, and submit a minimum of 12 months of long-term and 6 months of accelerated stability data, including failure rate due to leakage, for both upright as well as horizontal orientations.

- Two of the batches should be at least pilot scale batches. The process must be the one to be validated for routine production, and the batches must be manufactured using the to-be-marketed container/closure system.

- Assay results should be generated for leaking units whenever feasible.

2. Regarding the specification for the drug product:

- Update the specification for the drug product to include a specific and sensitive leakage test method and its acceptance criterion.

- The leakage test method must be validated and should not rely on   (b) (4)   to detect leaks. Validation data for the method must be provided.

3. Regarding integrity of the container closure system:

- Establish a control strategy to ensure the integrity of container closure system without leakage.

- Provide complete description of the to-be-marketed container/closure system and any modifications to the system since the initial submission of the NDA.

- Provide representative samples (three units) of the to-be-marketed product.

4. Regarding stability data:

- In addition to the data described in the Item 1 above, provide in-use stability data for the drug product packaged in the to-be-marketed container/closure system.

ADDITIONAL COMMENTS

The following comments are provided to enhance the Agency's understanding of the quality of clinical batches. They are not approvability issues. However, the requested information should be included in your resubmission.

- Appendix II of Report 129 states that all bottles from batch DP1444 were weighed, with the acceptance criteria to be specified in the batch record. Provide the following information:
  o the acceptance criteria;
  o weight results (summarized in table format); and
  o full accountability of all bottles; and the fate of bottles that failed the check.

- Report 129 states that leaking bottles from batch DP1453 were stored for further (b) (4) evaluation. Provide the following information:
  o results of (b) (4) evaluation (e.g., assay, weigh loss, etc.);

- o full accountability of all bottles sent to (b) (4), including those bottles sent to clinical studies; and
- o experimental details.

PREA REQUIREMENTS

The Agency does not concur with your proposal (b) (4)

You will need to update your Pediatric Study Plan (PSP) which describes your study proposals, or your PSP can provide additional information regarding the incidence and prevalence of onychomycosis in pediatric populations and comment on the feasibility of conducting adequate clinical trials in such populations (b) (4).

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach). For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.ht m . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.

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