CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203567Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW RESUBMISSION

Application Type	505(b)(1)
Application Number(s)	203-567
Priority or Standard	Standard
Submit Date(s)	20-DEC-2013
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Division / Office	DDDP/ODE III
Reviewer Name(s)	Gary Chiang MD, MPH
Review Completion Date	8-MAY-2014
Established Name	efinaconazole
(Proposed) Trade Name	Julia™
Therapeutic Class	antifungal
Applicant	Dow Pharmaceutical Sciences
Formulation(s)	Topical solution 10%
Dosing Regimen	Once daily
Indication(s)	Onychomycosis
Intended Population(s)	Adults 18 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Dow Pharmaceutical Sciences has re-submitted a New Drug Application for JUBLIA™ (efinaconazole solution, 10%) with a proposed indication of once daily topical treatment of onychomycosis of the toenail (tinea unguium) in patients 18 years and older. The applicant successfully demonstrated safety and efficacy in two adequate and well controlled clinical trials for the treatment of onychomycosis in patients 18 years and older, when used once daily for 48 weeks.

The original NDA was submitted on July 26, 2012 and this submission received a complete response due to Chemistry Manufacturing and Control (CMC) deficiencies on May 13, 2013, principally related to leakage of the container closure system (b) (4) The nonclinical, clinical pharmacology and clinical programs submitted with the original application were found generally acceptable though labeling negotiations were not initiated once it became clear that the bottle leakage would preclude approval of the application.

On December 20, 2013 the applicant re-submitted their NDA to with a new container closure system to address the CMC deficiencies. The applicant has redesigned the container closure system and provided data that no leakage has occurred. No new nonclinical information was provided, and no new clinical pharmacology or clinical trials were conducted for this resubmission.

The critical CMC review issues that concluded with a Complete Response from the first review cycle have been resolved. The new container closure system has been found to be acceptable for marketing and the applicant has provided appropriate information to provide sufficient data to assure the identity, strength, purity, and quality of the drug product. The new bottle with a brush applicator dispenses drug product with similar quantity and distribution as the container/closure system used in the Phase 3 clinical trials so that additional clinical trials are not required.

This reviewer is in agreement with the CMC recommendation for approval, and the clinical recommendation is for approval of this application.

1.2 Risk Benefit Assessment

The risk to benefit assessment for this application is primarily based on the clinical trial results, which were extensively reviewed in the initial cycle and documented in the clinical review dated April 13, 2013. In the two pivotal Phase 3 clinical trials, the most common adverse events associated with the drug product were application site reactions (application site dermatitis and application site vesicles). There were no deaths or serious adverse events attributed to the drug product. In the two combined pivotal Phase 3 clinical trials, a greater percentage of subjects in the JUBLIA™ group relative to the Vehicle group achieved "Complete Cure" (clinical cure as well as mycological cure) at Week 52 (16.6% versus 4.3%, respectively), demonstrating that the drug product was effective in treating toenail onychomycosis.

The proposed product labeling includes warnings and precautions regarding local sensitivity and irritation reactions. This drug product has minor local side effects and insignificant systemic effects. The adverse events associated with the drug product can be adequately informed by labeling. The label also provides adequate information for instructions for use.

In conclusion, there are few risks associated with the use of this topical product for the treatment of toenail onychomycosis. The effectiveness of this topical onychomycosis product ranges from 9.7% to 14.5% ("Complete Cure"). The benefits include relatively low systemic effects making this topical treatment ideal for patients that cannot take oral antifungals for the treatment of toenail onychomycosis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post-market risk evaluation or mitigation strategies are recommended. Labeling is adequate to convey benefits and risks to patients and prescribers.

1.4 Recommendations for Postmarket Requirements and Commitments

The initial review by the Pediatric Review Committee (PeRC) has recommended that the prevalence of onychomycosis in children is sufficient to warrant studies in ages 6 years and above. On the re-submission of this application, a Pediatric Plan was submitted with a request for a full waiver for subjects under the age of 12 years old. The Pediatric Plan submitted by the applicant did not include a pharmacokinetic evaluation. The review of this proposed study is in ***Section 7.6.3***.

Reviewer's comment: *The Division has reviewed a wide range of literature and concluded that studying onychomycosis in subjects 12 years and above is appropriate for onychomycosis as adequate numbers of culture positive subjects under age 12 are few in number and studies would be impractical. The review team discussed this issue with the PeRC and recommends a PMR with at least 40 pediatric subjects 12 years and older with a pharmacokinetic population of 16 subjects. . Efficacy can be extrapolated from the adult data.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The action recommended by the CMC reviewer is for approval. The applicant has demonstrated sufficient data to assure the identity, strength, purity, and quality of the drug product. The previous container closure issues related to leakage of the bottle have been resolved with a new bottle/brush assembly (b) (4) . There is no other safety or efficacy issue from other disciplines.

4.1 Chemistry Manufacturing and Controls

The original NDA 203567 was not approved during the first review cycle. The CMC deficiencies identified during the first review cycle were communicated to the sponsor in the CR action letter.

The deficiencies and remedies are captured in the CMC review.

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

In order to address deficiency 1, the sponsor was asked to provide the following 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.

B. Deficiency 2.
Inadequate specification for the drug product. 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.

In order to address deficiency 2, the sponsor was asked to provide the following information:

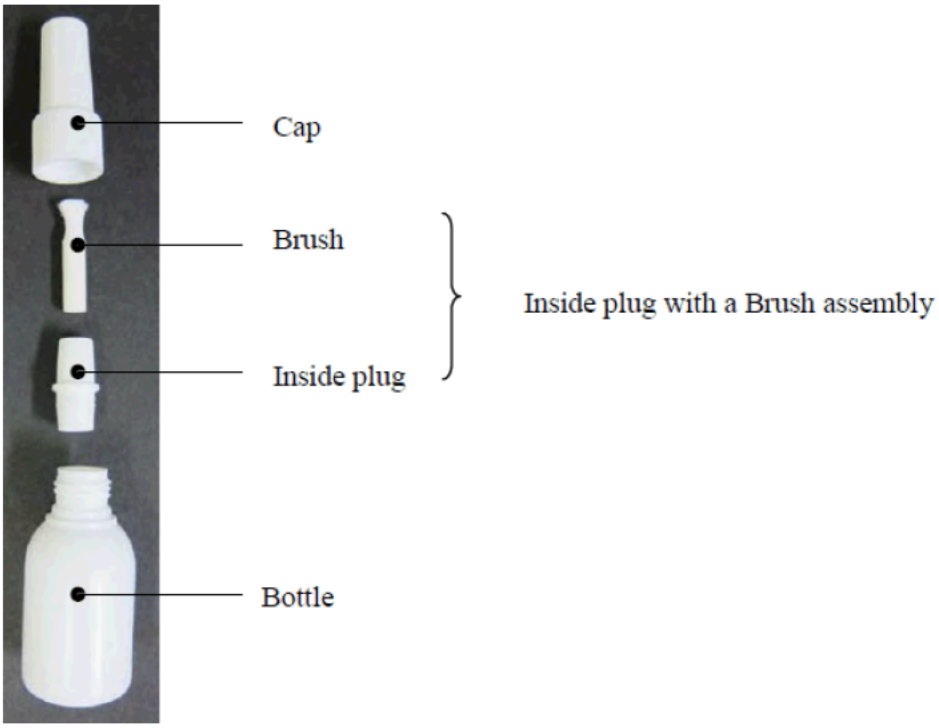
- Update the specification for the drug product to include a specific and sensitive leakage test method and its acceptance criterion.
- The leakage test method must be validated and should not rely on (b) (4) to detect leaks. Validation data for the method must be provided.

C. Deficiency 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. These observations indicate that the proposed container closure system does not provide adequate protection for the drug product.

In order to address deficiency 3, the sponsor was asked to provide the following information:

- 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.

The container closure system is fitted with a (b) (4) cap. The figure below shows components of the container/closure system:



The inside plug/brush (b) (4) . The bottle is made of HDPE, brush from (b) (4), and inside plug and cap of (b) (4). All materials are manufactured by (b) (4) .

D. Deficiency 4.
Inadequate stability data to assure the expiration dating period. The stability data presented in the application were generated from batches manufactured using a manufacturing process which is not representative of commercial production process.

In order to address deficiency 4, the sponsor was asked to provide the following information:

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

The CMC review concludes that the information provided in this resubmission to address the deficiencies is acceptable.

Reviewer's comments:
The applicant has provided sufficient data to assure the identity, purity, and quality of the drug product. The previous issue of container closure system has been resolved with the new assembly. The applicant has provided sufficient stability data, and the leaking bottle issues appear to have been successfully resolved with the container closure redesign.

The only outstanding issue as of the date of this review is the final report from the Office of Compliance regarding the recommendation for the manufacturing establishments and final, agreed upon labeling.

5 Sources of Clinical Data

No new clinical trial results or other information are presented in this resubmission. Only CMC information is presented in this submission.

6 Review of Efficacy

Efficacy Summary

The efficacy summary provided here is derived from the original review. No new clinical trial data was submitted in this review cycle.

The efficacy evaluation included one Phase 2 study and two Phase 3 clinical trials. A summary of the protocols are described in Section 5. The formulation of the Phase 2 study (DPSI-IDP-108-P2-01) is not the to-be-marketed formulation; whereas, the Phase 3 clinical trials used the final to-be-marketed formulation of the drug product.

Reviewer's Comment: *The summary of the primary efficacy endpoint provided in Table 1 will be used in the labeling of the product. Note that "Complete or almost complete cure" was specified in the second version of the SAP as defined by ≤5% affected toenail and mycological cure (negative KOH and culture).*

Table 1: Summary of Primary and Secondary Efficacy Endpoints at Week 52

	Study P3-01			Study P3-02		
	IDP-108	Vehicle	*p-value*	IDP-108	Vehicle	*p-value*
	N=656	N=214		N=580	N=201	
Complete Cure	117 (17.8%)	7 (3.3%)	<0.001	88 (15.2%)	11 (5.5%)	<0.001
Complete or almost complete cure *	173 (26%)	17 (7%)	<0.001	136 (23%)	15 (7%)	<0.001
Mycologic Cure	362 (55%)	36 (17%)	<0.001	310 (53%)	34 (17%)	<0.001
Unaffected new growth (mm)	5.0 (0.2)	1.6 (0.4)	<0.001	3.8 (0.2)	0.9 (0.4)	<0.001

Source: Agency Biostatistical Review (Dr. Kathy Fritsch)
* Endpoint specified in SAP version 2

6.1 Proposed Indication

JUBLIA™ (efinaconazole cream, 10%) is indicated for the topical treatment of onychomycosis in the toenails (tinea unguium) of adults 18 years and older.

7 Review of Safety

Safety Summary

The complete safety evaluation of the clinical program for JUBLIA™ (efinaconazole) Topical Solution, 10% was reviewed in the first cycle. No new data is presented in this re-submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

This application triggers PREA as directed to a new active ingredient.

The initial PeRC meeting was held on January 23, 2012 to discuss efinaconazole solution, 10%. The applicant's request (b) (4) was recommended to be denied on the evaluation that (b) (4)

In the re-submission, the applicant requests a full waiver for pediatrics age 0 to 11 years old. The applicant referenced published literature which shows that there is low prevalence of onychomycosis in patients 12 years and younger that would make a study in these subjects impractical due to an inability to enroll adequate number of subjects in a reasonable period of time. The applicant also requested a partial waiver for pediatric subjects 12 to 18 years of age, with reasoning that adult data is ready for approval and that a pediatric study will be completed with the proposed time line.

The proposed timeline:

Final Protocol Submission: September 2014 (based on 3 months after approval)

Final Subject Completion: March 2018

Final Study Report: September 2018

On 30-APR-2014, a second PeRC meeting was held to discuss efinaconazole topical solution for the treatment of onychomycosis. The PeRC again disagreed with the Division's recommendation (b) (4) The PeRC agreed that the incidence of onychomycosis in pediatric subjects is low relative to the incidence in adults; however, the sponsor's data suggest that there are a small but consistent number of visits each year for this diagnosis in children less than 12 years of age. The Division provided data that onychomycosis in North America for children under the age of 12 is significantly less than that of Greenland or Japan, where some of these studies showing higher incidences are done. The Division also pointed out that identifying culture positive onychomycosis subjects under age 12 would be impractical, despite literature date for "visits" for onychomycosis. Recommended endpoints for this indication require culture and KOH positive subjects. PeRC also recommended that studies be done in pediatrics down to 2 years of age and would ask the sponsor to attempt to enroll to that age, but if the sponsor is unable to enroll patients, despite good faith attempts, a waiver could be issue later.

The PeRC agreed with the Division that a deferral for pediatric subjects aged 2 to less than 17 years is appropriate as adult data is ready for the products approval.

Reviewer's comments: *The Division has reviewed the literature submitted by the applicant, as well as, researched literature independently, and it is our conclusion that the lack of prevalence with culture positive onychomycosis in children under the age of 12 will limit any successful clinical study to inform safety of this product. The Division concludes that such trials are impractical. The applicant has submitted a Pediatric Plan down to the age of 12 years old.*

Proposed Pediatric Plan: (b) (4)

(b) (4)

Reviewer's comment: *The safety of this trial in pediatric subjects is acceptable. At this time, the Division will accept the pediatric trial as proposed in subjects 12 years and older. The Division appreciates PeRC's input into the matter; however, in order to be consistent with other applications with the same indications, the Division will not require pediatric studies down to 2 years of age.*

(b) (4) *The Agency will require a pharmacokinetic sub study within this pediatric trial based on recommendations of the clinical pharmacology review team.*

9 Appendices

9.2 Labeling Recommendations

The trade name, JUBLIA™, has been found acceptable by the Office of Prescription Drug Promotion (OPDP).

Labeling negotiations are ongoing. The finalized label will be attached to the approval letter.

Currently Proposed Label:

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immeidately following this page

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not conducted because this drug product has clinically insignificant systemic absorption and causes few adverse events. The Agency's experience with topical azole antifungals is ample that advice from an Advisory Committee is not required with this drug product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GARY T CHIANG
05/08/2014

DAVID L KETTL
05/16/2014

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION III

DATE: May 13, 2013

FROM: Victoria Kusiak, M.D.

SUBJECT: Office Deputy Director Memo

TO: NDA 203567, efinaconazole Topical Solution, 10%
Dow Pharmaceutical Sciences

Summary

Efinaconazole is a new molecular entity that belongs to the triazole antifungal drug class. The proposed indication for this product is once daily topical treatment of onychomycosis of the toenail. This daily treatment should continue for 48 weeks. Efinaconazole is packaged in a 10 mL bottle with a brush applicator. It is not currently marketed in any country.

Onychomycosis is the condition of fungal infection of the nail and can be caused by yeasts and non-dermatophyte molds. It is characterized by hyperkeratosis of the nail bed, yellow to brownish discoloration of the nail plate, onycholysis and paronychial inflammation. The mechanism of action of efinaconazole is similar to that of other azole antifungal compounds and is secondary to lanosterol 14α-demethylase inhibition resulting in blockage of ergosterol depletion and accumulation of 14-α methyl sterols, leading to mycosal cell death.

The clinical program for efinaconazole consists of four Phase 1 trials which include a maximal use pharmacokinetic (PK) trial in subjects with severe onychomycosis and a PK trial in healthy subjects, one Phase 2 safety and efficacy trial and two Phase 3 safety and efficacy trials in subjects with mild to moderate onychomycosis. While clinical review identified no significant safety or efficacy issues that would have precluded approval, significant packaging integrity issues were identified early in the review cycle such that the product quality cannot be assured with the chemistry manufacturing and controls (CMC) procedures described within the application.

These CMC issues include (but are not limited to) problems with the brush-cap assembly, potential leachables from the container/closure system, incomplete details of the process/control information provided in the NDA, inadequate proposed product package integrity test(s), inadequate stability data, and produced batches with a leakage rate of (b) (4) These issues were communicated to the applicant in the 74 day letter, in a Discipline Review Letter (DRL) issued on March 8, 2013, and during a teleconference with the applicant for the purposes of clarification on March 20, 2013.

In summary, the Office of New Drug Quality Assessment (ONDQA) has determined that the information as provided in the NDA is not adequate to assure the identity, strength, purity and quality of the drug product, and as such the application cannot be approved.

This memo documents my concurrence with the recommendation of the Division of Dermatology and Dental Products (DDDP) for a complete response (CR) action for efinaconazole, 10% solution for the treatment of onychomycosis of the toenail in adults. Before this application may be approved, the following must be satisfactorily completed:

Regarding manufacturing process and control information:

- Update Section P.3 and the 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 and horizontal positions.
- Two of the batches should be at least pilot scale batches. The process used 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.

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.

Regarding the integrity of the container closure system:

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

Regarding stability data:

- In addition to the data described in the section headed manufacturing and control information, provide in-use stability data for the drug product packaged in the to-be-marketed container/closure system.

Regulatory History

A pre-IND meeting was held with the applicant on December 18, 2006. IND 077732 was opened on May 8, 2007 with a proposed 21 day cumulative irritation study to evaluate efinaconazole in healthy subjects. An end of phase 2 meeting was held August 4, 2009. No SPA review was requested.

The NDA was filed July 26, 2012. Packaging integrity issues were identified by the ONDQA team prior to the filing meeting, which was held on September 11, 2012.

The 74 Day Letter identified the following potential review issues:

- Inadequate information in the application to assure the strength, purity and quality of the drug product due to inadequate information to qualify the proposed brush/cap assembly.
- Inadequate information provided to demonstrate absence of significant contaminants in the formulation due to leachables from the proposed container/closure system.

Information requests were sent to the applicant during the review cycle requesting additional information referable to drug process controls. A DRL was sent to the applicant on March 8, 2013 detailing the deficiencies found by ONDQA in the application. A teleconference was held with the applicant on March 20, 2013 to provide further clarification concerning the above noted deficiencies.

The conclusion of the ONDQA review, as noted above and as documented in an addendum to the initial review dated April 11, 2013, affirms that the CMC information submitted in the initial application as well as in subsequent submissions to the NDA is not adequate for approval.

Chemistry, Manufacturing and Controls (CMC)

The specifics of the CMC issues are detailed in the ONDQA Division Director's review and are summarized here.

The proposed container/closure system for efinaconazole includes a white 10mL HDPE bottle (for a (b) (4) fill) with a directly attached brush applicator and a (b) (4) cap. The brush extends directly from the top of the bottle tip and is used without detaching. The user turns the bottle over and brushes the product onto the nail and surrounding skin.

The container closure system is a novel package intended to minimize the exposure of the packaged product to any potential external contamination from the infected nail, as the brush is not pushed back into the topical solution after wiping on the infected nail.

ONDQA reviewers noted that a high percentage of drug product bottles (greater than 50%) from the first large scale clinical batches (Batches 1444 and 1453F1) had evidence of leakage. The applicant investigated various factors that might be contributing to this leakage, (b) (4) and made modifications (b) (4) for subsequent batches. However, the application itself does not describe the adjusted filling/capping (b) (4) process with sufficient detail and specifics to ensure that the process is robust and can produce batches with acceptable leakage rates. The Pharmaceutical Development section of the application includes discussion of the applicant's proposed enhancements; however, none of the recommendations on the process improvements are officially implemented in the

manufacturing process and in the Master Batch Record. The ONDQA recommendation regarding the manufacturing process and control information is as follows:

- The application should be updated with the optimized process
- Three production batches should be produced using the optimized processes with 12 months of long-term and 6 month of accelerated stability data, including failure rates due to leakage (upright and horizontal).
- Two of the batches should be at least pilot scale batches. The process must be the one validated for routine production, and use the to-be-marketed container/closure system.
- Assay results should be generated for leaking units whenever feasible.

With regard to drug product specifications, these should include a specific and sensitive leakage test method and its acceptance criteria, and the leakage test method must be validated and not rely on (b) (4) alone to detect leaks.

According to ONDQA reviewers, a significant percentage of stability samples showed non-conforming package integrity. Leakage was evident (b) (4) for stability testing and is believed to have occurred in bottles subsequent to filling. Leakage was more likely for samples stored for ≥ one month. ONDQA has concluded that the residues found on the exterior surfaces were not exclusively due to (b) (4) dripping and vibrations of the manufacturing line belt, and that true leakage occurred subsequent to release. The following points are notable:

- True leakers and latent leakers have been detected for multiple batches in a weight loss study consisting of 10 units for each orientation (horizontal and vertical) per batch, totaling 60 units (3 batches, 2 orientations per batch).
- Each bottle was visually inspected prior to release and bottles with external residue were rejected. Therefore all bottles in the weight study were initially considered "non-leaking".
- There was greater failure incidence in the package integrity test for later time points, as opposed to earlier time points, indicating that the (b) (4) is not the only cause responsible for the container/closure failure.
- The non-specific (b) (4) method employed for leakage detection cannot discern the cause of exterior residue (i.e. filling line dripping/vibration or true leakage) and cannot detect non-residue producing leaks.

Additionally, the stability data provided are not considered to be representative of the stability characteristics of commercial batches which will be produced using an improved process, as additional improvements will need to be made in the filling/capping (b) (4) process as described above. The application should provide in-use stability data for the drug product packaged in the to-be-marketed container/closure system.

As currently documented in the application, this container/closure system does not provide proper protection against leakage, and DDDP has concluded that there is not

significant unmet medical need for this product to justify departure from acceptable CMC standards.

Microbiology

There were no clinical microbiology issues identified in this review. Potential labeling issues were identified but not addressed with the applicant, as labeling comments have been deferred until such time that the application is otherwise adequate.

Nonclinical Pharmacology/Toxicology

The review of nonclinical/toxicology data did not identify any critical review issues, nor identify any need for post-approval studies.

In particular, in 6 month repeat dose subcutaneous toxicity studies in rats treated with 30-40 mg/kg/day, the only finding was injection site toxicity in all dose groups, including the propylene vehicle control group.

In a 9 month dermal toxicity study in mini-pigs, at topical doses of up to 30% (maximum possible concentration), only mild skin irritation was seen in all dose groups, including the vehicle. No systemic toxicity was noted.

There was no evidence of mutagenic or clastogenic potential with efinaconazole based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster chromosome aberration assay) and one *in vivo* genotoxicity test (mouse micronucleus assay).

A dermal mouse carcinogenicity study showed no treatment related increase in the incidence of neoplasms; however, the effects of the vehicle (which were significant), confounded assessment of any skin effects due to efinaconazole.

No significant treatment related effects were seen in reproductive and developmental toxicity in rats and rabbits at doses up to 10/mg/kg/day. Higher doses were associated with maternal toxicity.

No effects on fertility were seen in male and female rats administered subcutaneous doses of efinaconazole up to 25 mg/kg/day (279 times the maximum recommended human dose).

Single dermal application of up to 10% efinaconazole solution to rabbits did not elicit dermal reaction in intact skin, but was a mild irritant to abraded skin. Efinaconazole did not elicit a photo-irritation response in guinea pigs.

Efinaconazole will be labeled as pregnancy category C.

Clinical Pharmacology

The applicant submitted two PK studies in support of efinaconazole: Trial DPSI-IDP-108-P1-03, a maximal use study in adult subjects with severe onychomycosis and Trial DPSI-IDP-108-P1-02 in healthy adult subjects. The parent compound is IDP-80 with a major metabolite H3 (inactive) and minor metabolite H4 (active).

The maximal use PK trial (DPSI-IDP-108-P1-03) was conducted in 20 adult subjects (male and female) with severe onychomycosis with at least 80% of the area of both great toenails involved and at least 4 other toenails involved. Study drug was applied once daily for 28 days to all 10 toenails and 0.5cm of adjacent skin. Serial blood samples were collected pre-dose and on day 1, 14, and 28, with a post-dose sample drawn within 2 weeks. Plasma samples were quantifiable for the parent drug (IDP-108) in 15/18 onychomycosis subjects on day 1 and in all subjects on days 14 and 28. The ratio of mean AUC and mean Cmin on Day 14 vs. Day 28 was ≤ 1.18 for the parent drug (IDP 108), suggesting that concentrations *in vivo* were near steady state by Day 14. The mean values of AUC (0-t) and Cmax on Day 28 for the parent drug were 12.15 ± 6.91 ng*h/mL and 0.67± 0.37 ng/mL, respectively. The concentration profile for the parent drug at steady state was relatively flat over the 24 hour dosing interval.

The potential for drug-drug interactions was also evaluated. H3 (inactive) was the major metabolite in human plasma. *In vitro,* H4 (active) was the major metabolite. *In-vivo,* H4 was quantifiable in only 4 subjects and in those subjects it was present at levels of <25% of those of the parent compound based on the ratio of the AUC's. Other minor metabolites were not explored.

Multiple CYP enzymes are involved in efinaconazole metabolism with CYP2C19 and CYP3A4 as the primary isozymes. Mean plasma levels of efinaconazole under maximal use conditions were low (< 2nM). Therefore the risk of CYP mediated drug-drug interactions is considered to be low.

Efficacy

Efficacy was demonstrated in two Phase 3 randomized, double blind, multicenter, vehicle controlled clinical trials of similar design. Trial P3-01 enrolled 870 subjects (656 efinaconazole/214 vehicle) while Trial P3-02 enrolled 785 subjects, 781 of whom received study drug (580 efinaconazole /201 vehicle). Both studies enrolled subjects who were 18 years and older with 20-50% involvement of the target toenail.

The primary efficacy endpoint was complete cure at week 52 defined as 0% clinical involvement of the target toenail plus KOH negative culture as recommended by DDDP. The pre-specified secondary efficacy endpoints were (1) clinical efficacy rate at week 52 (< 10% affected target nail area), (2) mycological cure rate at week 52 (negative KOH

and culture), and (3) unaffected new nail growth at week 52 (change from baseline in healthy nail measurement). Secondary endpoints were measured in sequential order.

Baseline demographics were generally balanced across groups for both trials. The mean age of subjects was 51 with approximately 13% of subjects age 65 or older. 75-80% of subjects were male. In Trial P3-01, 65% of subjects were white, while in Trial P3-02, 88% of subjects were white. Trial P3-01 enrolled subjects in Japan as well as in the US, and 29% of subjects in that trial were Asian, while only 2% of subjects in Trial P3-02 were Asian. In Trial P3-02, 6% of subjects were black and 22% were Hispanic. 12% of subjects in Trial P3-01 were Hispanic.

Both studies were statistically significant for the primary efficacy endpoint (Trial P3-01: efinaconazole 117 [17.8%] vs. vehicle 7 [3.3%] $p < 0.0001$ and Trial P3-02 efinaconazole 88 [15.2%] vs. vehicle 11 [5.5%] $p < 0.001$). All pre-specified secondary endpoints were also statistically significantly different from vehicle.

Safety

In the two Phase 3 trials, 1640 subjects reported 2763 adverse events (AEs). Most of the events occurred in < 1% of subjects. In general, similar percentages of subjects in each treatment arm experienced similar types of AEs. The only AES occurring at an incidence of ≥ 1% and more frequently in the treatment arm than the vehicle arm were application site dermatitis (2.2% efinaconazole vs. 0.2% vehicle), application site vesicles (1.6% efinaconazole vs. 0.% vehicle), and tinea pedis (considered not related). Application site pain occurred in 1.1% of subjects on efinaconazole and 0.2% of subjects on vehicle.

One efinaconazole-treated subject in each of the Phase 3 trials died; (b) (6) and one died of lung cancer. Both deaths were felt to be unrelated to study drug. Additionally there were 65 serious AEs, none of which was felt to be treatment related. 33 subjects discontinued the trials. All except one was in the efinaconazole group. Most were discontinuations due to application site reactions, many of which were considered to be treatment related.

DDDP feels that labeling will be sufficient to convey the potential AEs associated with the use of this product.

Advisory Committee

This application was not referred to an Advisory Committee because the clinical study design was acceptable, the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of disease, and outside expertise was not necessary.

Pediatric Considerations

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosage regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The applicant requested [redacted] (b) (4) . DDDP supported this request as both reasonable and consistent with recent precedents within the Division; however, the Pediatric Review Committee (PeRC), in a meeting held on January 23, 2013, did not agree with the waiver request. The PeRC recommended that studies be conducted in pediatric subjects ages 6-17 years.

The Division will request that a pediatric plan be submitted by the applicant; however absence of completed pediatric studies will not preclude approval of the application for adult subjects.

Product Labeling

Comment on proposed product labeling is deferred until such time as the application is otherwise adequate.

Tradename Review

On April 12, 2013, the Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology concluded that the tradename "Jublia" is acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTORIA KUSIAK
05/13/2013

Summary Review for Regulatory Action

Date	April 24th, 2013
From	Susan J. Walker, MD, FAAD
Subject	Division Director Summary Review
NDA #	203567
Applicant Name	Dow Pharmaceutical Sciences
Date of Submission	July 26th, 2012
PDUFA Goal Date	May 26th, 2013
Proprietary Name / Established (USAN) Name	Jublia/Efinaconazole
Dosage Forms / Strength	Topical solution/10%
Proposed Indication	Treatment of Onychomycosis
Action/Recommended Action	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Gary Chiang, MD
CDTL Review	David Kettl, MD
Statistical Review	Kathleen Fritsch, PhD; Alosh, PhD
Pharmacology Toxicology Review	Linda Pellicore, PhD; Hill; Jacobs
CMC Review	Bogdan Kurtyka, PhD; Ree, PhD; Ocheltree, PhD,RPh
Microbiology Review	Kerry Snow, MS
Clinical Pharmacology Review	Chinmay Shukla, PhD; Tran, PhD
OSE/DMEPA	Mena-Grillasca, RPh; Merchant; Taylor; Holquist

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
CMC=Chemistry, Manufacturing and Controls
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Division Director Summary Review

1. Introduction

This application proposes the use of a new molecular entity, efinaconazole, as a 10% topical solution for the treatment of onychomycosis. The drug substance is a triazole antifungal to be used on the toenails daily for 48 weeks in patients 18 years and older. The review team recommends a Complete Response action for this product due to lack of sufficient information to assure the identity, strength, purity, and quality of the drug product, and I concur with this recommendation. The clinical studies provided are acceptable; however, product leakage (b) (4) is a major outstanding issue. This review will summarize the current status of the application review, focusing on the chemistry, manufacturing and controls (CMC) issues.

2. Background

Efinaconazole is a triazole antifungal that inhibits fungal lanosterol 14-a demethylase involved in ergosterol biosynthesis. Accumulating sterols and loss of ergosterol in the fungal cell wall are reported to be responsible for the fungistatic and fungicidal activity of efinaconazole. The application supports a mechanism of action that is similar to other agents in the azole class of antifungals.

The clinical program consists of four Phase 1 studies including a maximal use pharmacokinetic (PK) trial in adult subjects with severe onychomycosis, a PK trial in healthy subjects, a foreign phase 2 safety and efficacy study, and two phase 3 studies in subjects with mild to moderate onychomycosis.

Packaging integrity issues were identified early in the review cycle for this product. The 74 day letter identifies problems with the brush-cap assembly and potential leachables from the container closure system. Appropriate information requests were communicated to the sponsor during this review cycle regarding drug process controls, with issuance of a Discipline Review Letter on March 8th, 2013 and a teleconference on March 20th to provide further clarification.

3. CMC

Efinaconazole solution 10% is a clear, colorless to pale yellow solution manufactured by (b) (4). The drug substance is practically insoluble in water and the alcohol content is approximately (b) (4) w/w, a volatile organic formula. The container/closure system includes a white 10mL HDPE bottle (for a (b) (4) fill) with a (b) (4) brush applicator and a (b) (4) cap. The brush extends directly from the top of

the bottle tip and is used without detaching. The user turns the bottle over and brushes the product onto the nail and surrounding skin.

The container closure system is a novel package, apparently selected due to the unique configuration intended to minimize the exposure of the packaged product to any potential external contamination from the infected nail, as the brush is not pushed back into the topical solution after wiping on the infected nail. The CMC reviewer, Dr. Bogan Kurtyka, notes a high percentage of drug product bottles (greater than 50%) from the first large scale clinical batches (Batches 1444 and 1453F1) had evidence of leakage. The applicant investigated various factors (b) (4) with modifications made (b) (4) for subsequent batches. However, the application does not describe the filling/capping (b) (4) process with sufficient detail and specifics to ensure the process is robust and can produce batches with acceptable leakage rates.

The Pharmaceutical Development section of the application includes discussion of the applicants proposed enhancements; however, none of the recommendations on the process improvement are officially implemented in the manufacturing process and in the Master Batch Record. Regarding the **manufacturing process and control information** still needed, as per the CMC recommendation:

- Application should be updated with the optimized process
- Three production batches should be produced using the optimized processes, with 12 months of long-term and 6 month of accelerated stability data, including failure rates due to leakage (upright and horizontal).
- Two of the batches should be at least pilot scale batches. The process must be the one validated for routine production, and use the to-be- marketed container/closure system.
- Assay results should be generated for leaking units whenever feasible

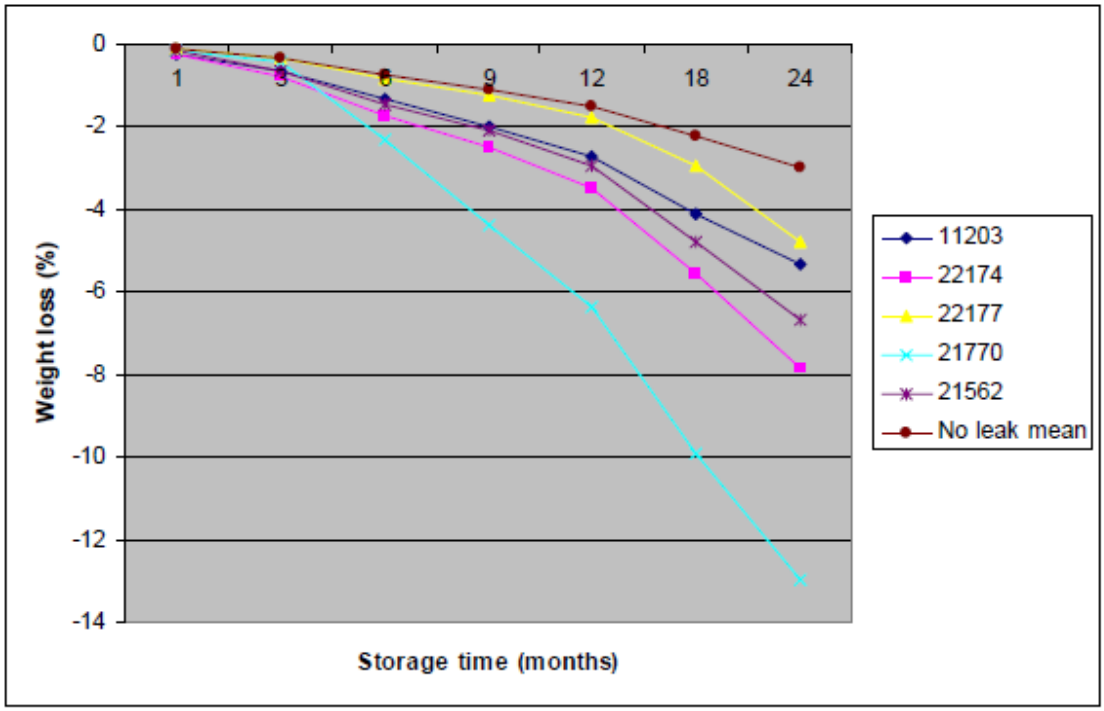
Specification for the drug product should include a specific and sensitive leakage test method and its acceptance criteria, and the leakage test method must be validated and not rely on (b) (4) alone to detect leaks. Leakage was evident (b) (4) for stability testing and is believed to have occurred in bottles subsequent to filling.

The application includes stability study information on (b) (4) for residue on the container. Long-term stability study results were provided for one batch at 30 months (1453F2) and two batches at 24 months (1473F1, 1474F4).

Stability studies on weight loss confirm a significant loss of formulation ingredients in multiple units, and these eventually showed residues on the outside of bottles. The weight loss study consisted of 10 units for each orientation per batch, totaling 60 units (3 batches, 2 orientations per batch). Each bottle was visually inspected prior to release and bottles with external residues were rejected, therefore these bottles were initially considered "non-leaking". The residues later found on the exterior surface of the 5 leaking units ("true leakers") are believed to be due to leaks, not (b) (4) dripping. The % weight change of "true leakers" ranges from 5% to 13% at 24 months, while the % weight change for the non-leaky bottles is 2.9% with a range of 2.5% to 3.3%. The manifestation of the leak is typically gradual, with

some units not showing the clear, unusual higher weight loss until Month 9 or 12. Visual detection of package integrity revealed one bottle with a significantly higher weight loss at 3, 6,9,12 and 18 months did not have detectable residue on the exterior surface of the sample until month 18.

Graph 1. Units with Unusually High Weight Loss Rate



The presence of latent leakers is supported by the package integrity test results. A summary of the results of three stability batches (below) shows the incidence of non-conforming to package integrity, i.e. where at least one stability sample at a given time point showed visual evidence of leakage. This visual inspection demonstrates leakage over time in products that were not leaking initially.

Batch	Position	Time point (months)							
		0	1	3	6	9	12	18	24
DP1453F2	horizontal	Pass	Pass	Pass	Fail*	Pass	Fail*	Fail*	Fail*
	upright	Pass	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*
DP1473F1	horizontal	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*	Fail*
	upright	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*	Fail*
DP1474F4	horizontal	Pass	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*
	upright	Pass	Pass	Pass	Pass	Pass	Pass	Fail*	Fail*

*Failure due to observed evidence of residue or leakage. Only one unit was pulled for package integrity per time point

Dr. Kurtyka concludes that a significant percentage of stability samples show non-conforming package integrity, leakage is more likely for samples stored 1 month or longer, and batch release results with conforming package integrity are not an indication of the possibility of container leakage on storage.

I concur with the CMC conclusion that the observations indicate that the proposed **container closure system** does not provide adequate protection for the drug product. The Agency has concluded that residues on the exterior surfaces were not due to (b) (4) dripping and vibrations for the following reasons:

- True leakers and latent leakers have been detected for multiple batches in the weight loss study
- The greater failure incidence in the 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) employed for leakage detection cannot discern the cause of exterior residue (i.e. filling line dripping/vibration or true leakage and cannot detect non-residue producing leaks.

I concur with the CMC conclusions and recommendations regarding the container closure systems – establish a control strategy, provide a complete description of the system and any modifications, and provide samples to the Agency.

The **stability data** provided are not considered to be representative of the stability characteristics of commercial batches which will be produced using an improved process, as additional improvements will need to be made in the filling/capping (b) (4) process. The two (b) (4) batches (1460 and 1461) are not considered by the Agency to be registration or registration supportive stability batches, and the application should provide in-use stability data for the drug product packaged in the to-be-marketed container/closure system.

Adequate container/closure systems should provide protection, compatibility, safety and performance. I concur with the chemistry reviewers recommendation that this system does not currently provide proper protection against leakage, and that there is not significant unmet medical need for this product to justify departure from acceptable standards.

4. Nonclinical Pharmacology/Toxicology

All appropriate nonclinical studies were conducted and reviewed.

I concur with the conclusions reached by the pharmacology/toxicology reviewer, Dr. Pellicore, that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The parent compound is IDP-80 with a major metabolite H3 (inactive) and minor metabolite H4 (active). A maximal use study (DPSI-IDP-108-P1-03) was conducted in 20 adult subjects with severe onychomycosis with at least 80% of the area of both great toenails and at least 4 other involved toenails. Study drug from batch 1453F1 was applied once daily for 28 days to all 10 toenails and 0.5cm of adjacent skin. No bottles were identified as leakers. Serial blood samples were collected predose and on day 1, 14, and 28, with a post-dose sample within 2 weeks. Results are shown below (table 3a) from Dr. Shukla's clinical pharmacology review. Plasma samples were quantifiable for the parent drug (IDP-108) in 15/18 onychomycosis subjects on day 1 and all subjects on days 14 and 28. In vivo H4 was quantifiable in 4 subjects and in those subjects it was present <25% of the parent compound based on the ratio of the AUC's. Other minor metabolites were not explored. Multiple CYP enzymes are involved in efinaconazole metabolism with CYP2C19 and CYP3A4 as the primary isozymes. Mean plasma levels of efinaconazole under maximal use conditions were low (<2nM) and the clinical pharmacology reviewer concludes that the risk of CYP mediated drug-drug interactions is low.

Table 3a: C_{max} and AUC (mean ± SD) in Trial DPSI-IDP-108-P1-03 (Maximal use PK trial)

Mean PK Parameters	Days 1-2	Days 14-15	Days 28-29
IDP-108			
$AUC_{(0-t)}$ (ng*h/mL)	1.79±2.04 (n=15)	10.29±5.90 (n=18)	12.15±6.91 (n=18)
C_{max} (ng/mL)	0.23±0.18 (n=18)	0.62±0.30(n=18)	0.67±0.37 (n=18)
H3			
$AUC_{(0-t)}$ (ng*h/mL)	1.50±1.13 (n=6)	40.03±34.02(n=18)	45.80±31.58(n=18)
C_{max} (ng/mL)	0.01±0.14 (n=18)	2.20±1.73 (n=18)	2.36±1.64 (n=18)
H4*			
$AUC_{(0-t)}$ (ng*h/mL)	BLQ	1.41 ± 1.34 (n=4)	2.30 ± 0.11 (n=4)
C_{max} (ng/mL)	BLQ	0.03 ± 0.06 (n=5)	0.05 ± 0.08 (n=5)

** In most subjects H4 concentrations were BLQ*

A 17-fold safety margin was calculated based upon animal toxicity data and the highest observed exposure to the parent compound (25.25 ng*h/mL).

A TQT study waiver was granted in 2010 based upon early PK results in Study 108-P1-02, where 0.42mL study drug was applied to healthy nails or 2.5mL was applied to the back, utilizing an open-label, two-period, cross over design. . The Cmax in this study was actually 5.27 fold higher than in the subsequent maximal use study 108-P1-03, in which 0.42mL was delivered to all 10 nails and adjacent skin.

The mean Cmax of IDP-108 in study 108-P1-03 was 0.67 ng/mL, which is still above the calculated 1nM concentration of 0.34839 ng/mL which has been considered a potential threshold for TQT studies. However, no potential for IDP-108 to delay cardiac repolarization was identified, based upon hERG inhibition, tissue distribution, cardiovascular safety pharmacology and ECG analysis in chronic studies. Periodic EKG's were collected in the phase 3 trial and no signal was identified.

I agree with the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The application proposes labeling for efficacy in treating a wide range of fungal species, however, the microbiology reviewer, Kerry Snow, has determined that for labeling purposes efinaconazole has been shown to be active against isolates of only *T. Rubrum* and *T. Mentagrophytes*.

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

I concur with the clinical summary from the CDTL, Dr. Kettl, presented below.

Efinaconazole solution 10% was superior to vehicle in the treatment of onychomycosis in Studies P3-01 and P3-02, which enrolled subjects, age 18 to 65 with a clinical diagnosis of onychomycosis and positive mycology. Subjects applied treatment once daily for 48 weeks.

The first Phase 3 trial (P3-01) enrolled 870 subjects (656 efinaconazole/214 vehicle) and the second Phase 3 trial (P3-02) enrolled 785 subjects (781 in the ITT: 580 efinaconazole/201 vehicle). Both studies enrolled subjects age 18 and older with 20-50% involvement of the target toenail.

The primary efficacy endpoint was complete cure at Week 52 (0% clinical involvement of target toenail plus negative KOH and negative culture) as recommended by the Agency. The secondary efficacy endpoints specified in the protocol were: (1) clinical efficacy rate at Week 52 (<10% affected target nail area), (2) mycological cure rate at Week 52 (negative KOH and culture), and (3) unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement). Secondary endpoints were analyzed in sequential order. The primary and secondary efficacy endpoints were all statistically significant and the results are presented in the table below from the biostatistical review by Dr. Kathleen Fritsch:

	Study P3-01			Study P3-02		
	Efinacon. N = 656	Vehicle N = 214	p-value	Efinacon. N = 580	Vehicle N = 201	p-value
Complete Cure	117 (17.8%)	7 (3.3%)	<0.001	88 (15.2%)	11 (5.5%)	<0.001
Clinical Efficacy	234 (36%)	25 (12%)	<0.001	180 (31%)	24 (12%)	<0.001
Mycologic Cure	362 (55%)	36 (17%)	<0.001	310 (53%)	34 (17%)	<0.001
Unaffected new growth (mm)	5.0 (0.2)	1.6 (0.4)	<0.001	3.8 (0.2)	0.9 (0.4)	<0.001

I concur with the clinical reviewer, Dr. Chiang and the biostatistics reviewer, Dr. Fritsch, that the product has demonstrated clinical efficacy based upon the results of the primary efficacy evaluations.

8. Safety

In the two Phase 3 clinical trials combined, 1640 subjects reported 2763 adverse events (AEs); most of the events occurred in a relatively few number of subjects (less than 1% of the subjects in each treatment group). In general, similar percentages of subjects in each treatment group experienced similar types of AEs. A comparison of all AEs experienced by 1% or more of the subjects in either treatment group indicated that the percentages of subjects experiencing individual events was significantly different only for application site dermatitis, application site vesicles, and tinea pedis ($p \leq 0.006$ in all pair wise comparisons).

Subjects on the efinaconazole arm demonstrated a higher rate of administration site adverse reactions than subjects on the vehicle arm, including application site dermatitis (2.2% vs. 0.2%), application site vesicles (1.6% vs. 0%), and application site pain (1.1% vs. 0.2%). Other administration site conditions and skin and subcutaneous tissues disorders were observed in at least 0.5% of efinaconazole subjects. These events can be adequately described in labeling.

None of the 65 serious adverse events (SAEs) were deemed to be treatment-related and most occurred in only one subject. Overall, 33 subjects, all but one of whom was in the efinaconazole group, discontinued either the study drug or the study because of an AE; most of the events were associated with application site reactions, and many of these were assessed as treatment-related. No significant laboratory or ECG findings were observed in any trial. No safety signals or unexpected trends associated with the use of efinaconazole were observed in clinical trials.

9. Advisory Committee Meeting

This application was not referred for advisory committee review as it presents no novel issues in regards to either the treatment of onychomycosis or the use of a topical triazole antifungal product. The active product is similar to several other antifungal products in structure and mechanism of action, and there are no concerns related to primary safety or efficacy determinations.

10. Pediatrics

The application was discussed at a Pediatric Review Committee (PeRC) in January 2013, and the DDDP recommended a waiver for pediatric patients 0-17 years consistent with other

product for onychomycosis. However, the PeRC disagreed as this application now triggers PREA, and the committee recommended that studies be conducted in pediatric patients 6-17 yrs. The Agency will request a pediatric plan from the sponsor, however, absence of completed pediatric studies should not preclude approval of the application at the time the adult studies are ready for approval.

11. Other Relevant Regulatory Issues

Inspection recommendations from the Office of Compliance on the manufacturing and testing sites have not been received.

12. Labeling

The proprietary name Jublia was approved on April 15th, 2013.

Labeling discussions were not concluded during this cycle, as the application is recommended for a Complete Response action.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – A *Complete Response* action is recommended, because there is insufficient information to assure the identity, strength, purity and quality of the drug product. Specific language for the action letter is included in the CMC review.

- Risk Benefit Assessment – Deferred.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – Deferred, however, no Postmarketing Risk Evaluation and Mitigation Strategies are anticipated.

- Recommendation for other Postmarketing Requirements and Commitments- Deferred

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/s/

SUSAN J WALKER
04/24/2013

Cross-Discipline Team Leader Review

Date	April 16, 2013
From	David Kettl, MD, FAAP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 203567
Applicant	Dow Pharmaceutical Sciences/Valeant
Date of Submission	July 26, 2012
PDUFA Goal Date	May 26, 2013
Proprietary Name / Established (USAN) names	Efinaconazole Topical Solution 10% (Trade name of *Jublia* tentatively accepted but pending final review)
Dosage forms / Strength	Topical Solution 10%
Proposed Indication(s)	Onychomycosis of the toenail in adults
Recommended:	***Complete Response***

1. Introduction

Dow Pharmaceutical Sciences submitted a 505 (b)(1) New Drug Application for JUBLIA™ (trade name pending approval), efinaconazole solution, 10%, with a proposed indication of once daily topical treatment of onychomycosis of the toenail in adults. The proposed product is a new molecular entity in the United States, and is not marketed in any other country.

While the applicant successfully completed two adequate and well controlled trials for the treatment of onychomycosis in patients 18 years and older, when used once daily for 48 weeks, there are critical CMC review issues that have not been resolved, and a complete response is recommended for this application based on the conclusions of the CMC review.

The clinical review, by Dr. Gary Chiang, identified no significant safety issues and concludes that the product was effective, and could have been recommended for approval if the identity, strength, purity, and quality of the drug product could be substantiated. However, critical container integrity issues were identified such that the drug product quality cannot be assured with the manufacturing process and controls described within the application.

There are no outstanding issues from other review disciplines. As a Complete Response is recommended by the review team, which this CDTL review completely concurs, labeling negotiations were not initiated with the sponsor.

Each review discipline provided preliminary recommendations for eventual product labeling, but draft labeling was not communicated to the applicant once the team recommendation for a complete response action was identified.

2. Background

Onychomycosis refers to nail infections caused by any fungus, including yeasts and non-dermatophyte molds. It is characterized by hyperkeratosis (hypertrophy of the skin/nail) of the nail bed, yellow to brownish discoloration of the nail plate, onycholysis (separation of the nail from nail bed along the lateral margins), and paronychial inflammation (inflammation due to infection of the skin fold at the nail margin)

Efinaconazole is an azole antifungal agent that is claimed to be effective against a wide range of pathogenic fungi. Efinaconazole has been shown *in vitro* to be effective against dermatophytes (*Trichophyton, Microsporum,* and *Epidermophyton* species) and yeasts (*Malassezia* species, *Candida albicans* and other *Candida* species). The mechanism of action of efinaconazole, like other azole antifungal compounds, is attributed to lanosterol 14α-demethylase inhibition resulting in blockage of ergosterol synthesis. Fungal cell membrane structure and function is compromised by the resulting ergosterol depletion and accumulation of 14-α methyl sterols, leading to cell death.

A Pre-IND meeting held with the applicant on December 18, 2006. IND 77,732 was opened on May 8, 2007 with a proposed 21-day cumulative irritation study to evaluate efinaconazole in healthy adult subjects. An End-of-Phase 2 meeting was held August 4, 2009. No SPA review was requested for this application.

Packaging integrity issues were identified by the ONDQA review team prior to the filing meeting on September 11, 2012. Preliminary review of the application reportedly produced batches with a leakage rate of (b) (4). The proposed product specification indicated that no leakage should be permitted.

The 74 day letter identified the following potential review issues:

1. The strength, purity and quality of the drug product can not be assured due to inadequate information provided to qualify the proposed brush-cap assembly.

2. The purity of the proposed drug product can not be assured due to inadequate information provided to demonstrate the absence of significant contaminants in the formulation due to leachables from the proposed container/closure system.

3. Provide a rationale as to why it is acceptable to extrapolate the foreign clinical data to the general US population for the treatment of mild to moderate toenail onychomycosis.

Appropriate information requests were communicated to the applicant during the review cycle requesting additional information related to drug process controls. A Discipline Review Letter was sent to the applicant on March 8, 2013. A teleconference was held with the applicant on March 20, 2013 to provide further clarification for the deficiencies outlined in the Discipline Review letter.

The conclusion of the ONDQA review, as documented in an addendum to the initial CMC review By Dr. Kurtyka dated April 11, 2013, affirms that the CMC information submitted in the initial application and multiple subsequent submissions to the NDA is not adequate for approval.

3. CMC/Device

Efinaconazole Solution, 10% is packaged in a white 10 mL HDPE bottle with an attached brush applicator and a (b) (4) cap. The brush extends from the top of the bottle tip for product application directly to the nail without detachment of the brush, and to the skin folds surrounding the nail, and to any accessible skin of the nail bed for the treatment of onychomycosis. The proposed fill of solution is (b) (4) mL.

Efinaconazole is combined in a non-aqueous solution containing 8 other substances (cyclomethicone, diisopropyl adipate, C12-15 Alkyl Lactate, Butylated Hydoxytolulene, Citric Acid, Anhydrous, Edetate Disodium, Purified water, and alcohol). The product is flammable and will require appropriate labeling for this aspect.

Failure of container integrity was noted during ONDQA review of the stability studies. The ONDQA review conclusion is that the drug product quality cannot be assured with the manufacturing process and controls described within the application. The review conclusion is a recommendation for Complete Response.

The CMC review, by Dr. Bogdan Kurtyka, identified the following deficiencies:

1. *Inadequate manufacturing process and control information:*
   - *Details of the process/control are not provided.*
   - *The submitted information indicated that the filling/packaging operation is incomplete and still evolving.*
2. *Inadequate specification for the drug product:*
   - *The currently proposed package integrity test (which includes a (b) (4) for leakage) is inadequate and is not capable of ensuring timely detection of leaks.*
3. *Inadequate integrity of the container/closure system, as evidenced by a high number of leaks observed.*
4. *Inadequate stability data to assure the expiration dating period:*

- *The data were obtained from batches manufactured utilizing a non-optimized process.*

On March 8, 2013, a Discipline Review Letter was sent to the applicant detailing the deficiencies found by CMC in the application. Several teleconferences have been conducted with the applicant to review and discuss the ONDQA findings and explain the possible remedies for adequate controls and substantiation of expiry dating.

The Clinical Review, by Dr. Gary Chiang, concurs with the CMC recommendation, and this CDTL review agrees that the issue of leaking product containers has not been adequately resolved during this cycle and a Complete Response is warranted. The applicant provided limited data comparing the product quality of the drug product in bottles that had leaked compared to bottles that had no apparent leakage. The information submitted to date, while not extensive, appears to validate the applicant's assertion that the product in containers that leaked was within specification in comparison to the product in containers that did not leak. As such, there does not appear to be significant clinical concerns about the safety or effectiveness conclusions of the conducted clinical trials due to lack of drug product quality or stability data.

Establishment inspection overall recommendations are still pending as of the date of this review.

The CMC review addendum dated April 11, 2013 (appended to the primary clinical review as well) provides extensive background regarding the product quality issues and the recommended remedies for the sponsor to address in the next cycle of review, and will form the basis of the action letter documenting an Agency action of Complete Response for this application.

4. Nonclinical Pharmacology/Toxicology

The review of nonclinical pharmacology/toxicology was conducted by Dr. Linda Pellicore, and did not identify any critical review issues, or identify any studies that might be recommended as a post-marketing requirement. Her review describes the study elements submitted by the applicant.

Repeat-dose systemic rodent toxicity and developmental and reproductive toxicity studies were conducted with subcutaneous administration of efinaconazole dissolved in propylene glycol. Efinaconazole appeared well tolerated but subcutaneous administration of propylene glycol was not well tolerated and resulted in significant injection site toxicity.

Efinaconazole solution was evaluated in a 9 month dermal toxicity study in minipigs with repeated daily dermal administration of up to 30% efinaconazole solution. The vehicle and efinaconazole solution produced mild skin irritation. Mild skin irritation (modest microscopic hyperkeratosis, acanthosis, and localized inflammation) was noted in all dose groups including

the vehicle control group. No systemic toxicity was noted at topical doses up to 30% efinaconazole solution, which is the maximum feasible concentration.

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one in vivo genotoxicity test (mouse peripheral reticulocyte micronucleus assay).

A dermal mouse carcinogenicity study was conducted with the to-be-marketed efinaconazole solution. Severe skin irritation was noted at the treatment site in all dose groups including the vehicle control group. This study was suboptimal due to the mice being very sensitive to severe dermal effects elicited by the vehicle. No treatment related increase in the incidence of neoplasms was observed in this study. However, the skin effects of the propylene glycol vehicle confounded assessment of any skin effects due to efinaconazole.

Reproductive and developmental toxicology studies have been conducted with efinaconazole in rats and rabbits. In a subcutaneous rat fertility study, skin thickening at the injection site was noted in all efinaconazole treated groups and the vehicle control group. No treatment related effects on male or female fertility parameters were noted at doses up to 25 mg/kg/day efinaconazole in this study.

A subcutaneous embryofetal development study in rats was conducted with doses up to 50 mg/kg/day efinaconazole. Skin thickening at the treatment site, an 11% decrease in maternal body weight gain, complete embryo resorption in two dams and an increased incidence of embryofetal death were noted at the 50 mg/kg/day dose. However, no drug-related malformations were noted at doses up to 50 mg/kg/day efinaconazole in this study.

A subcutaneous embryofetal development study in rabbits was conducted with doses up to 10 mg/kg/day efinaconazole. Injection site reactions were noted in all treatment groups including the vehicle control group. A decrease in body weight gain was noted in does at 10 mg/kg/day. There were no indications of test article related embryofetal toxicity or malformations at doses up to 10 mg/kg/day efinaconazole in this study.

A subcutaneous pre- and post-natal development study in rats was conducted with doses up to 25 mg/kg/day efinaconazole. Injection site swelling and masses were noted in all dose groups including the vehicle control group. Prenatal pup mortality was increased at 25 mg/kg/day. There were no toxicologically significant effects on duration of gestation or the ability of dams to deliver litters. No treatment related effects on postnatal development of F1 offspring were noted at doses up to 25 mg/kg/day efinaconazole in this study.

Single dermal application of up to 10% efinaconazole solution to rabbits did not elicit dermal irritation in intact skin but was a mild irritant to abraded skin. Efinaconazole solution, 10%, was a mild ocular irritant in rabbit eyes. Efinaconazole solution did not elicit a photo-irritation response in guinea pigs.

There are no other outstanding nonclinical issues that would impact an approval action.

5. Clinical Pharmacology/Biopharmaceutics

The applicant completed 2 PK trials, a maximal use PK trial in adult subjects with severe onychomycosis and one in healthy adult subjects. In addition to the above, the applicant also provided a summary of systemic PK results from the 2 non-IND Japanese trials.

The maximal use PK trial (DPSI-IDP-108-P1-03) was conducted in 20 adult male and female subjects (18 completed) with severe onychomycosis with at least 80% of the area of both great toenails and at least 4 other toenails with onychomycosis infection. The study drug was applied once daily for 28 days to all 10 toe nails and 0.5cm of adjacent surrounding skin. PK of the parent drug and 2 metabolites [H3 and H4] were assessed. Plasma concentrations of the parent drug were quantifiable in 15 out of 18 subjects on Day 1 and in all subjects on Day 14 and Day 28. The ratio of mean AUC and Mean C_{min} on Day 14 versus Day 28 was less than 1.18 for the parent drug suggesting concentrations *in-vivo* were near steady state by Day 14. The mean ± SD values of AUC(0-t) and C_{max} on Day 28 for the parent drug was 12.15 ± 6.91 ng*h/mL and 0.67 ± 0.37 ng/mL, respectively. The concentration profile for the parent drug at steady state on Day 28 was relatively flat over the 24 hour dosing interval.

Based on the highest observed exposure (25.25 ng*h/mL), the safety margin based on animal toxicity data is 17 fold.

The package integrity issues discussed above which caused leakage of the product did not affect the maximal use pharmacokinetic trial as none of the products used in this trial demonstrated leakage. Data from this batch was deemed reliable.

The applicant provided adequate information on drug metabolism and addressed the potential for drug-drug interaction. Metabolic drug-drug interaction potential of efinaconazole was evaluated *in vitro* by identifying the CYP enzymes involved in efinaconazole metabolism and by assessing its capacity for induction and inhibition of CYP activity. The potential for H3 to inhibit CYP enzymes was also tested.

Multiple CYP enzymes were involved in efinaconazole metabolism with CYP2C19 and CYP3A4 identified as the primary isozymes associated with oxidative metabolism. CYP2C19 appeared to be the main CYP enzyme mediating H4 formation from efinaconazole.

The applicant requested a TQT assessment waiver during the IND phase, and the Division granted the waiver request on 04/14/2010 following DCRP QT Interdisciplinary Review. No potential for efinaconazole to delay cardiac repolarization (based on hERG inhibition, tissue distribution, cardiovascular safety pharmacology and ECG analysis in chronic studies) was identified. Although results from the healthy subject PK trial were considered inconclusive, the QT Interdisciplinary Review Team recommended a waiver of TQT study based on the fact that the bioavailability of efinaconazole and H3 metabolite were low.

From a clinical pharmacology perspective, this application was found acceptable and no approvability issues were identified. If it is determined that pediatric studies for adolescents would be required in a subsequent cycle, PK information in that population will need to be obtained by the applicant.

6. Clinical Microbiology

The applicant provided sufficient information related to the proposed mechanism of action, microbiologic effects of efinaconazole, and information to support a lack of effect on resistance over time. Adequate data supporting the endpoint of "mycologic cure" in the clinical trials was reviewed and was determined to support the clinical microbiology aspects of the application.

The applicant submitted a study report that supports a mechanism of action similar to other agents described in the azole class of antifungal agents, by correlation of increased antifungal activity in isolates of *T. mentagrophytes* with an efinaconazole-concentration dependent decrease in ergosterol concentration in the fungal cell membrane sterol fractions.

The Applicant also submitted reports from three studies that demonstrate a low potential for the development of resistance in specific fungal pathogens (*T. rubrum*, *T. mentagrophytes*, and *C. albicans*) to efinaconazole. In investigations of *T. rubrum*, one isolate demonstrated a 4-fold MIC increase in serial passage studies (comparable to the comparator, itraconazole), but overall, the increase in MIC values over 10 passages, for the three tested pathogens, was 2-fold or less.

From a clinical microbiology perspective, the application was deemed approvable in the microbiology review by Dr. Kerry Snow, provided that changes are made to the proposed product labeling, as described below:

The Agency recommends the following changes to the proposed label:

1. Strike discussion of (b) (4) from the Mechanism of Action section. Studies performed to evaluate the in vitro significance of this (b) (4) were inconclusive (b) (4) and no clinical relevance of this finding has been established.
2. (b) (4)

As a complete response was recommended for this application, labeling negotiations were not initiated with the applicant, and the labeling recommendations will be considered once the container closure issues have been adjudicated in a subsequent cycle of the application.

There are no outstanding clinical microbiology issues beyond agreement on final labeling.

7. Clinical/Statistical- Efficacy

The clinical program consisted of four Phase 1 trials which include a maximal use pharmacokinetic (PK) trial in subjects with severe onychomycosis and a PK trial in healthy subjects, one Phase 2 safety and efficacy trial and two Phase 3 safety and efficacy trials in subjects with mild to moderate onychomycosis.

Product quality issues not withstanding, efficacy was nominally demonstrated in two adequate and well controlled clinical trials. Both the clinical review and biostatistical review concur that efficacy was adequately demonstrated by statistical superiority over vehicle.

Efinaconazole solution 10% was superior to vehicle in the treatment of onychomycosis in Studies P3-01 and P3-02, which enrolled subjects age 18 to 65 with a clinical diagnosis of onychomycosis and positive mycology. Subjects applied treatment once daily for 48 weeks.

The first Phase 3 trial (P3-01) enrolled 870 subjects (656 efinaconazole/214 vehicle) and the second Phase 3 trial (P3-02) enrolled 785 subjects (781 in the ITT: 580 efinaconazole/201 vehicle). Both studies enrolled subjects age 18 and older with 20-50% involvement of the target toenail.

The primary efficacy endpoint was complete cure at Week 52 (0% clinical involvement of target toenail plus negative KOH and negative culture) as recommended by the Agency. The secondary efficacy endpoints specified in the protocol were: (1) clinical efficacy rate at Week 52 (<10% affected target nail area), (2) mycological cure rate at Week 52 (negative KOH and culture), and (3) unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement). Secondary endpoints were analyzed in sequential order. The primary and secondary efficacy endpoints were all statistically significant and the results are presented in the table below from the biostatistical review by Dr. Kathleen Fritsch:

	Study P3-01			Study P3-02		
	Efinacon. N = 656	Vehicle N = 214	p-value	Efinacon. N = 580	Vehicle N = 201	p-value
Complete Cure	117 (17.8%)	7 (3.3%)	<0.001	88 (15.2%)	11 (5.5%)	<0.001
Clinical Efficacy	234 (36%)	25 (12%)	<0.001	180 (31%)	24 (12%)	<0.001
Mycologic Cure	362 (55%)	36 (17%)	<0.001	310 (53%)	34 (17%)	<0.001
Unaffected new growth (mm)	5.0 (0.2)	1.6 (0.4)	<0.001	3.8 (0.2)	0.9 (0.4)	<0.001

Baseline demographics were generally balanced across the treatment groups in the two trials. The mean age of subjects was about 51 years with approximately 13% of subjects aged 65 or older. The majority of subjects were male (75-80%). Approximately 65% of subjects in Study P3-01 and 88% of subjects in trial P3-02 were white, and approximately 6% of subjects were black. Because trial P3-01 enrolled subjects in Japan, approximately 29% of subjects in that trial were Asian, while only 2% of subjects in P3-02 were Asian. In addition, approximately 12% of subjects in trial P3-01 and 22% of subjects in trial P3-02 were Hispanic or Latino.

Trial P3-01 was conducted at 74 centers in the United States (34), Canada (7), and Japan (33). Because of the large number of centers and the low overall response rate on the vehicle arm no center was overly influential on the overall results.

Dr. Fritsch concludes in her review that "Both studies were statistically significant for the primary efficacy endpoint of complete cure at Week 52 ($p<0.001$). Treatment effects were generally consistent across subgroups and centers, and the conclusions were consistent across various assumptions regarding missing data. The clinical review by Dr. Chiang, and this CDTL review, concurs that efficacy was adequately demonstrated in the two pivotal trials. As no significant safety issues have been identified (see below), an approval action would be recommended on this basis if the product quality issues had been resolved in this cycle.

8. Safety

The clinical review by Dr. Gary Chiang concludes that "There are few safety concerns regarding this topical onychomycosis drug product." The only significant adverse reactions were local application site events and can be adequately captured in future product labeling. The CDTL review concurs with this assessment for this topical product.

There were no deaths in the Phase 1 or Phase 2 studies. Two subjects, one in each of the Phase 3 studies, died but the events are almost certainly unrelated to the study drug. One subject (b) (6) after being lost to follow-up. The other subject died due to lung squamous cell carcinoma (stage unspecified). Neither event is suspected to be due to study drug product.

In the two Phase 3 clinical trials combined, 1640 subjects reported 2763 adverse events (AEs); most of the events occurred in a relatively few number of subjects (less than 1% of the subjects in each treatment group). In general, similar percentages of subjects in each treatment group experienced similar types of AEs. A comparison of all AEs experienced by 1% or more of the subjects in either treatment group indicated that the percentages of subjects experiencing individual events was significantly different only for application site dermatitis, application site vesicles, and tinea pedis ($p \leq 0.006$ in all pair wise comparisons).

Subjects on the efinaconazole arm did have a higher rate of administration site adverse reactions than subjects on the vehicle arm, including application site dermatitis (2.2% vs. 0.2%), application site vesicles (1.6% vs. 0%), and application site pain (1.1% vs. 0.2%). Other administration site conditions and skin and subcutaneous tissues disorders were observed in at least 0.5% of efinaconazole subjects. Again, labeling will be adequate to describe these local events to inform prescribers.

None of the 65 serious adverse events (SAEs) were deemed to be treatment-related and most occurred in only one subject. Overall, 33 subjects, all but one of whom was in the efinaconazole group, discontinued either the study drug or the study because of an AE; most of the events were associated with application site reactions, and many of these were assessed as treatment-related. No significant laboratory or ECG findings were observed in any trial. No safety signals or unexpected trends associated with the use of efinaconazole were observed in clinical trials.

Labeling would be adequate to convey the potential adverse reactions of this proposed product for the treatment of onychomycosis, and the safety findings would not present an obstacle for an adequate risk benefit determination for an approval action if the product quality issues could be remedied.

9. Advisory Committee Meeting

Although efinaconazole is a new molecular entity, it was determined early in the application review cycle that this new azole antifungal presented no novel or complex regulatory issues that required the input of the DODAC advisory committee. The active product is similar to several other antifungal products in structure and mechanism of action, and there were no concerns related to primary safety or efficacy determinations.

10. Pediatrics

(b) (4)

At the Pediatric Review Committee (PeRC) meeting held on January 23, 2013, PeRC did not agree (b) (4) The Division of Dermatology and Dental Products (DDDP) is considering whether or not to request clinical trials in pediatric subjects in preparation for the next review cycle. In the event it is determined that pediatric trials should be requested, then evaluation of PK under maximal use conditions in pediatric subjects would be recommended as well.

It is recommended that the action letter, or the post-action meeting discussion, include a request to the sponsor to present additional data regarding the incidence and prevalence of onychomycosis in pediatric populations and to comment on the ability of the applicant to conduct clinical trials in such populations (b) (4)

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application.

Two study sites with large subject enrollments were referred to DSI for inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

GMP inspection of one manufacturing site, (b) (4), remains pending as of the date of this CDTL review. The overall Office of Compliance recommendation is still pending at this time.

12. Labeling

Labeling negotiations were not initiated with the applicant due to the ONDQA concerns identified above related to product quality and carton/container integrity. The review team completed internal discussions related to the proposed label.

The trade name of "Jublia" has been tentatively accepted by DMEPA.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommendation of the review team is for a ***complete response*** based on the ONDQA review conclusion that the product quality has not been assured by information in the application.

- Risk Benefit Assessment

The conclusion of the clinical review, concurred by this CDTL review, is that safety and efficacy of efinaconazole for adult onychomycosis of the toenail was supported by the clinical development program. However, the review team concurs that the product quality issues identified in the ONDQA reviews cannot be successfully remedied in the current review cycle, and a complete response action is warranted for this application.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Assuming the product quality issues can be successfully addressed in a subsequent cycle, this product would not require any risk management beyond product labeling. Labeling is adequate to inform prescribers and patients of expected adverse events and risks. A REMS would not need to be considered for this application upon eventual approval.

- Recommendation for other Postmarketing Requirements and Commitments

Discussion of relevant post marketing requirements should await a successful subsequent cycle. The applicant will need to provide additional data in the next review cycle to address the incidence of pediatric onychomycosis and the feasibility of pediatric trials which may need to be addressed as a post marketing trial.

- Recommended Comments to Applicant

The following product quality deficiencies and information to resolve such deficiencies are recommended to be communicated to the applicant in a complete response action letter:

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 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 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 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 the 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:*
  - *the acceptance criteria,*
  - *weight results (summarized in table format)*
  - *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:*
  - *results of (b) (4) evaluation (e.g., assay, weigh loss, etc.)*

- *full accountability of all bottles sent to* (b) (4)*, including those bottles sent to clinical studies*
- *experimental details*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID L KETTL
04/16/2013

CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	203-567
Priority or Standard	Standard
Submit Date(s)	July 26, 2012
Received Date(s)	July 26, 2012
PDUFA Goal Date	May 26, 2013
Division / Office	DDDP/ODE III
Reviewer Name(s)	Gary Chiang MD, MPH
Review Completion Date	April 15, 2013
Established Name	efinaconazole
(Proposed) Trade Name	Jublia™
Therapeutic Class	antifungal
Applicant	Dow Pharmaceutical Sciences
Formulation(s)	Topical solution 10%
Dosing Regimen	Once daily
Indication(s)	Onychomycosis
Intended Population(s)	Adults 18 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Dow Pharmaceutical Sciences has submitted a New Drug Application for JUBLIA™ (efinaconazole solution, 10%) with a proposed indication of once daily topical treatment of onychomycosis (tinea unguium). While the applicant was successful in two adequate and well controlled studies for treatment of onychomycosis in patients 18 years and older, when used once daily for 48 weeks, there are critical CMC review issues that are not resolved and a complete response is recommended for this application.

From a clinical perspective, the applicant's clinical trials reached statistical significance in the primary endpoint for the treatment of toenail onychomycosis, and this application could have been recommended for approval; however, the recommendation from the CMC review is a Complete Response. The CMC review states that: "The applicant has not provided sufficient information to assure the identity, strength, purity, and quality of the drug product." The main CMC issue is the lack of adequate protection of the drug product by the container/closure system causing the product to leak (b) (4). While the sponsor has attempted to address this issue in this review cycle, a complete response is warranted as the root cause of the leakage in the proposed container has not yet been identified nor remedied as of the date of this review.

This reviewer is in agreement with the CMC review, and the clinical recommendation is a Complete Response for this application.

1.2 Risk Benefit Assessment

The risk to benefit assessment for this application is primarily based on the clinical trial results. In the two pivotal Phase 3 clinical trials, the most common adverse events associated with the drug product were application site reactions (application site dermatitis and application site vesicles). There were no deaths or serious adverse events attributed to the drug product. In the two combined pivotal Phase 3 clinical trials, a greater percentage of subjects in the JUBLIA™ group relative to the Vehicle group achieved "Complete Cure" (clinical cure as well as mycological cure) at Week 52 (16.6% versus 4.3%, respectively), demonstrating that the drug product was effective in treating toenail onychomycosis.

The proposed product labeling includes warnings and precautions regarding local sensitivity and irritation reactions. This drug product has minor local side effects and insignificant systemic effects. The adverse events associated with the drug product can be adequately informed by labeling. The label also provides adequate information for instructions for use.

In conclusion, there are few risks associated with the use of this topical product for the treatment of toenail onychomycosis. The effectiveness of this topical onychomycosis product ranges from

9.7% to 14.5% ("Complete Cure"). The benefits include relatively low systemic effects making this topical treatment ideal for patients that cannot take oral antifungals for the treatment of toenail onychomycosis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post-market risk evaluation or mitigation strategies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The Pediatric Review Committee (PeRC) has recommended that the prevalence of onychomycosis in children is sufficient to warrant studies in ages 6 years and above. (b) (4)

Reviewer's comment: *The PeRC committee's recommendation will receive appropriate weighting in the decision to recommend studies for onychomycosis in the pediatric population.*

2 Introduction and Regulatory Background

2.1 Product Information

The active ingredient, efinaconazole, is a novel azole antifungal agent with potency against a wide range of pathogenic fungi. Efinaconazole has been shown *in vitro* to be effective against dermatophytes (*Trichophyton, Microsporum,* and *Epidermophyton* species) and years (*Malassezia* species, *Candida albicans* and other *Candida* species). The mechanism of action of efinazonazole, like other triazole antifungal therapeutics, is attributed to lanosterol 14α-demethylase inhibition resulting in blockage of ergosterol synthesis. Fungal cell membrane structure and function is compromised by the resulting ergosterol depletion and accumulation of 14-α methyl sterols.

The active ingredient is combined in a non-aqueous solution containing 8 other drug substances (cyclomethicone, diisopropyl adipate, C12-15 Alkyl Lactate, Butylated Hydoxytolulene, Citric Acid, Anhydrous, Edetate Disodium, Purified water, and alcohol). The drug product (IDP-108) is designed to be applied directly to the nail, to the skin folds surrounding the nail, and to any accessible skin of the nail bed for the treatment of onychomycosis.

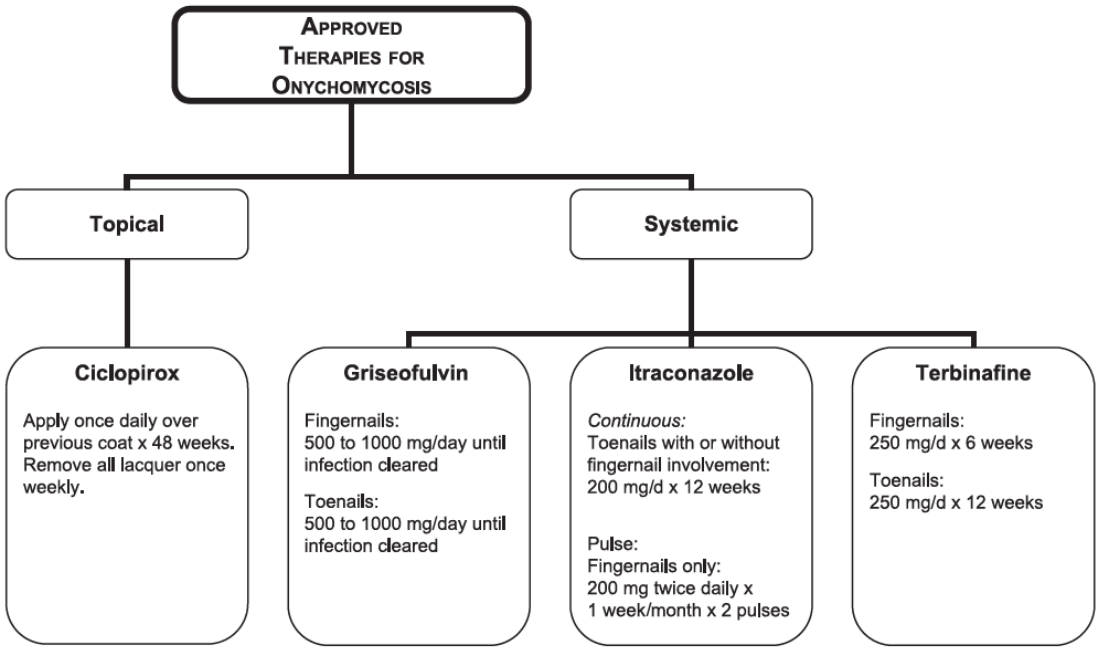
Efinaconazole Solution, 10% is packaged in a white 10 mL HDPE bottle with a brush applicator and a (b) (4) cap. The proposed fill of solution is (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Therapeutic options for the treatment of onychomycosis include no therapy, palliative care, mechanical or chemical debridement, topical and systemic antifungal agents, or a combination of

two or more of these modalities (**Figure 1**). Factors that influence the choice of therapy include the presentation and severity of the disease, the current medications the patient is taking, previous therapies for onychomycosis and their response, physician and patient preference, and the cost of therapy.

Figure 1: Summary of Approved Onychomycosis Therapies



Penlac® (ciclopirox) Nail Lacquer topical solution, 8% is the only approved topical product (1999) in the United States for the treatment of onychomycosis. Ciclopirox lacquer, approved in 1999, has demonstrated modest efficacy in treating mild to moderate onychomycosis not involving the lunula with reported complete cure rates of 8.5%; frequent nail debridement is required when using this product.

Oral treatment has been generally used for onychomycosis, but use may be limited in some patients by drug-drug interactions, especially in the elderly where there is frequent use of concomitant medications, other safety concerns (e.g., liver toxicity), and by the potential need for laboratory monitoring. Only itraconazole (Sporanox®) and terbinafine (Lamisil®) have been approved in the US, with respective cure rates of 14% and 38%. Hepatotoxicity is associated with systemic exposure in most oral antifungal medications.

2.3 Availability of Proposed Active Ingredient in the United States

Efinaconazole is not available in any form in the United States. This novel antifungal agent is a New Molecular Entity and has not been marketed in any other country.

2.4 Important Safety Issues With Consideration to Related Drugs

Penlac® (ciclopirox 8%) Nail Lacquer is the only topical treatment for onychomycosis approved in the United States. Ciclopirox is a broad-spectrum antifungal agent that exhibits fungicidal activity *in vitro* against dermatophytes, *Candida* species, and some nondermatophyte molds. Once daily application of ciclopirox nail lacquer for 6 months resulted in serum levels of the drug ranging between 12 and 80 ng/mL, and a mean absorption of less than 5% of the applied dose.[1]

During the two pivotal clinical studies of ciclopirox nail lacquer, the most common adverse events are the appearance of a rash (e.g., periungual erythema and erythema of the proximal nail fold), with some patients reporting a burning or tingling sensation at the application site. Nail disorders were infrequently reported for both the ciclopirox and vehicle group, and consisted of shape change, irritation, ingrown toenail, and discoloration.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The first interaction with this sponsor was a Pre-IND meeting held on December 18, 2006. IND 77,732 opened on May 8, 2007 with a proposed 21-day cumulative irritation study to evaluate IDP-108 on healthy adult subjects. A subsequent meeting request was granted on June 2, 2009. This End-of-Phase 2 meeting was held August 4, 2009 between Dow Pharmaceutical Sciences and the Agency. It was noted at the time that the Agency recommended the sponsor submit a SPA to reach agreements on their Phase 3 protocol and the statistical analysis plan. The sponsor did not submit a SPA and the Agency provided advice on primary endpoints for an onychomycosis clinical trial:

> "The Agency recommends that the primary endpoint, Complete Cure, be defined as follows:
>
> - Clinical Cure, defined as zero % clinical involvement of the target nails (nails are totally clear), *in addition to*
> - Mycological Cure, defined as negative KOH (potassium hydroxide) examination as well as negative culture of the target nail specimen."

Following the End-of-Phase 2 meeting, the sponsor submitted a TQT waiver request on May 19, 2009. On April 19, 2010, after evaluating the available QT data, the QT/IRT and the clinical team determined that there a TQT study for IDP-108 was not necessary, but ECGs should be collected in the Phase 3 clinical program to exclude large cardiovascular effects.

The Agency provided comments to multiple amendments of the Phase 3 clinical protocols, including the addition of ECGs to all Phase 3 clinical programs in approximately 300 of the 1600 patients.

1 Penlac nail lacquer (ciclopirox) topical solution, 8% prescribing information. Dermik Laboratories, Inc., 2000.

A Pre-NDA meeting was held on April 17, 2012 to discuss the filing of NDA 203-567. The sponsor justified a waiver for phototoxicity and photoallergy studies. In addition, (b) (4) was deemed reasonable by the Division. The Agency and the sponsor agreed upon the details of how the data should be submitted.

2.6 Other Relevant Background Information

Onychomycosis refers to nail infections caused by any fungus, including yeasts and nondermatophyte molds. It is characterized by hyperkeratosis (hypertrophy of the skin/nail) of the nail bed, yellow to brownish discoloration of the nail plate, onycholysis (separation of the nail from nail bed along the lateral margins), and paronychial inflammation (inflammation due to infection of the skin fold at the nail margin).[2] Dermatophytic onychomycosis (tinea unguium) occurs in three distinct forms: distal subungual (most common), proximal subungual, and white superficial. One or several toenails or fingernails may be involved, seldom all. A majority of toenail onychomycosis is due to dermatophytes, however many cases of fingernail onychomycosis are due to yeast.

Multiple factors may contribute to the prevalence rates for onychomycosis. These rates have been increasing especially in diabetic, immunologically challenged, and elderly patient population.[3] Multiple environmental factors may play a role in this increase including the rise in the use of broad-spectrum antibiotics.[4] Additional factors may predispose the nail to fungal infection are numerous and include: geography, ethnicity, social class, occupation, genetics, vascular disease, obesity, atrophy, participation in sports, trauma, acrylic nails, ill-fitting shoes, nutritional status, non-dermatophyte exposure, and poor nail grooming.[5]

The most common presentation of this disease is distal subungal onychomycosis most often caused by a dermatophyte *Trichophyton rubrum*. Proximal subungal onychomycosis is generally caused by the same organism as distal subungal onychomycosis. White superficial onychomycosis is usually caused by *T. mentagrophytes*, although *T. rubrum* have also been implicated. Yeast onychomycosis is most commonly due to *Candida albicans*. Since other nail diseases, including psoriasis, eczema, and lichen planus may have a similar clinical presentation, confirmation of onychomycosis via direct-microscopic examination, nail clip biopsy, and fungal culture is necessary prior to the start of therapy.[6]

2 Elewski BE, Hay RJ. Update on the management of onychomycosis: highlights of the Third Annual International Summit on Cutaneous Antifungal Therapy. Clin Infect Dis 1996; 23: 305-13
3 Weschler WP, Smith SA, Bondar GL. Treatment of onychomycosis in the elderly. Clin Geriatr 2002; 10: 19-24, 29-30
4 Levy LA. Epidemiology of onychomycosis in special-risk populations. J Am Podiatr Med Assoc 1997; 87: 546-50
5 Haneke E, Roseeuw D. The scope of onychomycosis: epidemiology and clinical features. Int J Dermatol 1999; 38 Suppl. 2: 7-12
6 Weinberg JM, Koestenblatt EK. Comparison of diagnostic methods in the evaluation of onychomycosis. Dermatol Online J 2001; 7: 236

It is important to establish the causative microbiologic agent of the onychomycosis prior to instituting antimycotic treatment. The suggested method of diagnosis is with KOH examination of nail scrapings and fungal culture to establish the causative organism.

Nail material should be obtained by scraping the undersurface or by clipping a fragment of the infected nail such that the entire nail thickness is sampled. However, this method does not assess the proximal nail region, which is where the most viable hyphae are found. Therefore, the sample should be collected from the proximal and subungual portions of the affected nail, because fungus collected from the distal portion may be older and non-viable.[7]

A potassium hydroxide (KOH) preparation of the nail material is then examined by direct microscopy and, if hyphal fragments are detected, a fungal culture of the nail material is required to determine viability of the fungus and fungus species.

3 Ethics and Good Clinical Practices

The Division of Scientific Investigators (DSI) was consulted to review the conduct of both clinical trials (DPSI-IDP-P3-01 and DPSI-IDP-P3-02). The applicant participated in the Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA review process. Two sites were identified by the Site Selection Tool (SST). The San Diego site (Walter Nahm) and the Miami site (Hector Wiltz) was selected using the SST ranking total risk by using multiple factors, including the substantial enrollment of subjects for their respective protocols.

Reviewer's comment: *The overall assessment by DSI of the clinical sites was "No Action Indicated". The report noted: "The data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication." It would appear that the data generated by Dr. Nahm and Dr. Wiltz are accurate.*

3.1 Submission Quality and Integrity

Overall, the quality of the application is acceptable.

3.2 Compliance with Good Clinical Practices

The applicant affirmed that the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized tripartite guidelines for Good Clinical Practice and the compliance with local and FDA regulatory requirements. The protocol and Informed Consent Forms were reviewed by the Investigations Review Board (IRB) associated with the trial sites or by consulting central IRB. Written informed consents were obtained from subjects at the first (baseline) visit.

7 Midgley G, Moore MK, Cook JC, et al. Mycology of nail disorders. J Am Acad Dermatol 1994; 31 (3 pt 2): S68-74

3.3 Financial Disclosures

The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators. It was also affirmed that none of the clinical investigators disclosed any proprietary interest in the product, or significant equity interest in the sponsor company. Certification was made that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The action recommended by the CMC reviewer is a Complete Response. This recommendation is due to the applicant's lack of sufficient data to assure the identity, strength, purity, and quality of the drug product related to container integrity issues. There was no other safety or efficacy issue from other disciplines.

4.1 Chemistry Manufacturing and Controls

In this section, a summary of the CMC review will be presented.

Efinaconazole solution 10% is a clear, colorless to pale yellow solution. The inactive ingredients of the formulation are commonly used in topical products. All except one (C12-15 alkyl lactate) excipient are listed in the Inactive Ingredients Database and the proposed amounts do no exceed previously approved levels. The efinaconazole solution is packaged in a 10 mL HDPE bottle with a brush applicator in a (b) (4) cap. The information included in the application DOES NOT demonstrate that the proposed container/closure system meets all recommendations of the relevant USP monographs and the Agency's guidance.

The applicant provided 30 months long-term stability studies for one batch and 24 months stability studies for two batches of drug product, and proposed a (b) (4) month expiration dating period under controlled room conditions. However, based on the submitted stability data, the proposed expiration dating period cannot be granted. Failure of container integrity attribute during stability studies indicate that the drug product quality cannot be assured with the manufacturing process and controls described within the application.

To sum up, the following is the list of deficiencies which should be resolved to meet the regulatory requirements for the approval of this application:

- Inadequate manufacturing process and control information
- Inadequate specification for the drug product
- Inadequate integrity of the container closure system
- Inadequate stability data to assure the expiration dating period.

Additional deficiencies were as follows:

- No final recommendation from the office of Compliance for the facilities
- Unresolved label/labeling issues

"Because of these unresolved issues, from the ONDQA perspective, this NDA is not recommended for approval in its present form per 21 CFR 314.125(b)(1), (6), and (13)."

The data compiled for the Complete Response was obtained from the summary of applicant Report 129. This report evaluated the leaking bottles to determine the quality of the drug product prior to clinical distribution. Two batches of drug products were used in the two Phase 3 clinical trials (Batch DP1444, manufactured (b) (4) and Batch DP1453F1, manufactured on (b) (4). Batches for clinical trials were packaged in the presentation of (b) (4) mL of solution in 10 mL bottle. The chronological events related to leakage of clinical supplies for the Phase 3 clinical trials include:

1. Discovery of leakage

   Samples of Batch DP1444 arrived at Dow Pharmaceutical Sciences, Inc. (DPSI) on (b) (4). The boxes were shrink-wrapped in pallets and all boxes were in the upright position. Box (b) (4) of the drug product was opened and smearing was found on some of the bottles. Some bottles showed small amounts of liquid at the cap-bottle interface. 100% inspection of Box (b) (4) showed that 75 out of 150 bottles were smudged (50%). Additional inspection of Box (b) (4) showed approximately 89% of bottles had smeared.

2. Initial investigation of leakage

   Fifty smudged and 20 un-smudged bottle from Batch DP1444 were selected and the following test were conducted:

   - weight checks (acceptable range (b) (4))
     - All un-smudged bottles were in acceptance ranges, 1 smudged bottle was outside the range (no exact number given).
   - Torque testing (acceptable removal torque of (b) (4) inch)
     - 9 out of 20 un-smudged bottles and 21 out of 50 smudged bottles were outside the range (no exact numbers given).
   - Assay (acceptable range (b) (4) LC)
     - Smudged-bottle test results of 6 bottles average (b) (4)% LC, un-smudged average (b) (4)% (only average results given). For comparison at release, the assay was (b) (4)% LC.
   - Swabbing-assay of the exterior of the smudged bottles
     - Less than (b) (4)% of drug substance content was found on the external surface of the bottles.

3. Decision on Batch DP1444

After initial investigation, it was decided to:

- Weigh all the bottles. Wipe down exterior of all bottles with ethanol
- All bottles to be re-torqued
- Cleaned bottles to be transferred to Clinical Labeling and release for studies.

4. Process improvements

   The applicant reported some improvements in the process; however, the next batch DP1453F1 was manufactured before implementation of all improvements.

5. Batch DPI1453F1

   Batch DP1453 was manufactured on (b) (4). (b) (4) of filled bottles was used as a monitor to assess the effectiveness of filing process improvement. Report 129 states that Batch DP1453F1 had 15.7% leakers in the (b) (4) mL presentation (part of the batch was filled at the quantity of (b) (4) mL). The report goes on to state that leaking bottles were stored for further (b) (4) evaluations.

6. Assay results from leaking bottles found on stability

Table 1: Summary of Leaking Bottles from Clinical Batches (Report 129)

Batch number (10 mL & 6 mL)	Duration	Orientation	No. of bottles with product residue	No. of bottles evaluated	% of bottles with product residue
DP1443/DP1444 (Protocol 655-G)	24 months	Upright	15	353	4.2
		Horizontal	22	356	6.2
DP1453 (Protocol 666-G)	18 months	Upright	10	480	2.1
		Horizontal	28	506	5.5
DP1473/DP1474 (Protocol 681-G)	12 months	Upright	32	564	5.7
		Horizontal	69	564	12.2

Note: the data in the table are pooled together for (b) (4) fill levels, and the batch of placebo (DP1443) is also included.

The Appendix V of Report 129 included results of assay testing of stability samples with signs of leakage. Five bottles (two from batch DP1444, two from batch DP1473F1, and one from batch DP1474F1 were analyzed in duplicates. The assay results vary from (b) (4) % LC to (b) (4) % LC. The appendix does not specify the extent of the leakage (such as % of weight lost). The analyses were performed (b) (4), so the ages of samples were as follows:

- Batch DP1444 – 28 months

- Batch DP1473F1 – 17 months
- Batch DP1474F1 – 17 months

The CMC review conclusion: "The 'Container Closure System' of section *P2* indicates that the sponsor was not ready for manufacturing of the proposed drug product at the time of submitting the application and the container/closure and filling operation were not well understood and controlled. In particular:

- Leaking containers are considered to negatively impact drug product quality, and also safety by making labels unreadable
- Despite efforts to resolve the issue, estimated percent of leaking containers remains at the level of (b)(4)% after all improvements were estimated

It was noticed that Report 129 was signed in May 2012. This indicates that the sponsor does not have long-term data concerning container integrity after improvements (b) (4). Since stability data indicate that incidents of leaking were more frequent after drug product storage, the (b)(4)% failure rate is likely underestimated."

To further clarify the issue of product quality in the clinical trials, an addendum to the CMC review was generated. Dr. Kurtyka, the CMC reviewer stated:

"As stated in the Review #1, the submitted data are not sufficient to allow to state with certainty that the assay values of the clinical samples were within the acceptance criterion range ((b) (4) % LC) throughout duration of the clinical studies. However, based on the submitted data, it is possible to state with high confidence that assay values of the clinical batches were not higher that (b) (4)% LC (in the worst case).

This conclusion is based on following reasoning:

- In the worst case, non-leaking bottles may show increased assay values of up to (b)(4)% on storage for about 24 months (probably due to evaporation of ethanol as indicated by stability study)
- Once opened, due to, again, the evaporation of ethanol, the assay value of a bottle may increase another (b)(4)% (as indicated by in-used study)
- It is estimated that leakage may contribute to maximum of (b)(4)% increase of assay. This estimation is based on the observation that (b) (4) (b) (4) show assay increase of (b)(4)% in 12 months. Therefore low level of formulation in container promotes assay increase through evaporation of ethanol. However, container weigh decrease measured during stability studies showed that leakages were never as extensive as lost of (b)(4)% of formulation. Very few samples from batch DP1473F1 showed high leakage of up to (b)(4)% (indicated by weight change), however, majority of leaking bottles lost much less weight (up to several percent) and this leads to a conclusion that the additional (b)(4)% increase of assay due to the leakage is a reasonable upper limit estimate."

Reviewer's comments:

- *The CMC reviewer concluded that the leakage of the container/closure is not acceptable.*
- *The estimated (b) (4)% failure (b) (4) is likely an underestimate.*
- *The applicant's manufacturing process was not finalized prior to submission of the NDA.*
- *There is inadequate stability data to assure the expiration dating period.*
- *As for the clinical trials product quality, the information submitted to date, while not extensive, appears to validate the sponsor's assertion that the product in containers that leaked was within specification in comparison to the product in containers that did not leak. As such, there does not appear to be clinical concerns about the validity of the conducted clinical trials due to lack of drug product quality or stability data.*

The CMC review goes on to state"

"To resolve these issues, the following information is needed:

1. **Regarding manufacturing process and control information**
   - 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.
   - Additional process development information for the optimized commercial process, and refinements in container/closure in order to achieve acceptable container/closure integrity.
   - Master Batch Records for the optimized commercial manufacturing process.

2. **Regarding the specification for the drug product**
   - Updated specification including leakage test method and its acceptance criterion. The leakage test method must be a validated one and not rely on (b) (4) to detect the leak. Method validation data must be provided.

3. **Regarding integrity of the container closure system**
   - Proposed control strategies for preventing the leakage
   - Complete description of the to-be-marketed container/closure system and any modifications to the system since the initial submission of the NDA.

4. **Regarding stability data**
   - Stability data from 3 batches manufactured using the optimized commercial process according to ICH Q1A. 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.
   - In-use stability data for the drug product packaged in the to-be-marketed container/closure system

5. **Final "Acceptable" recommendation from the Office of Compliance.**

6. **Finalized label/labeling**

In addition, to further understanding of the quality of clinical batches, the following information is needed:

- Appendix II of the Report 129 states that all bottles from batch DP14444 were weighted, with the acceptance criteria to be specified in the batch record. The sponsor needs to provide:
  - the acceptance criteria,
  - weighing results (summarized in table format)
  - full accountability of all bottles; and the fate of bottles that failed the check.
- Report 129 states that leaking bottles from batch DP1443 were stored for further (b) (4) evaluation. The sponsor needs to provide:
  - results of (b) (4) evaluation (e.g. assay, weigh loss, etc.)
  - full accountability of all bottles sent to (b) (4) including those bottles sent to clinical studies
  - experimental procedures."

Reviewer's Comment: *The above CMC comments will be conveyed in the Complete Response letter.*

On 8-MAR-2013, a Discipline Review Letter was sent to the applicant detailing the deficiencies found by CMC in the application.

The letter outlines four main issues:

1. Inadequate manufacturing process and control information:
   - Details of the process/control are not provided.
   - The submitted information indicated that the filling/packaging operation is incomplete and still evolving.

2. Inadequate specification for the drug product:
   - The currently proposed package integrity test (which includes a (b) (4) for leakage) is inadequate and is not capable of ensuring timely detection of leaks.

3. Inadequate integrity of the container/closure system, as evidenced by a high number of leaks observed.

4. Inadequate stability data:
   - The data were obtained from batches manufactured utilizing a non-optimized process.

To further make the applicant aware of these issues, the Agency held a teleconference with the applicant on 12-MAR-2013 to verbalize the Agency's concerns.

***Reviewer's comment**: A teleconference was held on 12-MAR-2013 to make the applicant aware of the CMC deficiencies. It was made clear during the teleconference that the Discipline Review Letter does not signify the final Agency decision. Additionally, a second teleconference was held on 20-MAR-2013 to provide further clarifications for the deficiencies outlined and for the sponsor to discuss their concerns.*

In addition to the teleconferences held with the sponsor, The Agency met internally to discuss the Complete Response recommendation. CMC has amended the ONDQA review to capture the details of the deficiencies found in the application. The recommended language from CMC is included in Appendix 9.4.

4.2 Clinical Microbiology

The recommendation from Clinical Microbiology is an approvable action.

A summary of Dr. Kerry Snow's completed Clinical Microbiology review is included in this section.

The applicant investigated the *in vitro* antifungal activity of efinaconazole in several studies. Study 07-42, conducted in Cleveland in 2010, determined minimum inhibitory concentrations (MICs) on 118 clinical isolates. Study DSIN-7001-A6HP-27-11 done at the University of Texas Health Science Center in 2012, compared the *in vitro* activity of efinaconazole, itraconazole, ciclopirox, amorolfine, and terbinafine against clinical isolates of *T. rubrum* and *T. mentagrophytes* using susceptibility testing methods. Other studies were conducted in Japan where efinaconazole was compared to several antifungals on 27 clinical isolates of *T. mentagrophytes*.

According to Dr. Snow's review, "The applicant has submitted study reports that support a claim for *in vitro* antifungal activity of efinaconazole against isolates of *T. rubrum* and *T. mentagrophytes* (the fungal pathogens included in the proposed indications for this drug). Data from these studies suggest an MIC_{90} against isolates of *T. rubrum* ranging from 0.0015-0.06 mcg/mL, and for an MIC_{90} against isolates of *T. mentagrophytes* ranging from 0.004-0.13 mcg/mL. The highest MIC observed for efinaconazole against any isolate of the two significant species tested (*T. rubrum* and *T. mentagrophytes*) was 0.13 mcg/mL."

In addition, the applicant has submitted sufficient information to demonstrate a low potential for the development of resistance in specific fungal pathogens (T. rubrum, T. mentagrophytes, and C. albicans) to efinaconazole. Other studies were conducted to evaluate the drugs pharmacodynamics and pharmacokinetics. The details of these studies are discussed in the Clinical Microbiology review.

The recommended labeling changes from Clinical Microbiology can be found in Section 9.2 of this review.

Reviewer's comment: *Sufficient microbiological evidence of the drug's action against specified fungal isolates have been submitted for efinaconazole. The labeling recommendations from Clinical Microbiology are acceptable pending resolution of the outstanding CMC issues.*

4.3 Preclinical Pharmacology/Toxicology

This section will summarize the Pharmacology/Toxicology review by Dr. Linda Pellicore. The action recommended by Dr. Pellicore is approvable from a Pharmacology/Toxicology perspective.

The evidence provided is as follows:

"Repeat-dose systemic rodent toxicity and developmental and reproductive toxicity studies were conducted with subcutaneous administration of efinaconazole dissolved in propylene glycol. Efinaconazole appeared well tolerated but subcutaneous administration of propylene glycol was not well tolerated and resulted in significant injection site toxicity.

The primary toxicity noted in the 6 month repeat dose subcutaneous toxicity study in rats conducted with doses up to 30 (males) and 40 (females) mg/kg/day efinaconazole was injection site toxicity noted in all dose groups including the vehicle (propylene glycol) control group.

Efinaconazole solution was evaluated in a 9 month dermal toxicity study in minipigs with repeated daily dermal administration of up to 30% efinaconazole solution. The efinaconazole solution used in the chronic dermal minipig study was similar to the to- be-marketed formulation. The minor differences in a few excipients in the formulation were determined to not be of toxicological significance. The vehicle and efinaconazole solution produced mild skin irritation. Mild skin irritation (modest microscopic hyperkeratosis, acanthosis, and localized inflammation) was noted in all dose groups including the vehicle control group. No systemic toxicity was noted at topical doses up to 30% efinaconazole solution, which is the maximum feasible concentration.

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one *in vivo* genotoxicity test (mouse peripheral reticulocyte micronucleus assay).

A dermal mouse carcinogenicity study was conducted with the to-be-marketed efinaconazole solution. Severe skin irritation was noted at the treatment site in all dose groups including the vehicle control group. This study was suboptimal due to the mice being very sensitive to severe dermal effects elicited by the vehicle. No treatment related increase in the incidence of

neoplasms was observed in this study. However, the skin effects of the propylene glycol vehicle confounded assessment of any skin effects due to efinaconazole.

Reproductive and developmental toxicology studies have been conducted with efinaconazole in rats and rabbits.

In subcutaneous rat fertility study skin thickening at the injection site was noted in all efinaconazole treated groups and the vehicle control group. No treatment related effects on male or female fertility parameters were noted at doses up to 25 mg/kg/day efinaconazole in this study. A tendency to slightly prolong the estrous cycle was noted in 25 mg/kg/day treated females but the copulation index was 100% in all dose groups.

A subcutaneous embryofetal development study in rats was conducted with doses up to 50 mg/kg/day efinaconazole. Skin thickening at the treatment site, an 11% decrease in maternal body weight gain, complete embryo resorption in two dams and an increased incidence of embryofetal death were noted at the 50 mg/kg/day dose. Embryofetal resorption and/or embryofetal death may be related to the effects seen in the placenta noted at the 50 mg/kg/day dose. However, no drug-related malformations were noted at doses up to 50 mg/kg/day efinaconazole in this study.

A subcutaneous embryofetal development study in rabbits was conducted with doses up to 10 mg/kg/day efinaconazole. Injection site reactions were noted in all treatment groups including the vehicle control group. A decrease in body weight gain was noted in does at 10 mg/kg/day. There were no indications of test article related embryofetal toxicity or malformations at doses up to 10 mg/kg/day efinaconazole in this study.

A subcutaneous pre- and post-natal development study in rats was conducted with doses up to 25 mg/kg/day efinaconazole. Injection site swelling and masses were noted in all dose groups including the vehicle control group. Prenatal pup mortality was increased at 25 mg/kg/day. There were no toxicologically significant effects on duration of gestation or the ability of dams to deliver litters. No treatment related effects on postnatal development of F1 offspring were noted at doses up to 25 mg/kg/day efinaconazole in this study.

Single dermal application of up to 10% efinaconazole solution to rabbits did not elicit dermal irritation in intact skin but was a mild irritant to abraded skin. Efinaconazole solution, 10%, was a mild ocular irritant in rabbit eyes. Efinaconazole solution did not elicit a photoirritation response in guinea pigs."

Reviewer's comment: *The submitted Pharmacology/Toxicology data is sufficient to support approval of the drug product. The ECAC meeting on November 27, 2012 discussed the dermal mouse carcinogenicity study. The committee concluded that there were no drug-related neoplasms in the dermal mouse carcinogenicity study.*

4.4 Clinical Pharmacology

This section will summarize the completed Clinical Pharmacology review by Dr. Chinmay Shukla. Dr. Shukla concluded:

"From a Clinical Pharmacology Standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Sponsor. However, due to package integrity issues causing leakage of the product used in the Phase 3 trials, the safety and efficacy data produced in the Phase 3 trials are not considered reliable at this stage in the review cycle. The package integrity issue did not affect the maximal use PK trial as none of the products used in this trial leaked."

4.4.1 Mechanism of Action

Efinaconazole is an azole antifungal agent that inhibits fungal lanosterol 14α-demethylase involved in ergosterol biosynthesis. The accumulation of 14α-methyl sterols and subsequent loss of ergosterol in the fungi cell wall may be responsible for the fungistatic and fungicidal activity of efinaconazole.

The drug product, JUBLIA™ (efinaconazole solution, 10%), contains 10% w/v of active ingredient efinaconazole (IDP-108) in a solution dosage form for topical application. It is a clear, colorless to pale yellow solution with an alcohol content of approximately (b) (4) w/w. The qualitative and quantitative composition of the drug product is shown in Table below.

Table 2: Qualitative and Quantitative Composition of efinaconazole solution, 10%

Ingredient	Grade	Function	Concentration (%w/w)
Efinaconzole	N/A	Active	10.0
Cyclomethicone	NF	(b) (4)	
Diisopropyl Adipate	Cosmetic		
C12-15 Alkyl Lactate	Cosmetic		
Butylated Hydroxytoluene	NF		
Citric Acid, Anhydrous	USP		
Edetate Disodium	USP		
Purified Water	USP		
Alcohol	USP		

Source: Applicant's submission

The drug product is packaged in a 10 mL white bottle with a brush applicator and (b) (4) cap. The amount of solution in the to-be-marketed container is (b) (4)

4.4.2 Pharmacodynamics

The pharmacodynamics of this drug product is unknown.

4.4.3 Pharmacokinetics

To support this NDA the Sponsor has completed 2 PK trials. Trial DPSI-IDP-108-P1-03 was a maximal use PK trial in adult subjects with severe onychomycosis and Trial DPSI-IDP-108-P1-02 was conducted in healthy adult subjects. In addition to the above, the Sponsor has also provided a summary of systemic PK results from the 2 non-IND Japanese trials, Trial KP-103-03 which evaluated concentrations in effected versus normal toenails and Trial KP-103-02 which was skin irritation and photosensitization trial in healthy subjects.

The maximal use PK trial (DPSI-IDP-108-P1-03) was conducted in 20 adult male and female subjects (18 completed) with severe onychomycosis with at least 80% of the area of both great toenails and at least 4 other toenails with onychomycosis infection. The study drug was applied once daily for 28 days to all 10 toe nails and 0.5cm of adjacent surrounding skin. Serial PK blood samples were collected at pre-dose and post dose on Day 1, Day 14 and Day 28, and a single sample was obtained any time during the 2 weeks post treatment follow up visit. PK of the parent drug (IDP-108) and 2 metabolites [H3 and H4] were assessed. Plasma concentrations of the parent drug were quantifiable in 15 out of 18 subjects on Day 1 and in all subjects on Day 14 and Day 28. The ratio of mean AUC and Mean C_{min} on Day 14 versus Day 28 was less than 1.18 for the parent drug (IDP-108) suggesting concentrations in-vivo were near steady state by Day 14. The mean ± SD values of AUC(0-t) and C_{max} on Day 28 for the parent drug was 12.15 ± 6.91 ng*h/mL and 0.67 ± 0.37 ng/mL, respectively. The concentration profile for the parent drug at steady state on Day 28 was relatively flat over the 24 hour dosing interval.

Reviewer's comment: *Sufficient evaluation of the PK of this drug product is presented by the applicant to support proposed labeling pending resolution of the outstanding CMC issues..*

5 Sources of Clinical Data

Notwithstanding the container integrity issues outlined above, the evidentiary requirements of efficacy and safety are supported by results from the two pivotal Phase 3 clinical trials. Both trials share identical objectives, inclusion/exclusion criteria, study designs, and analysis endpoints. These trials were conducted simultaneously at investigational centers in the US, Canada, and Japan. Both trials evaluated the to-be-marketed formulation of IDP-108 (efinaconazole) solution, 10%. A total of 1655 subjects with mild to moderate onychomycosis applied the randomized study drugs (IDP-108 and Vehicle) to the target toenails, once daily for 48 weeks.

A summary of all clinical trials conducted in the development of IDP-108 is presented in **Table 3**. Note that the Phase 2 (DPSI-IDP-108-P2-01) dose-ranging study, with and without semi-

occlusion, was conducted with the original formulation of IDP-108 and *not* with the final to-be-marketed formulation.

5.1 Tables of Studies/Clinical Trials

Table 3: Summary of Clinical Studies

Type of Study	Objective(s) of Study	Study Design	Dose Regimen	Number of Subjects	Type of Subjects	Duration of Treatment
Phase 1 PK [a] DSP-IDP-108-P1-02	To evaluate the systemic exposure and characterize the plasma PK profile of IDP-108 and its major metabolite	Single center, randomized, open-label, two-period crossover study	IDP-108 solution [1] 10% topically applied once daily	10	Healthy subjects	28 days
Phase 1 PK [a] DPSI-IDP-108-P1-03	To evaluate the safety and systemic exposure of IDP-108 10% solution	Open label, single center	IDP-108 10% Solution [1] topically applied once daily	20	Severe onychomycosis	28 days
Phase 1 [b] DPSI-IDP-108-P1-01	To determine the comparative dermal irritation of seven test articles plus a positive and negative control	Single center, test site randomized, positive and negative control	IDP-108A (vehicle 1%, 5%, 10%) IDP-108B (vehicle, 1%, and 5%) [2] 0.2% sodium lauryl sulfate, deionized water applied topically	55	Healthy subjects	21 days
Phase 1 [a] RIPT DPSI-IDP-108-P1-04	To evaluate IDP-108 10% Solution and vehicle for the induction of contact sensitization by repetitive application	Single center double masked, vehicle control	IDP-108 10% Solution [1] and vehicle topically applied once daily	239	Healthy Subjects	8 weeks
Phase 2 [b] Efficacy and Safety DPSI-IDP-108-P2-01	To evaluate the safety and efficacy of IDP-108 solutions	Multicenter, evaluation blind, randomized, vehicle controlled, parallel group study	IDP-108 5% and 10% Solution [2] applied topically once daily	135	Mild to moderate onychomycosis of the toenails	40 weeks
Phase 3 [a] Efficacy and Safety DPSI-IDP-108-P3-01	To evaluate the safety and efficacy of IDP-108 10% solution	Multicenter, double blind, randomized, vehicle controlled	IDP-108 10% Solution [1], vehicle topically applied once daily	870	Mild to moderate onychomycosis of the toenails	52 weeks
Phase 3 [a] Efficacy and Safety DPSI-IDP-108-P3-02	To evaluate the safety and efficacy of IDP-108 10% solution	Multicenter, double blind, randomized, vehicle controlled	IDP-108 10% Solution [1], vehicle topically applied once daily	781	Mild to moderate onychomycosis of the toenails	52 weeks

a Conducted with the to-be-marketed formula of IDP-108 solution (the concentration of efinaconazole may have varied)
b Conducted with the original formulation (concentration of efinaconazole may have varied)
Source: Applicant's synopses of individual studies.

Two Phase 1 studies were conducted outside of the IND; KP-103-03 is an investigation of efinaconazole concentration in nails and KP-103-02 is a skin irritation and photosensitization study.

5.2 Review Strategy

The safety review will consist of evaluation of the Phase 2 study separately from the two Phase 3 clinical trials. The efficacy of the Phase 2 study is used as supportive of the Phase 3 clinical trials. The Phase 3 clinical trials will be pooled to determine safety and efficacy of efinaconazole solution, 10% for the treatment of toenail onychomycosis. A brief discussion of the study designs are provided in this section. The supportive studies from the Phase 1 topical safety and the Japanese clinical studies will be discussed in later sections.

5.3 Discussion of Individual Studies/Clinical Trials

A brief summary of the Phase 2 study and the Phase 3 clinical trials will be presented in this section. Full evaluation of the efficacy data (section 6) and safety data (section 7) will be presented in later sections. Note that the Phase 2 study (DPSI-IDP-108-P2-01) utilized an earlier formulation than that of the final-to-be marketed formulation used in the Phase 3 clinical trials.

DPSI-IDP-108-P2-01: Phase 2 Dose-Ranging Study

Title: A Phase II Dose-Ranging, Safety, and Efficacy Study of IDP-108 Topical Solution *vs*. Vehicle in Subjects with Mild to Moderate Onychomycosis of the Toenails.

Objectives: To evaluate the safety and efficacy of 2 concentrations (10% solution [with and without semi-occlusion], and 5% solution) of the topical antifungal IDP-108 in the treatment of mild to moderate onychomycosis of the toenails. To provide information to power Phase 3 studies.

Number of subjects: 140

Study Plan: This is a multi-center, randomized, 4-arm, double-blind, vehicle-controlled, efficacy and safety study in subjects with mild to moderate onychomycosis of at least one great toenail. Approximately 140 subjects will be randomly assigned to one of four topical dosing arms: 10% with overnight semi-occlusion (6-10 hours), 10% without semi-occlusion, 5% and vehicle alone, with approximately 40 subjects in each active arm and approximately 20 subjects assigned to the vehicle group.

Ten subjects in the treatment arm will be selected for plasma study drug levels at Baseline (pre-study drug exposure), Weeks 4, 8, 12, 24, & 36 and follow-up (week 40) or early termination.

Duration of Treatment: 9 months

Efficacy: Efficacy of the target nail was done by Investigator's clinical examination (measurement of healthy nail from the proximal margin of the affected area and estimation of % of the nail infected, after trimming). KOH examination and fungal culture of nail scraping and subungual debris was performed on target nail at Weeks 12, 24, and 36 and the follow-up visit at 30 days after the final dose.

Safety: Safety was evaluated by type and frequency of adverse events (AEs) and review of all concomitant medications.

DPSI-IDP-108-P3-01 and -02: Phase 3 Clinical Trials

The Phase 3 clinical trials are identical in design and conducted simultaneously. A summary of the clinical trial will be presented in this section.

Title: A Phase 3, Multicenter, Randomized, Double-Blind Study Evaluating the Safety and Efficacy of IDP-108 Topical Solution versus Vehicle in Subjects with Mild to Moderate Onychomycosis of the Toenails.

Objective: To evaluate the safety and efficacy of 48 weeks of once daily application of IDP-108 compared with vehicle in the treatment of mild to moderate onychomycosis of the toenails.

Study Plan: This is a multicenter, randomized, 2-arm, double-blind, vehicle-controlled, parallel-comparison study designed to assess the safety and efficacy of IDP-108 10% topical solution in subjects with mild to moderate onychomycosis of at least one great toenail confirmed by fungal culture of the toenail. Approximately 800 subjects will be randomly assigned to receive treatment with either IDP-108 10% topical solution or vehicle in a 3:1 ratio. Subjects applied study drug to each toenail suspected of having an infection with a dermatophyte, as determined by the investigator, once a day at bedtime for 48 weeks.

The target nail clinical evaluation and photography (when applicable) was performed after clipping. The target nail was assessed at every visit.

Table 4: Schedule of Assessments (Phase 3 Clinical Trials)

PROCEDURES	Visit 1 Screening Up to Day -42	Visit 2 Baseline Day 0	Visit 3 Wk 4 Day 28 ±5d	Visit 4 Wk 8 Day 56 ±5d	Visit 5 Wk 12 Day 84 ±5d	Visit 6 Wk 16 Day 112 ±5d	Visit 7 Wk 20 Day 140 ±5d	Visit 8 Wk 24 Day 168 ±5d	Visit 9 Wk 28 Day 196 ±5d	Visit 10 Wk 32 Day 224 ±5d	Visit 11 Wk 36 Day 252 ±5d	Visit 12 Wk 40 Day 280 ±5d	Visit 13 Wk 44 Day 308 ±5d	Visit 14 [1] Wk 48 Day 336 ±5d	Visit 15 4 Week F/U Day 364 ±5d
Informed Consent	X														
Demographics	X														
Medical History	X	X[2]													
Study Eligibility Criteria	X	X[2]													
Previous Therapies	X	X[2]													
Serum Pregnancy Test	X				X			X						X	
Urine Pregnancy Test [3]		X	X	X		X	X			X			X		X
Administer OnyCOE-t™		[4]						X[4]			X				X[4]
Clip toenails [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Notch Target Great Toenail [6]	X	X													
Measure Target Toenail Growth (distance from PNF to Notch) [6]			X	X	X	X	X	X	X	X	X	X	X	X	X
Target Toenail Assessments [7]	X	X			X			X						X	X

PROCEDURES	Visit 1 Screening Up to Day -42	Visit 2 Baseline Day 0	Visit 3 Wk 4 Day 28 ±5d	Visit 4 Wk 8 Day 56 ±5d	Visit 5 Wk 12 Day 84 ±5d	Visit 6 Wk 16 Day 112 ±5d	Visit 7 Wk 20 Day 140 ±5d	Visit 8 Wk 24 Day 168 ±5d	Visit 9 Wk 28 Day 196 ±5d	Visit 10 Wk 32 Day 224 ±5d	Visit 11 Wk 36 Day 252 ±5d	Visit 12 Wk 40 Day 280 ±5d	Visit 13 Wk 44 Day 308 ±5d	Visit 14 [1] Wk 48 Day 336 ±5d	Visit 15 4 Week F/U Day 364 ±5d
Non-Target Nail Assessments		X			X			X						X	X
Baseline Photography (all sites)		X								X					
F/U Photography (selected sites)								X							X
KOH Examination [8]	X				X			X			X			X	X
Fungal Culture [8]	X				X			X			X			X	X
Abbreviated Physical Examination [9]		X												X	
Vital Signs		X			X			X						X	
Blood and Urine Samples for Safety Lab Tests	X				X			X		X				X [10]	
12-lead ECG [11]		X	X							X				X	
Subject Randomization		X													
Review Dosing Instructions		X	X	X	X	X	X	X	X	X	X	X	X		
First Dose Applied in Clinic		X													

PROCEDURES	Visit 1 Screening Up to Day -42	Visit 2 Baseline Day 0	Visit 3 Wk 4 Day 28 ±5d	Visit 4 Wk 8 Day 56 ±5d	Visit 5 Wk 12 Day 84 ±5d	Visit 6 Wk 16 Day 112 ±5d	Visit 7 Wk 20 Day 140 ±5d	Visit 8 Wk 24 Day 168 ±5d	Visit 9 Wk 28 Day 196 ±5d	Visit 10 Wk 32 Day 224 ±5d	Visit 11 Wk 36 Day 252 ±5d	Visit 12 Wk 40 Day 280 ±5d	Visit 13 Wk 44 Day 308 ±5d	Visit 14 [1] Wk 48 Day 336 ±5d	Visit 15 4 Week F/U Day 364 ±5d
Weigh / Dispense Study Drug		X	X	X	X	X	X	X	X	X	X	X	X		
Collect / Weigh Study Drug			X	X	X	X	X	X	X	X	X	X	X	X	
Compliance Reviewed			X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Diary		X	X	X	X	X	X	X	X	X	X	X	X		
Collect / Review Diary			X	X	X	X	X	X	X	X	X	X	X	X	
Localized Skin Reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exit Study															X

ET = early termination, F/U = follow up

All visit dates are in reference to Visit 2 (Baseline), e.g., Visit 8 occurs 163 to 173 days after Visit 2.

[1] For subjects who terminate early during the treatment period, all Week 48 procedures should be completed at the time of termination.

[2] Confirm at Baseline

[3] Urine pregnancy tests must have a minimum sensitivity of 25mIU - HCG/mL of urine.

[4] Administer prior to any study-related procedures to subjects whose native language is English.

[5] The nails should be clipped prior to Nail Assessments.

[6] Transverse notch inscribed at Baseline should be enhanced as needed at subsequent visits to allow continued measurement of nail growth over the course of the study. If the initial notch inscribed at Baseline has grown out or is clipped away, inscribe a new notch in the nail adjacent to the proximal nail fold and continue with measurements of nail growth.

[7] Assess percent involvement of target toenail having onychomycosis and measure distance from PNF to proximal onychomycotic border.

[8] KOH examination and fungal culture specimens will be obtained from study eligible toenails at Screening, and from the target great toenail only at Weeks 12, 24, 36, 48/ET and at the 4-Week F/U Visit.

[9] Height and weight will be measured at Baseline, and weight only will be measured at Week 48/ET.

[10] Any clinically significant laboratory abnormality present at Week 48/ET is to be followed to resolution or until clinically stable as determined by the Investigator.

[11] ECGs will be collected for subjects enrolled in the US and Canada post implementation of Amendment 3. At the Baseline visit, ECG will be collected prior to study drug application. Post-baseline ECGs should, ideally, be collected at the same time of day as the Baseline ECG.

Primary Efficacy: percentage of subjects in each treatment group who achieved a "Complete Cure" (defined as 0% clinical involvement of the target toenail, in addition to both a negative KOH examination and a negative fungal culture of the target toenail) at Week 52.

Secondary Efficacy: Clinical Efficacy, Mycological Cure, Unaffected new toenail growth, Complete or Almost Completed Cure rates.

Safety: Localized skin reactions, AEs, Physical Examination, Vital signs, Safety Laboratory testing, Pregnancy test, ECGs.

Reviewer's comments: *The Phase 3 clinical trials are appropriately designed to evaluate onychomycosis. The primary endpoint is appropriate for to determine primary efficacy of the drug product and is consistent with prior Agency advice, as well as previous applications. The proposed secondary endpoints do not reflect clinically meaningful endpoints* (b) (4)

6 Review of Efficacy

Efficacy Summary

The efficacy evaluation included one Phase 2 study and two Phase 3 clinical trials. A summary of the protocols are described in Section 5. The formulation of the Phase 2 study (DPSI-IDP-108-P2-01) is not the to-be-marketed formulation; whereas, the Phase 3 clinical trials used the final to-be-marketed formulation of the drug product.

The single Phase 2 study evaluated the 10% formulation with and without semi-occlusion and the 5% formulation relative to Vehicle. This study included 135 subjects with mild to moderate onychomycosis. While no primary efficacy endpoint was designated, the efficacy analyses in the study were based on the percent toenail involvement of the target and non-target toenails measured with and without the use of 3M™ Blenderm™ Medical Tape (Blenderm tape), the length of the unaffected part of the target and non-target great toenails measured with and without Blenderm™ tape, the microscopic examination and mycological culture outcomes for the target toenail, and the Investigator's Global Assessment (IGA) of the non-target toenails. Based on the efficacy analyses, the percentage of subjects with "treatment successes" in each of the active groups was numerically greater than the percentage of subjects with "treatment successes" in the Vehicle group at Week 36 and at the 30-day post-treatment follow-up visit; none of the treatment-group differences were statistically significant.

The two Phase 3 clinical trials were designed and conducted identically at different investigational centers. Efinaconazole solution, 10% was superior to vehicle in the treatment of onychomycosis in both Phase 3 clinical trials. Trials P3-01 and P3-02 enrolled subjects age 18 to 65 with a clinical diagnosis of onychomycosis and positive mycology. Subjects applied treatment once daily for 48 weeks. In both studies, the primary efficacy endpoint was the percentage of subjects at Week 52 who achieved a "Complete Cure" (defined as 0% clinical involvement of the target toenail, in addition to a Mycological Cure, which was defined as both a negative potassium hydroxide [KOH] examination and a negative fungal culture of the target toenail sample). The secondary efficacy endpoints specified in the protocol were: (1) clinical efficacy rate at Week 52 (<10% affected target nail area), (2) mycological cure rate at Week 52 (negative KOH and culture), and (3) unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement). Both studies met their primary and secondary efficacy endpoints and showed greater efficacy relative to Vehicle.

Table 5: Summary of Primary and Secondary Efficacy Endpoints at Week 52

	Study P3-01			Study P3-02		
	IDP-108	Vehicle	*p-value*	IDP-108	Vehicle	*p-value*
	N=656	N=214		N=580	N=201	
Complete Cure	117 (17.8%)	7 (3.3%)	<0.001	88 (15.2%)	11 (5.5%)	<0.001
Clinical Efficacy	234 (36%)	25 (12%)	<0.001	180 (31%)	24 (12%)	<0.001
Mycologic Cure	362 (55%)	36 (17%)	<0.001	310 (53%)	34 (17%)	<0.001
Unaffected new growth (mm)	5.0 (0.2)	1.6 (0.4)	<0.001	3.8 (0.2)	0.9 (0.4)	<0.001

Source: Agency Biostatistical Review (Dr. Kathy Fritsch)

6.1 Proposed Indication

JUBLIA™ (efinaconazole cream, 10%) is indicated for the topical treatment of onychomycosis in the toenails (tinea unguium) of adults 18 years and older.

6.1.1 Methods

The efficacy review will focus on the two Phase 3 pivotal clinical trials with the primary endpoint of "Complete Cure" (clinical cure and mycological cure). The Phase 2 study will be included in the demographics discussion, but not in the efficacy discussion since it included a different formulation of the drug product and did not reach statistical significance in its efficacy endpoints.

6.1.2 Demographics

In general, patient demographics were comparable across the study groups. The Phase 2 study is evaluated separately due to the different study drug formulation and having the study conducted entirely in Mexico. The two Phase 3 clinical trials were designed identically and conducted simultaneously across three countries (US, Japan, and Canada); therefore, these two studies will be pooled for evaluation.

Phase 2 Study: DPSI-IDP-108-P2-01

This Phase 2 study included male and female subjects 18 to 65 years of age with the clinical diagnosis of stable or exacerbating distal lateral subungual onychomycosis affecting at least one great toenail. The study was done in Mexico across 11 investigational centers.

Table 6: Subject Demographics (ITT subjects, DPSI-IDP-108-P2-01)

	IDP-108 with semi-occlusion N=36	IDP-108 N=39	IDP-108 5% N=38	Vehicle N=22	Total N=135
Age (years)					
Mean (SD)	43.1 (13.02)	42.7 (11.72)	41.6 (110.11)	4.2 (10.74)	42.8 (11.67)
Minimum to maximum	19 to 64	20 to 63	20 to 63	25 to 62	19 to 64
Sex, n (%)					
Male	16 (44.4)	18 (46.2)	19 (50.0)	9 (40.9)	62 (45.9)
Female	20 (55.6)	21 (53.8)	19 (50.0)	13 (59.1)	73 (54.1)
Ethnicity, n (%)					
Hispanic/Latino	36 (100.0)	39 (100.0)	38 (100.0)	22 (100.0)	135 (100.0)
Not Hispanic/Latino	0	0	0	0	0
Race, n (%)					
White	0	1 (2.6)	0	0	1 (0.7)
Other: Mestizo	36 (100.0)	39 (100.0)	38 (100.0)	22 (100.0)	135 (100.0)

Source: Table 11.2.1 and Table 11.2.2 in DPSI-IDP-108-P2-01 Clinical Study Report

A total of 135 subjects were included in the ITT analysis, 39 (28.9%) were randomized to the IDP-108 groups, 36 (26.7%) were randomized to the IDP-108 with semi-occlusion group, 38 (28.1%) were randomized to the IDP-108 5% group, and 22 (16.3%) were randomized to the Vehicle group.

Across the treatment groups, the mean (standard deviation) ages, heights, and weights of the randomized subjects (ITT) were 42.8 (11.67) years, 166 (9.25) cm, and 74.4 (14.3) kg, respectively. The percentages of male and females were 45.9% and 54.1%, respectively; all subjects were Hispanic or Latino and belonged to the Mestizo race. The four treatment groups were comparable with respect to demographic and baseline characteristics.

DPSI-IDP-108-P3-01 and -02: Phase 3 Clinical Trials

The combined Phase 3 clinical trials enrolled 1655 subjects aged 18 to 75 years old randomized to treatment or Vehicle (1239 in the IDP-108 group and 416 in the Vehicle group).

Table 7: Subject Demographics and Baseline Characteristics (ITT Subjects, Phase 3 studies Combined)

	IDP-108 N=1236	Vehicle N=415	Total N=1651
Age (years)			
Mean (Standard Deviation)	51.5 (11.4)	51.4 (11.4)	51.4 (11.4)
Minimum to maximum	18.0 to 71.0	18.0 to 70.0	18.0 to 71.0
Sex, n (%)			
Male	953 (77.1)	322 (77.6)	1275 (77.2)
Female	283 (22.9)	93 (22.4)	376 (22.8)
Ethnicity, n (%)			
Hispanic/Latino	193 (15.6)	77 (18.6)	270 (16.4)
Not Hispanic/Latino	1042 (84.3)	338 (81.4)	1380 (83.6)
Race, n (%)			
White	947 (76.6)	304 (73.3)	1251 (75.8)
Black or African American	70 (5.7)	28 (6.7)	98 (5.9)
American Indian/Alaskan Native	3 (0.2)	2 (0.5)	5 (0.3)
Asian	200 (16.2)	69 (16.6)	269 (16.3)
Native Hawaiian/Pacific Islander	2 (0.2)	1 (0.2)	3 (0.2)
Other	14 (1.1)	11 (2.7)	25 (1.5)
Percent of affected toenail (%)			
Mean (Standard Deviation)	36.4 (10.6)	36.7 (10.5)	36.5 (10.6)
Number of affected non-target toenails			
Mean (Standard Deviation)	2.8 (1.6)	2.8 (1.7)	2.8 (1.6)

Source: Table 14.1.1.1 and Table 14.1.4.1, applicant's data

Of these subjects, 1436 (86.6%) completed the treatment phase of the trails (48 weeks) and 1420 (85.8%) completed the full durations of the trials (52 weeks). A total of 4 subjects were excluded from the ITT analysis set; these subjects were randomized in error and never received study drug. Within the ITT analysis set, the subjects had a mean (SD) age of 51.5 (11.4) years (range: 18-71 years), were primarily male (77.2%) and not Hispanic/Latino (83.6%). A majority of subjects were White (75.8%). The mean (SD) area of the affected toenail 9as a percent) was 36.5% (10.6) and the mean (SD) number of affected non-target toenails was 2.8 (1.6). There were no clinically meaningful differences between treatment groups in regard to demographics or baseline characteristics.

Table 8: Baseline Disease Characteristics

	Trial P3-01		Trial P3-02	
	IDP-108 N=656	**Vehicle** N=214	**IDP-108** N=580	**Vehicle** N=201
Mean percent (SD) of affected toenail	36.7 (10.4)	36.8 (10.6)	36.2 (10.7)	36.7 (10.5)
Mean number (SD) of affected non-target toenails	2.8 (1.7)	2.8 (1.7)	2.7 (1.6)	2.8 (1.7)
Screening Culture				
T. rubrum	604 (92%)	191 (89%)	540 (93%)	193 (96%)
T. mentagrophytes	47 (7%)	22 (10%)	33 (6%)	8 (4%)
E. floccosum	5 (1%)	0 (0%)	4 (1%)	0 (0%)
T. tonsurans	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
No dermatophyte	0 (0%)	1 (<1%)	2 (<1%)	0 (0%)

Source: Agency Biostatistical Review (Dr. Kathy Fritsch) and applicant study report

Reviewer's comment: *Baseline characteristics were generally balanced in the two studies. The majority of subjects were male (77.2%). Because trial P3-01 enrolled subjects in Japan, approximately 29% of subjects in that study were Asian, while only 2% of subjects in trial P3-02 were Asian.*

6.1.3 Subject Disposition

In the Phase 2 study (DPSI-IDP-108-P2-01), a total of 135 subjects were randomized to treatment across 11 investigational centers in Mexico. Overall, 117 (86.7%) subjects completed the study. The most frequent reported reasons for discontinuation were lost to follow-up (5.9%), AE (2.2%), and subject request (2.2%). None of the enrolled subjects were excluded from the ITT analysis set, but 24 subjects (17.8%) were excluded from the per-protocol (PP) analysis set. The most common reasons for exclusion from the PP analysis set were missing the Week 36 visit (15 of 24 subjects [62.5%]) followed by entry criteria violations (6 of 24 subjects [25%]).

In the combined Phase 3 clinical trial, a total of 118 investigational center participated in the trials across the US, Japan, and Canada. Overall, 1655 subjects were randomized to treatment (1239 in IDP-108 and 416 in Vehicle). Of these subjects 1436 (86.8%) completed the treatment phase of the studies (48 weeks) and 1420 (85.8%) completed the full duration of the studies (52 weeks). A total of 4 subjects were excluded from the ITT analysis set, these subjects were randomized in error and never received study drug. Separately, 330 subjects were excluded from the PP analysis set. This included 233 subjects in the IDP-108 group (18.8%) and 97 (23.3%) in the Vehicle group. Across both groups, the primary reason for exclusion from the PP analysis set were having missed the Week 52 visit (163 of the 330 subjects [49.9%]) or having the Week 52 visit that occurred out-of-window (84 of 330 subjects [25.5%]).

Reviewer's comment: *In general, acceptable numbers of subjects completed the clinical studies.*

6.1.4 Analysis of Primary Endpoint(s)

The Phase 2 study was not powered to show significance of the primary endpoint. This study indicated that both IDP-108 (with and without semi-occlusion) and IDP-108 5% were generally more effective than vehicle. The result of the Phase 2 trial revealed that there were no advantages in semi-occlusion, which led the applicant to use IDP-108 without occlusion in the Phase 3 clinical program.

Phase 3 Study DPSI-IDP-108-P3-01:

A total of 74 investigational centers in the US (34 center), Japan (33 centers), and Canada (7 centers) participated in this study. Overall 870 subjects were enrolled and included the ITT analysis set, 656 (75.4%) of whom were randomized to treatment with IDP-108 and 214 (24.6%) were randomized to treatment with Vehicle. There were no clinically significant differences in the demographics of the randomized arms (see above).

For the primary efficacy endpoint, 17.8% of the subjects in the IDP-108 group had "Complete Cure" at Week 52 compared with 3.3% of the subjects in the Vehicle group (p <0.001); an absolute difference of 14.5%.

Table 9: Analysis of the Primary Efficacy Endpoint at Week 52 (ITT subjects, DPSI-ISP-108-P3-01)

	IDP-108	Vehicle	
Number of subjects	656	214	
Complete Cure at Week 52 [a]			***P*-Value**
Success, n (%)	117 (17.8)	7 (3.3)	< 0.001 [b]
Failure, n (%)	539 (82.2)	207 (96.7)	

a A Complete Cure was defined as both 0% clinical involvement of the target toenail in addition to a Mycological Cure (negative KOH examination and a negative fungal culture of the target toenail)
b P-value from a Cochran-Mantel-Haenszel test, stratified by analysis center
Source: Agency Biostatistical Review (Dr. Kathy Fritsch) and applicant study report

Phase 3 Study DPSI-IDP-108-P3-02:

A total of 44 investigational centers in the US (36 centers) and Canada (8 centers) participated in this second Phase 3 clinical trial. Overall, 785 subjects were enrolled, four of whom were randomized in error, did not received study drug, and were not included in the ITT analysis set. Of the 781 subjects in the ITT analysis set, 580 (74.3%) were randomized to treatment with IDP-108 and 201 (25.7%) were randomized to treatment with Vehicle. There were no clinically significant differences in the demographics of the randomized arms.

For the primary efficacy endpoint, 15.2% of the subjects in the IDP-108 group had Complete Cure at Week 52 compared with 5.5% of the subjects in the Vehicle group (p <0.001); an absolute difference of 9.7%.

Table 10: Analysis of the Primary Efficacy Endpoint at Week 52 (ITT Subjects, DPSI-IDP-108-P3-02)

	IDP-108	**Vehicle**	
Number of subjects	580	201	
Complete Cure at Week 52 [a]			***P*-Value**
Success, n (%)	88 (15.2)	11 (5.5)	< 0.001 [b]
Failure, n (%)	492 (84.8)	190 (94.5)	

a A Complete Cure was defined as both 0% clinical involvement of the target toenail in addition to a Mycological Cure (negative KOH examination and a negative fungal culture of the target toenail)
b P-value from a Cochran-Mantel-Haenszel test, stratified by analysis center
Source: Agency Biostatistical Review (Dr. Kathy Fritsch) and applicant study report

Reviewer's comment: *IDP-108 was superior to vehicle on the primary efficacy endpoint of "Complete Cure" at Week 52 in both studies (p <0.001). For the ITT analysis, the primary method of handling missing data was LOCF. The results of the ITT and per protocol analyses were similar.*

Table 11: Complete Cure at Week 52 (PP Analysis)

Study P3-01		**Study P3-02**	
Efinaconazole N = 533	Vehicle N = 173	Efinaconazole N = 473	Vehicle N = 146
102 (19.1%)	7 (4.0%)	78 (16.5%)	7 (4.8%)
p<0.001		p<0.001	

Source: Agency Biostatistical Review (Dr. Kathy Fritsch) and applicant study report

The Phase 3 Studies Combined:

The combined Phase 3 clinical trials were similar in design and conducted simultaneously across a total of 74 investigational centers in the US, Japan, and Canada. Each study enrolled subjects of any race who were 18 to 70 years of age, and had clinical diagnoses of distal lateral subungual onychomycosis affecting at least one great toenail. The primary efficacy endpoint of "Complete Cure" at Week 52 was 16.6% in the IDP-108 versus 4.3% in the Vehicle group; an absolute difference of 12.3%.

Overall, 1655 subjects were randomized to treatment, including 1239 in the IDP-108 group and 416 in the Vehicle group. A total of 4 subjects were excluded from the ITT analysis set; these subjects were randomized in error and never received study drug. There were no notable

differences between the ITT and PP analysis sets in regard to either subject demographics or baseline characteristics (see above).

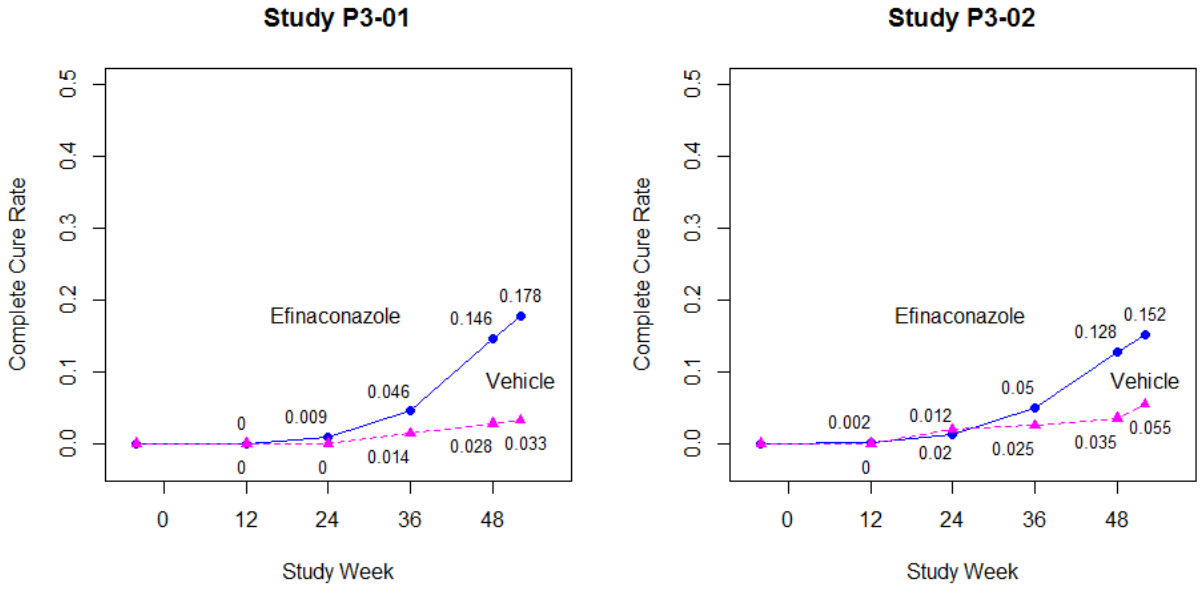
Table 12: Analysis of the Primary Efficacy Endpoint at Week 52 (ITT Subjects, Phase 3 Studies, Combined)

	IDP-108	Vehicle
Number of subjects	1236	415
Complete Cure at Week 52 [a]		
Success, n (%)	205 (16.6)	18 (4.3)
Failure, n (%)	1031 (83.4)	397 (95.7)

a A Complete Cure was defined as both 0% clinical involvement of the target toenail in addition to a Mycological Cure (negative KOH examination and a negative fungal culture of the target toenail)
Note: The last observation carried forward method was used to impute missing data prior to the analysis
Source: Table 14.2.2.2.1 in the Integrated Summary of Efficacy

The combined Phase 3 clinical trials showed a greater percentage of subjects in the IDP-108 group relative to the Vehicle group achieved a Complete Cure at Week 52 (16.6% versus 4.3%, respectively). Furthermore, analysis of the primary efficacy over time revealed that the percentage of subjects achieved "Complete Cure" was greater in the IDP-108 than in the Vehicle group by Week 36 (**Figure 2**).

Figure 2: Complete Cure Rates over Time (LOCF)



Source: Agency Biostatistical Review (Dr. Kathy Fritsch)

Although statistical comparisons between treatment groups were not performed at any of the study visits, these results show a trend towards increased efficacy in the IDP-108 treatment group versus Vehicle group.

Reviewer's comments:

- *The efficacy rate of 12.3% in the combined Phase 3 clinical trials is comparable to the other approved topical onychomycosis product (i.e., Penlac® (ciclopirox) Nail Lacquer). The potential advantage of this product over the approved Penlac® product is that a comprehensive program of nail debridement was deemed unnecessary.*
- *In regards to the validity of the clinical trial due to the clinical drug batch quality, it is likely that the leakage of the clinical trial samples did not substantially affect the results of the Phase 3 clinical trial.*
- *The application of the drug product in real-life conditions can obviate the variability of the drug concentrations, as random applications of the drug product by patients can change the penetration of the drug. It is possible that the variance of the drug product quality, though within specifications, described in the CMC review does not substantially affect the results of safety or efficacy of the final drug product.*
- *As the quality and concentration of the drug product in the Phase 3 clinical trials seems to fall within the acceptable CMC range (as discussed in the CMC section), this reviewer does not question the validity of the clinical trials conducted at this time.*

6.1.5 Analysis of Secondary Endpoints(s)

The applicant proposed two statistical analysis plans (SAPs) for the Phase 3 clinical trials which differed in the definition and ordering of the secondary supportive endpoints. The first SAP reflected the way the secondary endpoints had been defined in the protocol. The three secondary endpoints were originally specified as follows:

- Clinical efficacy rate at Week 52 (<10% affected target nail area)
- Mycological cure rate at Week 52 (negative KOH and culture)
- Unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement)

The second version of the SAP introduced a new secondary endpoint, removed one secondary endpoint, and rearranged the ordering of the secondary endpoints. The new list of secondary endpoints was as follows:

- Complete or almost complete cure rate at Week 52 (≤5% affected target nail area and negative KOH and culture)
- Unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement)
- Mycological cure rate at Week 52 (negative KOH and culture)

According to the Agency biostatistical review, the applicant approved both SAPs prior to database lock. "Although the protocols were not reviewed under a Special Protocol Assessment,

the Agency had expressed no disagreement with the applicant's original list of secondary endpoints when the protocols were reviewed."

Reviewer's comments: The secondary endpoints were supportive to the primary efficacy of this drug product. All of the secondary endpoint meets the statistical significance criteria specified in the two SAPs. The endpoints discussed in this section are not useful clinically and will not be included in the product labeling. In addition," because of the concerns regarding the differences of the second SAP relative to the protocol, 'complete or almost complete cure' is not suitable for any efficacy claims, as we cannot be assured that the Type I error is adequately controlled for this endpoint."[8]

Phase 3 Study DPSI-IDP-108-P3-01:

Among the secondary efficacy variables, the clinical efficacy rate at Week 52 was 35.7% in the IDP-108 group compared with 11.7% in the Vehicle group (p <0.001). Additionally, 55.2% of the IDP-108 subjects had a Mycological Cure at Week 52 compared with 16.8% of Vehicle subjects (p <0.001). The mean unaffected new toenail growth at Week 52 was 5.0 mm in the IDP-108 group compared with 1.6 mm in the Vehicle group (p <0.001). Lastly, 26.4% of the IDP-108 subjects had a Complete or Almost Complete Cure at Week 52 compared with 7% of the Vehicle subjects (p <0.001).

Phase 3 Study DPSI-IDP-108-P3-02:

Among the secondary efficacy variables, the clinical efficacy rate at Week 52 was 31.0% in the IDP-108 group compared to 11.9% in the Vehicle group (p <0.001). Additionally, 53.4% of the IDP-108 subjects had a mycological cure at Week 52 compared with 16.9% of the Vehicle subjects (p <0.001). The mean unaffected new toenail growth at Week 52 was 3.8 mm in the IDP-108 group compared with 0.9 mm in the Vehicle group (p <0.001). Lastly, 23.4% of the IDP-108 subjects had a complete or almost complete cure at Week 52 compared with 7.5% of the Vehicle subjects (p <0.001).

8 Agency Biostatistical Review of NDA 203567 by Kathy Fritsch, PhD.

Table 13: Secondary Efficacy Endpoints Analysis

	Trial P3-01			Trial P3-02		
	IDP-108. N = 656	Vehicle N = 214	*p*-value	IDP-108. N = 580	Vehicle N = 201	*p*-value
Clinical Efficacy	234 (36%)	25 (12%)	<0.001	180 (31%)	24 (12%)	<0.001
Mycologic Cure	362 (55%)	36 (17%)	<0.001	310 (53%)	34 (17%)	<0.001
Unaffected new growth (mm)	5.0 (0.2)	1.6 (0.4)	<0.001	3.8 (0.2)	0.9 (0.4)	<0.001
Complete or almost complete cure*	173 (26%)	17 (7%)	<0.001	136 (23%)	15 (7%)	<0.001

*Endpoint specified in SAP version 2
Source: Agency Biostatistical Review (Dr. Kathy Fritsch)

In regards to the supportive secondary endpoints, the trends indicate greater efficacy for IDP-108 relative to Vehicle were observed in the analyses of clear nail, almost clear nail, clinical efficacy, and the change from baseline in the number of affected non-target toenails. These secondary endpoints are considered supportive to the primary efficacy.

Reviewer's comment: *In the opinion of this reviewer, the supportive secondary measures are not clinically relevant* (b) (4).

6.1.6 Other Endpoints

Finally, the applicant completed analyses of the OnyCOE-t questionnaire, where the subjects were asked to complete a quality of life questionnaire. The results were indicative of better outcomes compared with subjects in the Vehicle group. No formal statistical analyses were completed with the patient reported outcome questionnaire.

Reviewer's comment: *The OnyCOE-t questionnaire does not appear to have been validated or represent any clinical significance* (b) (4).

6.1.7 Subpopulations

The efficacy variables were not evaluated within subgroups in the Phase 2 study.

In the Phase 3 clinical trials, the primary efficacy endpoint was evaluated by treatment group within subgroups based on median age (<53 years and ≥53 years), sex, ethnicity, race, and median percent affected toenail area (<40% and ≥40%). In the pooled Phase 3 analyses, the subgroup trended towards a greater percentage of subjects in the IDP-108 group achieving Complete Cure versus subjects in the Vehicle group.

Table 14: Subset Analysis of the Primary Efficacy Endpoint (ITT Subjects Phase 3 Studies Combined)

Gender	**Males**		**Females**	
	IDP-108	Vehicle	IDP-108	Vehicle
Complete Cure at Week 52	(N=953)	(N=322)	(N=283)	(N=93)
Success	134 (14.1%)	12 (3.7%)	71 (25.1%)	6 (6.5%)
Failure	819 (85.9%)	310 (96.3%)	212 (74.9%)	87 (93.5%)
Age	**< 53 years**		**≥53 years**	
	IDP-108	Vehicle	IDP-108	Vehicle
Complete Cure at Week 52	(N=612)	(N=202)	(N=624)	(N=213)
Success	112 (18.3%)	9 (4.5%)	93 (14.9%)	9 (4.2%)
Failure	500 (81.7%)	193 (95.5%)	531 (85.1%)	204 (95.8%)
Ethnicity	**Hispanic/Latino**		**Not Hispanic/Not Latino**	
	IDP-108	Vehicle	IDP-108	Vehicle
Complete Cure at Week 52	(N=193)	(N=77)	(N=1042)	(N=338)
Success	41 (21.2%)	0 (0.0%)	164 (15.7%)	18 (5.3%)
Failure	152 (78.8%)	77 (100.0%)	878 (84.3%)	320 (94.7%)

A complete cure is defined as zero percent clinical involvement of the target nail (nail is totally clear) in addition to mycological cure./
Source: Applicants data, ISE

Despite varying subgroup sample sizes, within the IDP-108 groups, a greater trend towards efficacy was observed in female subjects compared with male subjects (25.1% success versus 14.1% success, respectively), in Asian subjects compared with white and black/African American subjects (24.5% success versus 14.7% success and 12.9% success, respectively), and in subjects who had less than 40% affected toenail area compared with subjects who had 40% or more affected toenail area (21.5% success versus 12.0% success, respectively). Subgroup differences based on age and ethnicity were not clearly indicative of any trends.

Reviewer's comment: *Treatment effects were generally consistent across gender, race, age, and country in both clinical trials. There were no clear trends in the subgroup analyses to require further evaluations.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Efinaconazole is a novel azole antifungal agent derived from a group of well-characterized azole class of antifungal therapeutics. Phase 2 dose-ranging and efficacy under semi-occlusion was conducted to provide information on proper application of treatment and to help power Phase 3 clinical trials. A maximal use pharmacokinetic study concluded low systemic penetration of this drug product. In the pivotal Phase 3 clinical trials, patients were instructed to place two drops, once daily of IDP-108 on the affected target toenail, and one drop once daily for any other infected toenails. The to-be-marketed drug product will be supplied in a (b) (4) fill squeeze bottle with a built-in flow-through brush applicator.

Reviewer's comment: *The dosing regimen is acceptable. Sufficient information for the use of the applicator to dispense the drug product on affected nails will be included in labeling.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

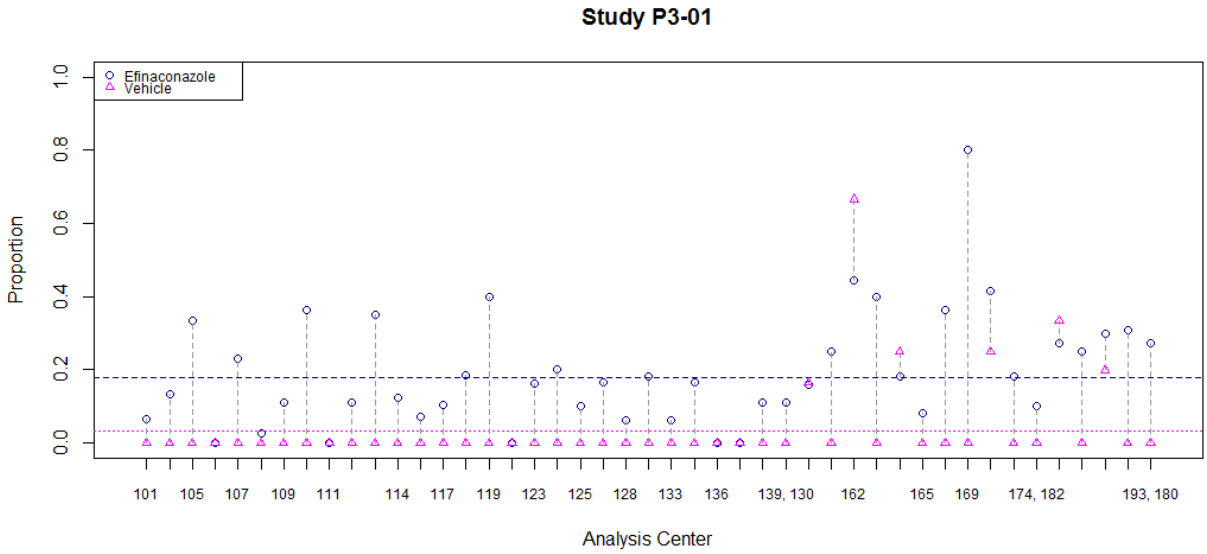
The efficacy of IDP-108 was evaluated from the Phase 2 and Phase 3 clinical studies. Subjects used the study drug for 48 weeks and the effects persisted through Week 52. The effects of the study drug were consistent in the studies. No assessments of persistence of efficacy were conducted and no tolerance effects were observed or evaluated.

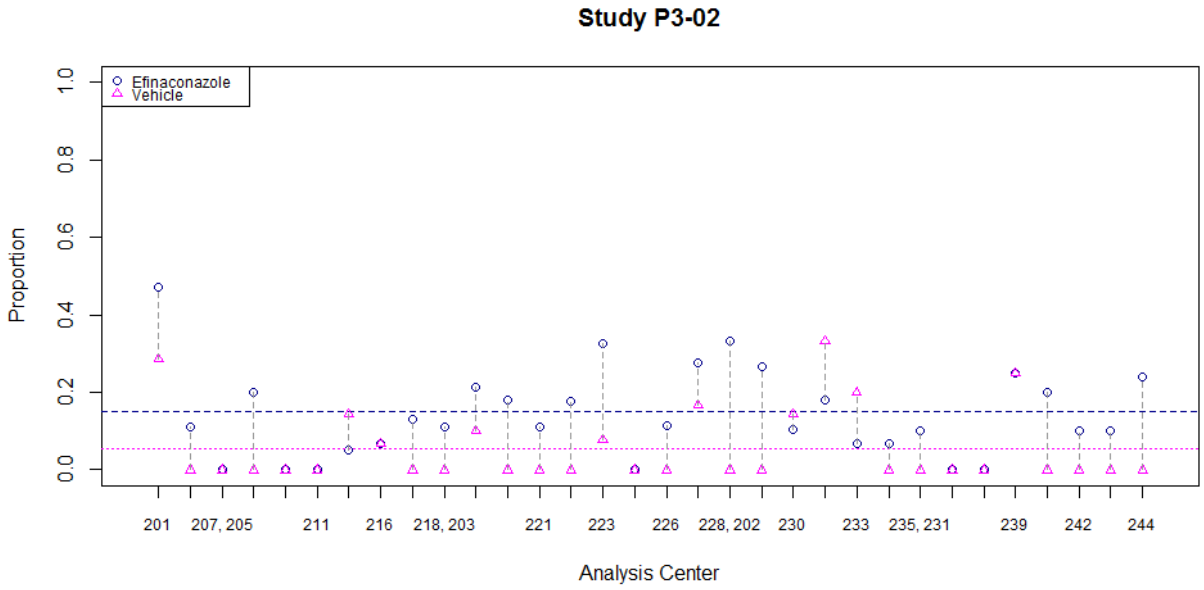
6.1.10 Additional Efficacy Issues/Analyses

Efficacy by Center:

The Agency biostatistical analysis conducted by Dr. Fritsch evaluated the efficacy by center. In clinical trial P3-01, 74 centers in the United States (34), Canada (7), and Japan (33) enrolled a total of 870 subjects. Small centers were pooled within country to ensure a minimum of nine IDP-108 and three vehicle subjects per analysis center. After the pooling algorithm was applied, Study P3-01 had 45 analysis centers (25 US, 4 Canadian, and 16 Japanese). Study P3-02 was conducted at 44 centers in the United States (36) and Canada (8). A similar pooling algorithm was applied leading to 32 analysis centers (26 US, 6 Canadian) in Study P3-02.

Figure 3: Complete Cure Rate by Analysis Center (Trials P3-01 and P3-02)





Source: Agency Biostatistical Review (Dr. Kathy Fritsch)

Because of the large number of centers and the low overall response rate on the vehicle arm no center is overly influential on the overall results.

Reviewer's comments:

- *The analyses conducted by Dr. Fritsch did not find any overly influential results from any specific center.*
- *The highest efficacy and enrollment center in each of the Phase 3 clinical trial was selected for DSI review. No significant findings were reported on the basis of DSI inspections.*
- *In conclusion, the statistical and collective evidence is adequate to determine that IDP-108 (efinaconazole) topical solution, 10% is effective for the topical treatment of toenail onychomycosis.*
- *Generally, topical drug products are difficult to develop for the treatment of onychomycosis. Aside from the currently marketed Penlac® (ciclopirox solution, 8%), there are no effective topical treatments for onychomycosis. The addition of this topical antifungal product to the armamentarium of treatment options would be beneficial to clinicians.*

7 Review of Safety

Safety Summary

The clinical program for JUBLIA™ (efinaconazole) Topical Solution, 10% included four Phase 1 studies, one Phase 2 study, and two Phase 3 clinical trials. The four Phase 1 studies support safety and the Phase 2 and Phase 3 studies support safety and efficacy (**Table 15**).

7.1 Methods

Due to the differences in study designs, subject populations, and study drug formulation of the Phase 1 study (DPSI-IDP-108-P1-01) and Phase 2 study (DPSI-IDP-108-P2-01), the results of these studies will be evaluated separately from the identical Phase 3 clinical trials. The safety population from the Phase 3 clinical trials will be pooled for analyses.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Seven clinical studies (four Phase 1, one Phase 2, and two Phase 3) are included in the evaluation of the safety of IDP-108. A total of 1663 subjects were exposed to various concentrations/formulations of IDP-108, and 1495 were exposed specifically to the to-be-marketed formulation of IDP-108 with an efinaconazole concentration of 10%.

Table 15: Summary of Studies Evaluated for Safety of IDP-108

Study	Objective(s)	Study Design	Treatment Groups and Mode of Administration	n	Type of subjects	Duration
DPSI-IDP-108-P1-01 (Phase 1)	To determine the comparative dermal irritation of seven test articles plus a positive and negative control	Single center, test side randomized, positive and negative control	IDP-108A, Solution (Vehicle, 1%, and 5% efinaconazole solution); 0.2% sodium lauryl sulfate; deinonized water Applied topically via 15 separate patch applications over 21 days	55	Healthy US subjects	21 days
DPSI-IDP-108-P1-02 (Phase 1)	To evaluate the systemic exposure and characterize the plasma PK profile of IDP-108 and its major metabolites	Single center, randomized, open-label, two-period crossover study	IDP-108 Applied topically each period via application to back skin on 8 days and as a toenail application on 8 other days	10	Healthy US subjects	28 days
DPSI-IDP-108-P1-03 (Phase 1)	To evaluate the safety and systemic exposure of IDP-108	Open-label, single center	IDP-108 Applied topically to the toenails, once daily for 28 days	20	US subjects	42 days
DPSI-IDP-108-P1-04 (Phase 1)	To evaluate IDP-108 and Vehicle for the induction of contact sensitization by repetitive application	Single center, double blind, vehicle controlled HRIPT study	IDP-108; Vehicle Applied topically via repeat patch application to the skin for 21 days, followed by a single challenge, and possibly a single re-challenge	239	Healthy US subjects	8 weeks
DPSI-IDP-108-P2-01 (Phase 2)	To evaluate the safety, PK profile, and	Multicenter, double blind, randomized,	IDP-108 (with and without semi-occlusion); IDP-108 5%; Vehicle	135	Subjects in Mexico	40 weeks

	efficacy of IDP-108	vehicle controlled, parallel group study	Applied topically to the toenails, once daily for 36 weeks			
DPSI-IDP-108-P3-01 (Phase 3)	To evaluate the safety and efficacy of IDP-108	Multicenter, double blind, randomized, vehicle controlled, parallel group study	IDP-108; Vehicle Applied topically to the toenails, once daily for 48 weeks	870	Subjects in US, Japan, and Canada	52 weeks
DPSI-IDP-108-P3-02 (Phase 3)	To evaluate the safety and efficacy of IDP-108	Multicenter, double blind, randomized, vehicle controlled, parallel group study	IDP-108; Vehicle Applied topically to the toenails, once daily for 48 weeks	785	Subjects in US, Japan, and Canada	52 weeks
KP-103-02 (Phase 1- non-IND)	To evaluate the skin irritation and photosensitization	Positive and negative controlled patch test following single application; evaluation of skin irritation following repeated application for 7 days	IDP-108 1%; IDP-108 5%; IDP-108; placebo (Vehicle); 0.2% sodium lauryl surface; deionized water Applied topically via test strips to the skin in a single application and as once daily application for 7 days	56	Healthy adult male subjects in Japan	7-12 days
KP-103-03 (Phase 1- non-IND)	To investigate efinaconazole solution concentrations in the affected versus normal toenails, as well as the great versus second toenail with different toenail thicknesses	Open-label study with repeated application of efinaconazole solution to all toenails	IDP-108 5%; IDP-108 Applied topically to the toenails, once daily for 28 days	41	Subjects in Japan	42 days

Source: Applicant's submission, ISS

7.1.2 Categorization of Adverse Events

Coding for adverse events employed different versions of MedDRA for the studies that comprised of the safety population. The pivotal Phase 3 clinical trials consistently used MedDRA Version 12.1 and this version was used in the combined analysis of the Phase 3 safety results.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In the Phase 2 study, 94 subjects (69.6%) reported 271 AEs. In general, less than 10% of the subjects in any treatment group reported events within a single system organ class. The exceptions were in the system organ classes of gastrointestinal disorders (reported by 9.1% to 15.8% of the subjects), general disorders and administrative site conditions (reported by 0.0% to 13.6% of the subjects), immune system disorders (reported by 0% to 11.1% of the subjects), infections and infestations (reported by 36.4% to 50.0% of the subjects), injury, poisoning, and procedural complications (reported by 5.6% to 18.4% of the subjects), musculoskeletal and connective tissue disorders (reported by 5.1% to 19.4% of the subjects), nervous system disorders (reported by 7.9% to 22.7% of the subjects), and skin and subcutaneous tissue disorders (reported by 9.1% to 18.4% of the subjects). Within these classes, however, the only individual events to be experienced by 10% or more of the subjects were influenza and headache. These events were not assessed by the investigators to be related to the study drug, were experienced by two to eight subjects across treatment groups, and were not indicative of a safety signal or trend

In the two Phase 3 clinical trials combined, 1640 subjects reported 2763 AEs; most of the events occurred in a relatively few number of subjects (less than 1% of the subjects in each treatment group). In general, similar percentages of subjects in each treatment group experienced similar types of AEs. A comparison of all AEs experienced by 1% or more of the subjects in either treatment group indicated that the percentages of subjects experiencing individual events was significantly different only for application site dermatitis, application site vesicles, and tinea pedis ($p \leq 0.006$ in all pair wise comparisons). The most commonly reported treatment-related events (i.e., AEs experienced by 1% or more of the subjects in either study drug group regardless of seriousness or severity) included application site dermatitis and application site vesicles. None of the 65 serious adverse events (SAEs) were treatment-related and most occurred in only one subject. Overall, 33 subjects, all but one of whom was in the IDP-108 group, discontinued either the study drug or the study because of an AE; most of the events were associated with application site reactions, and many of these were assessed as treatment-related. No safety signals or unexpected trends associated with the use of IDP-108 were observed in these studies.

Table 16: Adverse Events (Safety Population)

	Study P3-01		**Study P3-02**	
	IDP-108 N=653	Vehicle N=213	IDP-108 N=574	Vehicle N=200
Any Adverse Event	431 (66.0%)	130 (61.0%)	370 (64.5%)	117 (58.5%)
Serious Adverse Event	25 (3.8%)	6 (2.8%)	21 (3.7%)	1 (0.5%)
Discontinued due to AEs	21 (3.2%)	1 (0.5%)	11 (1.9%)	0 (0.0%)

Source: Applicant submission, ISS and study reports for P3-01 and P3-02.

Reviewer's comment: *On review of the most common adverse events experienced by 10% or more of the subjects, influenza and headache stood out. These events are generally experienced by the general population whether on medication or not. This reviewer does not believe that the study population experienced these adverse events greater than that of the general population. In addition, there is little rational plausibility that these events could be connected with the drug product, given the low systemic absorption and the proposed mechanism of action of this drug.*

7.2 Adequacy of Safety Assessments

The safety assessments included evaluation of adverse events, laboratory analysis, and ECG evaluations. Overall exposure is discussed in this section. Patient population and demographic were discussed in Section 6.1.2. Local safety events were the most commonly reported AEs. The safety assessments were adequate for a topical onychomycosis drug product.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, the seven principal studies included 2113 subjects, 1663 (78.7%) of whom were exposed to various concentrations/formulations of IDP-108 (original formulation or the to-be-marketed formulation with efinaconazole concentrations of 1%, 5%, or 10%), and 1495 (70.7%) of whom were exposed specifically to the to-be-marketed formulation of IDP-108 with an efinaconazole concentration of 10%.

In the Phase 2 study (DPSI-IDP-108-P2-01), a total of 135 subjects were enrolled and randomized to IDP-108 with semi occlusion (36 subjects), IDP-108 (39 subjects), IDP-108 5% (38 subjects), or Vehicle (22 subjects). This study used the original formulation and not the to-be-marketed formulation. All subjects administered the topical study drug as 1 or 2 drops on each of the 10 toenails. Subjects in the occlusive treatment group applied the semi-occlusive dressing to the target toenail after allowing the topical solution to dry; the dressing were worn for approximately 6 to 10 hours.

Table 17: Extent of Exposure (Safety Subjects, DPSI-IDP-108-P2-01)

	IDP-108 with Semi-occlusion	IDP-108	IDP-108 5%	Vehicle	Total
Number of days of application					
N	36	39	38	22	135
Mean (standard deviation)	231.2 (45.77)	225.7 (62.45)	237.6 (48.66)	219.7 (72.90)	229.5 (56.38)
Minimum to maximum	32.0 to 257.0	7.0 to 258.0	30.0 to 290.0	2.0 to 266.0	2.0 to 290.0
Total usage, gm					
N	36	39	38	22	135
Mean (standard deviation)	57.4 (37.06)	52.6 (36.70)	58.7 (31.19)	59.2 (41.80)	56.6 (35.92)
Minimum to maximum	5.3 to 148.5	0.0 to 130.9	3.7 to 127.9	0.0 to 147.8	0.0 to 148.5
Average monthly usage, gm/month					
N	36	39	38	22	135
Mean (standard deviation)	7.1 (4.15)	6.5 (4.16)	7.1 (3.36)	7.3 (4.75)	7.0 (4.02)
Minimum to maximum	1.2 to 17.8	0.0 to 15.6	1.5 to 14.1	0.0 to 17.6	0.0 to 17.8
Average daily usage, gm/day					
N	36	39	38	22	135
Mean (standard deviation)	0.24 (0.138)	0.22 (0.139)	0.24 (0.112)	0.24 (0.158)	0.23 (0.134)
Minimum to maximum	0.04 to 0.59	0.00 to 0.52	0.05 to 0.47	0.00 to 0.59	0.00 to 0.59

Source: Table 14.3.1.14 in DPSI-IDP-108-P2-01 Clinical Study Report

The mean number of days that subjects applied treatment within the IDP-108 with semi-occlusion, IDP-108, IDP-108 5%, and Vehicle groups, was 231.2, 225.7, 237.6, and 219.7, respectively. Overall, the mean amount of study drug applied by subjects did not vary across treatment groups.

Within the Phase 3 studies, subjects applied the to-be-marketed formulation of IDP-108 (with an efinaconazole concentration of 10%) once daily for up to 48 weeks. A total of 1227 subjects applied the active study drug at least once. In these studies combined, 1161 subjects applied the active study drug for at least 24 weeks (i.e., 6 months), 1115 subjects applied the active study drug for at least 36 weeks (i.e., 9 months), and 780 subjects applied the active study drug for at least 48 weeks (i.e., nearly a year of once daily exposure to the study drug).

Table 18: Extent of Exposure—Dosing Compliance (Safety Subjects, Phase 3 studies Combined)

	IDP-108	Vehicle
Number of subjects	1227	413
Number of applications		
N	1180	386
Mean	316	313.7
Standard Deviation	52.8	60.3
Median	332	333
Minimum to maximum	1.0 to 365	1.0 to 378
Amount of study drug used, gram		
N	1069	353
Mean	49.3	51.3
Standard Deviation	23.8	23.7
Median	47.2	51.1
Minimum to maximum	0.4 to 150.5	0.3 to 121.5
Exposure, n (%)		
≥ 1 Day	1227 (100)	413 (100)
≥ 12 Weeks	1203 (98)	394 (95.4)
≥ 24 Weeks	1161 (94.6)	376 (91)
≥ 36 Weeks	1115 (90.9)	365 (88.4)
≥ 48 Weeks	780 (63.6)	257 (62.2)
≥ 52 Weeks	3 (0.2)	1 (0.2)

Source: Table 14.3.0.1 in Appendix 12.1 (Application)

Of the 1655 enrolled subjects, 1436 (86.8%) completed the treatment period of the study (48 weeks) and 1420 (85.8%) completed the entire study (52 weeks). There were no significant differences in clinical exposure between active drug and vehicle.

Reviewer's comment: *Subjects in the IDP-108 and Vehicle arms used similar amounts of study treatment. Sufficient drug exposure to the patient population was observed.*

7.2.2 Explorations for Dose Response

Exploration of dose-response was conducted in Phase 1, as a non-IND study (KP-103-03). The study evaluated efinaconazole solution in concentrations of 5% and 10% (marketed formulation) in affected versus normal toenails, as well as the great versus second toenail with different toenail thicknesses. This was an open-label study with 41 subjects conducted in Japan. It was concluded that patients tolerated the 5% and 10% concentrations equally and there were no differences in observed adverse events. The plasma concentration of the drug was consistent and did not readily transfer into the blood.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was conducted.

7.2.4 Routine Clinical Testing

Routine clinical testing included laboratory assessments, physical examinations, vital signs, and ECGs (in a subpopulation). Overall, the observed vital sign measurements, ECG findings, and physical examinations provided no clinically meaningful deviations. There were no signs of QT interval prolongation observed.

7.2.5 Metabolic, Clearance, and Interaction Workup

Pharmacokinetic evaluations of efinaconazole and its metabolites (H3 and H4) were variously conducted in studies DPSI-IDP-108-P1-02, DPSI-IDP-108-P1-03, and DPSI-IDP-108-P2-01. PK evaluations were not included in the Phase 3 clinical trials.

In study DPSI-IDP-108-P1-03, subjects applied IDP-108 once daily for 28 days to all 10 toenails (maximal use study). By the end of the treatment period, the mean concentrations of the H3 metabolite 2.4 ng/mL and the efinaconazole concentration was barely detectable (0.669 ng/mL). The H4 metabolite showed no meaningful systemic availability with a mean maximum concentration less than 0.05 ng/mL.

In study DPSI-IDP-108-P2-01, onychomycosis subjects applied IDP-108 5% (with and without occlusion) and Vehicle to their toenails once daily for 36 weeks. A majority of the subjects within each active treatment group had measureable levels of efinaconazole and H3 metabolite at the beginning of Week 4 which persisted until the end of the treatment period at Week 36. The efinaconazole plasma concentrations measured across all active treatment groups were less than or equal to 7.050 ng/mL at all time points. The H3 metabolite plasma concentrations measured across all active treatment groups were less than or equal to 5.680 ng/mL at all time points. By the follow-up visit (30 day post-treatment), the efinaconazole and H3 metabolite concentration levels were below the limit of quantification in a majority of the subjects in the active treatment groups.

None of the clinical studies conducted with IDP-108 evaluated the potential for drug interactions. Azole antifungals are known to inhibit cytochrome P (CYP) enzymatic activity. The major plasma metabolite of efinaconazole, H3, has much less CYP inhibition activity. Due to the topical application, this drug product has low systemic exposure, and, hence, limited potential for drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Penlac® Nail Lacquer (ciclopirox) Topical Solution, 8% is the only US approved topical onychomycosis treatment. The label lists the most common adverse reactions as “rash-related”.

These adverse events include: periungual erythema and erythema of the proximal nail fold. Other treatment related adverse events that are causally related to the drug include nail disorders such as shape change, irritation, ingrown toenail, and discoloration. Application site reactions and/or burning of the skin occurred in 1% of patients treated with Penlac®.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the Phase 1 or Phase 2 studies. Two subjects, one in each of the Phase 3 studies, died and the events are unlikely related to the study drug. One subject (b) (6) after being lost to follow-up (subject 119-004). The other subject (subject 218-021) died due to lung squamous cell carcinoma (stage unspecified).

Subject 119/004:

A 48 year old female with onychomycosis was randomized to the IDP-108 treatment group on January 18, 2011. On study Day (b) (6) She was last seen in the clinic for study visit on October 6, 2010 and was lost to follow-up after. Additional information is not available. The investigator was not aware of any relevant past history or attempted suicide (b) (6)

Subject 218/021:

A 46 year old male with onychomycosis randomized to the IDP-108 group on September 9, 2010. On study Day (b) (6) he was diagnosed with squamous cell carcinoma of the lung. On (b) (6), a PET scan revealed he had metastasis to the brain and radiation treatment was initiated. The patient was withdrawn from the IDP-108 study on September 21, 2010 and died on (b) (6)

Reviewer's comment: *The majority of AEs related to investigational drug product are application site reactions, some of which caused discontinuation of study drug or study. The two deaths involved in the Phase 3 clinical trials are unlikely related to investigational drug. The first subject died of (b) (6). It is unlikely that a topical antifungal with low systemic absorption would cause (b) (6) In the second case of squamous cell carcinoma, the advance stage of the disease and metastasis tells this reviewer that the patient likely had undiagnosed lung cancer prior to the start of the onychomycosis trial. It is unlikely that this drug product increased the likelihood of metastasis or caused the squamous cell lung cancer.*

7.3.2 Nonfatal Serious Adverse Events

Study DPSI-IDP-108-P2-01 was a Phase 2, multicenter, randomized, double-blind, vehicle controlled, parallel-group safety and efficacy study included 135 adult subjects randomized (2:2:2:1) to receive IDP-108 with semi-occlusion, IDP-108 (without occlusion), IDP-108 5%, or Vehicle. Subjects applied the assigned study drug once daily to all 10 toenails for 36 weeks. All subjects had clinical diagnoses of stable or exacerbating distal lateral subungual onychomycosis affecting at least 1 great toenail.

Five subjects reported a total of seven SAEs, all of which were assessed by the investigators as unrelated to the study drugs. None of the SAEs resulted in subject discontinuation. Separately, three subjects (2.2%) discontinued due to mild to moderate AEs that were assessed by the investigators to be unrelated to the study drugs. Four treatment-related AEs were reported (three in the IDP-108 5% group [blister, contact dermatitis, and erythema] and one in the IDP-108 group [ingrown nail]). None of the related AEs resulted in subject discontinuation from the study.

Table 19: Serious Adverse Events (Safety Subjects, DPSI-IDP-108-P2-01)

System Organ Class, n (%) Preferred Term n (%)	IDP-108 with semi-occlusion (N=36)	IDP-108 (N=39)	IDP-108 5% (N=38)	Vehicle (N=22)
Gastrointestinal disorders	0	0	1 (2.6)	0
Inguinal hernia	0	0	1 (2.6)	0
Infections and infestations	0	1 (2.6)	1 (2.6)	0
Gastrointestinal infection	0	0	1 (2.6)	0
Papilloma viral infection	0	1 (2.6)	0	0
Musculoskeletal and connective tissue disorders	1 (2.8)	0	0	0
Back pain	1 (2.8)	0	0	0
Nervous system disorders	1 (2.8)	0	0	0
Arachnoiditis	1 (2.8)	0	0	0
Nerve root lesion	1 (2.8)	0	0	0
Reproductive system and breast disorders	1 (2.8)	0	0	0
Uterine polyp	1 (2.8)	0	0	0

Source: Table 14.3.1.8 in the DPSI-IDP-108-P2-01 Clinical Study Report

In the two identical, multicenter, randomized, double-blind, vehicle controlled, parallel group Phase 3 clinical trials (DPSI-IDP-108-P3-01 and DPSI-IDP-P3-02), the safety and efficacy of IDP-108 relative to Vehicle in subjects with mild to moderate onychomycosis of the toenails was evaluated. Subjects were randomized (3:1) to received IDP-108 or Vehicle, and all subjects applied the study drug to their affected toenails once daily at bedtime for 48 weeks. A combined 1227 subjects were randomized to IDP-108. Fifty-one (51) subjects (44 in the IDP-108 group and 7 in the Vehicle group) experienced 63 non-fatal SAEs; 2 additional subjects (both in the IDP-108 group) experienced a fatal SAE.

Of the 63 (2.4%) non-fatal SAEs, all but 5 were experienced uniquely by a single subject. The percentage of subjects who experienced AEs and SAEs was slightly greater in the IDP-108 group than in the Vehicle group (65.3% vs. 59.8% and 3.7% vs. 1.7%, respectively). The most commonly reported treatment-related events included application site dermatitis and application site vesicles.

Table 20: Serious Adverse Events Occurring in More than One Subject (Safety Subjects, Phase 3 Studies Combined)

	IDP-108 (N=1227)	Vehicle (N=413)
System Organ Class, n (%) Preferred Term, n (%)		
Cardiac disorders	8 (0.7)	0
Coronary artery disease	2 (0.2)	0
Myocardial infarction	2 (0.2)	0
Musculoskeletal and connective tissue disorders	6 (0.5)	1 (0.2)
Osteoarthritis	3 (0.2)	0
Nervous system disorders	5 (0.4)	0
Intracranial aneurysm	2 (0.2)	0
Respiratory, thoracic and mediastinal disorders	3 (0.2)	0
Pulmonary embolism	3 (0.2)	0

Source: Table 14.3.1.2.9

The individual SAEs of coronary artery disease, myocardial infarction, and intracranial aneurysm were each experienced by 2 subjects in the IDP-108 group, and the individual SAEs of osteoarthritis and pulmonary embolism were each experienced by 3 subjects in the IDP-108 group. No individual SAE was experienced by more than one subject in the Vehicle group.

Reviewer's comments: *The SAEs experienced by the subjects in the combined Phase 3 clinical trials are unlikely related to study drug. None are recommended for labeling by this reviewer.*

7.3.3 Dropouts and/or Discontinuations

In the two Phase 3 studies combined, 33 subjects (32 in IDP-108 and 1 in the Vehicle group) discontinued either the study drug or the study because of 21 AEs. Most of the events that led to discontinuation were associated with application site reactions, many of which were treatment related. Of the 21 events, only eight occurred in more than one subject and only one occurred at an incidence of more than 1% (application site dermatitis, 1.1%).

Table 21: Summary of Adverse Events that Led to Discontinuation of the Study Drug and/or Discontinuation of the Study (Safety Subjects, Phase 3 Studies Combined)

	IDP-108 (N=1227)	Vehicle (N=413)
Subjects who discontinued the study drug and/or the study due to adverse events, n (5)	32 (2.6)	1 (0.2)
Adverse Event, n (%)		
Acute psychosis	1 (0.1)	0
Application site dermatitis	13 (1.1)	0
Application site eczema	2 (0.2)	0
Application site erythema	4 (0.3)	0
Application site exfoliation	1 (0.1)	0
Application site irritation	2 (0.2)	0
Application site pain	1 (0.1)	0
Application site pruritis	3 (0.2)	0
Application site reaction	1 (0.1)	0
Application site swelling	3 (0.2)	0
Application site vesicles	6 (0.5)	0
Blood glucose abnormal	1 (0.1)	0
Dermatitis	1 (0.1)	0
Dermatitis contact	2 (0.2)	0
Headache	1 (0.1)	0
Intracranial aneurysm	1 (0.1)	0
Lung squamous cell carcinoma stage unspecified	1 (0.1)	0
Lymphadenopathy	1 (0.1)	1 (.02)
Osteoarthritis	0	0
Prostate cancer	1 (0.1)	0
Ventricular extra systoles	1 (0.1)	0

Source: Table 14.3.1.2.2

Reviewer's comment: *Subjects in the IDP-108 arm had a higher rate of administration site adverse reactions than subjects in the Vehicle arm. The adverse events that led to discontinuation can be captured adequately in labeling. The most common are treatment site dermatitis, vesicles, and erythema.*

7.3.4 Significant Adverse Events

Overall, IDP-108 was well tolerated and no safety signal or trends were observed based on AEs reported among subjects exposed to IDP-108 in the various concentrations and formulations. In the Phase 2 study, 94 subjects (69.6%) reported 271 AEs. In general, less than 10% of the subjects in any treatment group reported events within a single organ class.

In the two Phase 3 studies combined, 1640 subjects reported 2763 AEs; most of the events occurred in a relatively few number of subjects (less than 1% of subjects in each treatment

group). A comparison of all AEs experienced by 1% or more of the subjects in either treatment group indicated that the percentages of subjects experiencing individual events was significantly different only for application site dermatitis, application site vesicles, and application site pain.

Table 22: Adverse Events Reported by at Least 1% of Subjects (Safety Population)

	IDP-108 (N=1227)	Vehicle (N=413)
Adverse Event, n (%) [a]		
Application site dermatitis	27 (2.2)	1 (0.2)
Application site vesicles	20 (1.6)	0 (0.0)
Application site pain	13 (1.1)	1 (0.2)
Ingrown nail	28 (2.3)	3 (0.7)
Contact dermatitis	27 (2.2)	6 (1.5)
Eczema	25 (2.0)	7 (1.7)
Rash	13 (1.1)	1 (0.2)

a Counts reflect numbers of subjects reporting one or more adverse events using the MedDRA preferred term. Subjects are only counted once

Source: Table 14.3.1.2.6 in Appendix 12.1 (Applicant) and Agency Biostatistical Review (Dr. Kathy Fritsch)

The most commonly reported treatment-related events included application site dermatitis and application site vesicles. None of the 65 serious adverse events (SAEs) were deemed treatment-related. Thirty-three (33) subjects discontinued the study drug or the study because of an AE; most of the events were associated with application site reactions.

Reviewer's comment: *There are few safety concerns regarding this topical onychomycosis drug product. Other adverse events described in greater than 1.5% of the safety population includes common population events. These include nasopharyngitis (12.2%), upper respiratory tract infections (6.2%), sinusitis (4.0%), and headache (3.3%). These common adverse events are in line with the occurrence in the general population and are unlikely related to the study drug. The adverse events related to the study drug can be adequately captured in labeling.*

7.3.5 Submission Specific Primary Safety Concerns

Only mild to moderate topical safety issues are associated with this drug product. There are no systemic safety concerns.

7.4 Supportive Safety Results

Supportive Phase 1 safety studies included cumulative irritation and contact sensitization. In addition, the sponsor provided the safety data from two non-IND studies. These studies were Phase 1 irritation and photosensitization, and a dose ranging study with different concentrations of IDP-108. None of the supportive safety results provided any significant clinical safety concerns with IDP-108.

7.4.1 Common Adverse Events

The adverse events associated with the supportive safety studies are discussed in section 7.4.5.

7.4.2 Laboratory Findings

Routine clinical laboratory testing was conducted in Phase 1, Phase 2, and Phase 3 studies. Only the Phase 3 clinical trials will be pooled for analysis.

In the four Phase 1 studies, laboratory evaluations were conducted as part of the safety assessments in three of the Phase 1 studies. No clinically significant abnormal laboratory values were observed for any subject in either the IND studies or the two non-IND studies.

In the maximum use study (DPSI-IDP-108-P1-03), blood and urine sample were collected for routine clinical laboratory tests (hematology, chemistry, and urinalysis) at Screening, Day 0, Day 14, Day 29, and at the two-week post-treatment follow visit. In this study, no mean changes in laboratory parameters over time and no shifts in the percentages of subjects who had normal values at baseline. No laboratory results were reported as an AE.

Reviewer's comment: *There were no trends or safety signals reported based on the review of Phase 1 laboratory data.*

In the Phase 2 study (DSPI-IDP-108-P2-01), blood and urine were collected from the subjects at Screening, Baseline, and Weeks 4, 8, 12, 24, and 36 for clinical laboratory analyses. Fourteen subjects had chemistry parameter values that exceeded Grade 2 (CTCAE). Five subjects had abnormal ALT and four subjects had increase total bilirubin. Three subjects had abnormal hemoglobin findings. All subjects continued to receive study drug and completed the study.

Reviewer's comment: *On review of the Grade 2 (CTCAE) abnormalities, the majority of liver function abnormalities were elevations without other factors. This reviewer suspects they are transient fluctuations and are unlikely to be related to study drug. Furthermore, on review of the clinical pharmacology and clinical toxicology data, the maximum drug exposure under maximal-use conditions had ~ 10 fold margin of safety based on animal toxicity data. Based on this information, further evaluations of laboratory findings are not recommended,* (b) (4) ..

In the Phase 3 clinical trials, blood and urine samples were collected (hematology, serum chemistry, and urinalysis) at Screening, Weeks 12, 24, 36, and 48. On review of the parameters, no individually significant changes to the results reported as AEs. Slight changes to the mean were observed, but no trends were apparent between IDP-108 and Vehicle groups.

7.4.3 Vital Signs

In the two Phase 3 clinical trials, subjects applied either IDP-108 or Vehicle to their toenails once for 48 weeks and were followed for an additional four weeks after cessation of treatment. Descriptive statistics were used to evaluate changes from baseline to Weeks 12, 24, 36, and 48 in systolic and diastolic blood pressure, heart rate, body temperature, and respiratory rate.

Across all assessments at all time points in each treatment group, the mean changes (combined) in systolic and diastolic blood pressures ranged from -0.5 to 1.3 mmHg, the mean change sin heart rate ranged from -0.9 to 0.1 bpm, the mean changes in body temperature ranged from 0.0°C to 0.1°C, and the mean changes in respiratory rate ranged from -0.3 to 0.0 breaths/min. No clinically relevant differences were observed between treatments groups in any vital sign parameters based on changed from baseline to any subsequent study visit at which measurements were obtained.

7.4.4 Electrocardiograms (ECGs)

The applicant requested a waiver for a TQT study under the IND during development. The waiver request was reviewed by Dr. Brenda Vaughan (see review in DARRTS dated 03/18/2010 under IND 077732). According to Dr. Vaughan, CDER's DCRP QT Interdisciplinary Review Team was consulted who took into consideration the PK results from Study DPSI-IDP-108-P1-02, that was conducted in 10 healthy subjects by applying the drug to healthy nails or back. Additionally, no potential for IDP-108 to delay cardiac repolarization (based on hERG inhibition, tissue distribution, cardiovascular safety pharmacology and ECG analysis in chronic studies) were identified. Although results from Study DPSI-IDP-108-P1-02 were considered inconclusive, the QT Interdisciplinary Review Team recommended a waiver of TQT study based on the fact that the bioavailability of IDP-108 and H3 metabolite were low. The team however, recommended that periodic ECGs should be collected in all Phase 3 trials.

In the two Phase 3 clinical trials, 12-lead ECGs were obtained at Baseline, Week 4, and Week 48 for subjects who were enrolled at investigational centers in the US and Canada. Overall, ECGs were obtained at Baseline for 233 subjects in the IDP-108 group and for 78 subjects in the Vehicle group. Analysis of QTc interval prolongation associated with the use of IDP-108 versus Vehicle was conducted. Secondary analysis included heart rate, respiration rate, PR, QRS, QT, QTcB, and QTcF. The analyses showed no clinically or statistically significant ECG changes between the IDP-108 group compared to the Vehicle group after 4 and 48 weeks of treatment.

Reviewer's comment: *The narratives and ECG data was reviewed. This reviewer agrees with the applicant's analysis. No significant ECGs findings for prolonged QTc interval or large cardiovascular effects were seen. Heart Rate, PR interval, and QRS interval was generally consistent. This reviewer did not notice any clinically significant cardiovascular effects in the treatment group to warrant further evaluations.*

In addition to the ECGs collected during clinical trials, the PK studies contributed to the evaluation of systemic cardiac effects. As discussed in the Clinical Pharmacology Review, the maximal use PK study showed that the mean Cmax of IDP-108 was above the sub-nanomolar range (0.67 ng/mL). The data used for the decision to granted the TQT waiver was from the healthy subject PK study, which observed a 5-fold higher systemic level than the maximal use study. Given that that no hERG inhibition was observed, the waiver for TQT study was granted.

Reviewer's comment: *Sufficient cardiac safety data is presented by the applicant.*

7.4.5 Special Safety Studies/Clinical Trials

Four dermal safety studies were conducted to support the safety of IDP-108. A waiver was granted by the Agency for the phototoxicity and photoallergenicity studies. The submitted spectra for IDP-108A solutions, 5% and 10% w/w, and the IDP-108 (CAED) solutions, 1% and 10%, and their excipient do not demonstrate any absorbance in the wavelength range of 290 to 700 nm.

Study DPSI-IDP-108-P1-01 (Phase 1)
This study determined the comparative dermal irritation of seven test articles (IDP-108A Solution [the original formulation of IDP-108]: Vehicle, and 1%, 5%, and 10% efinaconazole solutions; IDP-108B Solution [a formulation used only in this study]: Vehicle, and 1% and 5% efinaconazole solutions) plus a positive and negative control (0.2% sodium lauryl sulfate and deionized water, respectively). Fifty-five subjects were enrolled and applied 15 separate study patches over a 21-day period. Two subjects experienced three AEs (seasonal allergy, sinus disorder, and dizziness). Only the dizziness was recorded as serious, which resulted in the subjects discontinuation from the study. Separately, five subjects discontinued the study due to reactions to the occlusive tape. There were no trends associated with the observed AEs that would affect the safety evaluation of IDP-108.

Study DPSI-IDP-108-P1-02 (Phase 1)
This study evaluated the systemic exposure and characterized the plasma pharmacokinetic (PK) profile of IDP-108 (the to-be-marketed formulation) and its major metabolites. This was a two-period crossover study in 10 healthy subjects (U.S.) that applied the study drug topically to the back skin on eight days and as a toenail application on eight other days. One subjects experienced a rash on the back near the drug application site. No other treatment related AEs were reported during the study and no subjects discontinued the study for any reason.

Study DPSI-IDP-108-P1-P3 (Phase 1)
This study evaluated the safety and systemic exposure of IDP-108 (the to-be-marketed formulation) in an open-label fashion of 20 subjects with onychomycosis of the toenails. The study drug was applied topically to the toenails once daily for 28 days. Of the 19 subjects who applied IDP-108, four experienced at least one AE. None of the events were serious or related to the study drug. All four events resolved, tow with the use of concomitant therapy and two without the need for corrective treatment. One event was severe (skin laceration) . No subjects

discontinued use of the study drug, had a change in the frequency of study drug application, or discontinued from the study because of an AE.

Study DPSI-IDP-108-P1-04 (Phase 1)
This study evaluated the potential of IDP 108 (the to-be-marketed formulation) and Vehicle for the induction of contact sensitization by repetitive application. In this human repeat insult patch test (HRIPT) study, 239 healthy subjects applied the randomized study drug via repeat patch application to the skin for 21-days; followed by a single challenge and possibly, a single re-challenge application. Twenty-one subjects reported a total of 23 AEs and 5 SAEs. The AEs showed no specific trends. The only events that occurred in more than 1 subject were tape dermatitis (2 subjects) and cold (2 subjects). There were no trends associated with the SAEs (**Table 23**).

Table 23: Summary of Serious Adverse Events (P1-04)

Verbatim Adverse Event Term	Number of Subjects, n (%) (N=239)
Serious Adverse Events, n (%)	
Coronary artery disease	1 (0.4)
Seizure	1 (0.4)
Colon infection	1 (0.4)
Pneumonia	1 (0.4)
Leg numbness	1 (0.4)

Source: Section 10.9.5 and Section 10.9.7 in the DPSI-IDP-108-P1-04 Clinical Study Report

Reviewer's comment: *The safety studies conducted are appropriate. The adverse events in the Phase 1 studies are not significant. The dermal safety studies are conducted in accordance with the current recommendations from the Agency*.

7.4.6 Immunogenicity

No studies were conducted for immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the non-IND dose ranging study (KP-103-03), no specific AEs were associated with the higher concentration of the study drug. There were no trends associated with the observed AEs.

7.5.2 Time Dependency for Adverse Events

Time dependency for AEs was not explored.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not explored.

7.5.4 Drug-Disease Interactions

Susceptibility to onychomycosis is not related to sex, race, or ethnicity, although the prevalence increases with age. None of the clinical trials conducted with IDP-108 showed any safety signals or trends that revealed drug-disease differences.

7.5.5 Drug-Drug Interactions

The drug-drug interaction studies were reviewed by the Clinical Pharmacology reviewer. Dr. Shukla's review provides the information described here.

"The applicant provided information on drug metabolism and addressed the potential for drug-drug interaction. In-vivo, H3 was the major metabolite in human plasma but it is inactive. In-vitro, H4 was the major metabolite and it is active. In-vivo H4 was quantifiable only in 4 subjects and in those subjects it was present < 25% of the parent compound based on the ratio of the AUCs (Mean ratio = 0.14). All other metabolites were formed in very low levels in-vivo, and did not warrant further investigation. Multiple CYP enzymes were involved in efinaconazole metabolism with CYP2C19 and CYP3A4 identified as the primary isozymes.

Efinaconazole reversibly inhibited CYP2C8, CYP2C9, CYP2C19 and CYP3A4 and there was minimal inhibition of CYP1A2, CYP2E1, CYP2D6 and CYP2A6 activity. The major metabolite H3, had much less CYP activity. Efinaconazole was not an inducer of CYP1A2 or CYP3A4 in human hepatocytes in-vitro. The levels of efinaconazole following administration to patients with onychomycosis under maximal use conditions were low and the risk of CYP mediated drug-drug interaction appears to be low."

In the maximal use PK trial (DPSI-IDP-108-P1-03) the highest steady state C_{max} on Day 28 was 1.47 ng/mL for parent (mean C_{max} = 0.67 ng/mL) and 7.45 ng/mL for H3 (mean C_{max} = 2.4 ng/mL). These concentrations were low with the R value (1 + [I]/Ki) below 1.1 (based on in-vitro efinaconazole CYP inhibition data for the most sensitive isoform was CYP2C9 with K_i of 0.26 μM or 91 ng/mL and the R value was 1.007). Hence, the potential for drug interactions due to CYP inhibition is unlikely. Therefore, further in-vivo evaluations were not undertaken.

Efinaconazole was not an inducer of CYP1A2 or CYP3A4 in human hepatocytes in vitro at concentrations as high as 350 ng/mL. The mean steady state plasma levels in onychomycosis patients under maximal use conditions on day 28 was 0.67 ng/mL, efinaconazole is not expected to induce CYP1A2 and CYP3A4 in vivo. The Sponsor did not evaluate the induction potential on CYP2B6.

Reviewer's comment: *No other drug-drug interaction studies are recommended. Labeling should include a discussion of the efinaconazole as a non-inhibitor of the CYP450 enzyme family. The available drug-drug interaction assessments are adequate for eventual labeling.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed. Please see the Pharmacology/Toxicology section for a brief description of the animal carcinogenicity study.

7.6.2 Human Reproduction and Pregnancy Data

The Phase 3 clinical trials excluded the participation of pregnant women. Nursing women were similarly not included in the studies. There is no information available for the use of IDP108 in pregnant or lactating women.

Reviewer's comment: *This drug product should be labeled to reflect the lack of data available for use in pregnant or lactating women.*

7.6.3 Pediatrics and Assessment of Effects on Growth

The PeRC meeting was held on January 23, 2012 to discuss efinaconazole solution, 10%. (b) (4) The Agency will request a pediatric plan with elements to include a maximal use PK, safety, and efficacy study in patients 6-17 years of age, or a rationale why those studies cannot be reasonably conducted.

Onychomycosis in infants and small children under the age of 6 is rare. A partial waiver is recommended by this reviewer as well as PeRC for children under the age of 6 years.

No assessment of effects on growth was evaluated, but this reviewer concurs that this is unnecessary given the pharmacokinetics of the product as discussed above.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no overdose, drug abuse potential, or withdrawal and rebound issues for this drug product.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

No post-marketing experience is available; efinaconazole is not currently marketed in any country.

9 Appendices

9.1 Literature Review/References

1. Elewski BE, Hay RJ. Update on the management of onychomycosis: highlights of the Third Annual International Summit on Cutaneous Antifungal Therapy. Clin Infect Dis 1996; 23: 305-13

2. Haneke E, Roseeuw D. The scope of onychomycosis: epidemiology and clinical features. Int J Dermatol 1999; 38 Suppl. 2: 7-12

3. Levy LA. Epidemiology of onychomycosis in special-risk populations. J Am Podiatr Med Assoc 1997; 87: 546-50

4. Midgley G, Moore MK, Cook JC, et al. Mycology of nail disorders. J Am Acad Dermatol 1994; 31 (3 pt 2): S68-74

5. Weinberg JM, Koestenblatt EK. Comparison of diagnostic methods in the evaluation of onychomycosis. Dermatol Online J 2001; 7: 236

6. Weschler WP, Smith SA, Bondar GL. Treatment of onychomycosis in the elderly. Clin Geriatr 2002; 10: 19-24, 29-30

9.2 Labeling Recommendations

The drug labeling is currently under review. The label provided in this section is the most recent Agency revised label. This label is not considered final. Due to the impending Complete Response, labeling negotiations have been suspended.

The trade name, JUBLIA™, has been found acceptable by the Office of Prescription Drug Promotion (OPDP).

Currently Proposed Label:

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not conducted because this drug product has clinically insignificant systemic absorption and causes few adverse events. The Agency's experience with topical azole antifungals is ample that advice from an Advisory Committee is not required with this drug product.

9.4 Complete Response Letter Recommendations

DEFICIENCIES
The quality of the product cannot 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.

However, 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.

Report 129 in the Developmental Section concluded with recommendations on processes improvement, stating that additional enhancements are necessary as follows:

- (b) (4)

But none of the recommendations of the Report 129 on the process improvement are officially implemented in the Section P3 (manufacturing process) and in Master Batch Record (Note that Report 129, included in Section 3.2.P.2, is not considered a binding agreement with the Agency).

2. **Inadequate specification for the drug product**

Stability study results on weight loss for the (b) (4) mL 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. Table 1 below summarizes the weight loss data of all five true leakers found in the weight loss study on the (b) (4) mL fill bottles. For comparison, the mean values of all non-leaking units (55 units) are shown in the last column.

The weight loss study consisted of 10 units for each orientation per batch. Therefore, the total number of units set aside for the weight loss evaluation of the (b) (4) L configuration was 60 units (3 batches, 2 orientations per batch). Note that all three stability batches were 100%

visually inspected prior to release for clinical/stability studies, and any bottles found with residues on the exterior surface were rejected (approximately 5% rejection for the (b) (4) mL fill size per batch, see p.28 of Report 129). Therefore, these 60 units set aside for weight loss evaluation were considered to be "non-leaking" initially. Five true leakers were identified among the 60 units by examining the weight loss rate. The residues found at later time points on the exterior surface of these five units are believed to be due to (b) (4) dripping).

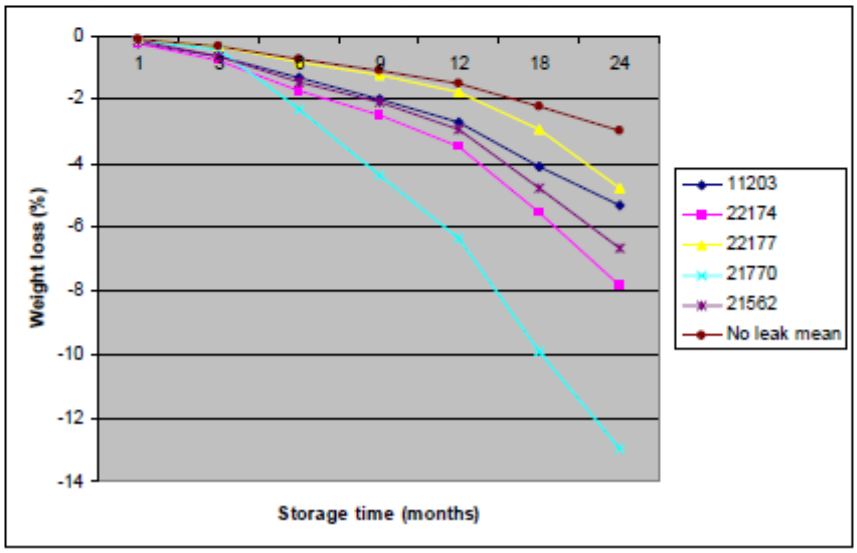
Table 1. Weight Loss Data (% Weight Change) for Units with Unusually High Weight Loss Rate

Month	Batch DP1453F2 Sample # 00011203 upright	Batch DP1473F1 Sample # 00022174 horizontal	Batch DP1473F1, Sample # 00022177 horizontal	Batch DP1474F4 Sample # 00021770 horizontal	Batch DP1474F4 Sample # 00021562 upright	Mean of non-leaking units (n=55)
1	-0.2140	-0.2298	-0.1123	-0.1211	-0.1439	-0.1048
3	-0.6158	-0.7544	-0.3298	-0.4018	-0.6105	-0.3248
6	-1.3035*	-1.7000	-0.7982	-2.2912*	-1.4404	-0.6982
9	-1.9877*	-2.4930	-1.2070	-4.3684*	-2.0789	-1.0343
12	-2.7070*	-3.4561	-1.7596	-6.3263*	-2.9474	-1.4428
18	-4.0789*	-5.5158*	-2.9281	-9.8860*	-4.7842	-2.1362
24	-5.3035*	-7.8439*	-4.7825*	-12.9842*	-6.6719*	-2.9088

*Observation of residue on the container was noted in the stability data tables of Section 3.2.P.8.

The graphic presentation of Table 1 is shown on the following page:

Graph 1. Units with Unusually High Weight Loss Rate



As shown in Table 1, the % weight change of the true leakers ranges from 5% to 13% at 24 month time point. The mean weight change of the non-leaky bottles at 24 month is 2.9% with a range from 2.5% to 3.3% (range data not shown in Table 1).

The manifestation of a leak is typically gradual, and some units did not show clear, unusual higher weight loss rate until Month 9 or 12 (e.g., Sample # 00022177, the second line from the top). Furthermore, true leakers may not have residues on the exterior surface of the bottle, as evidenced in Sample # 00022174 (5th line from the top). Residue was not detected on the exterior surface of this sample until Month 18 despite a significant higher weight loss at every time point (Table 1), indicating that (b) (4) of residue may not be a reliable indicator for leakage.

The presence of latent leakers is supported by the package integrity test results submitted in Section 3.2.P.8. The test is a (b) (4) of the bottle. Table 2 is a summary the results of three stability batches manufactured according to the process described in the Section P.3. All three batches show more and more incidence of failure as time goes by despite being visually inspected and found no leaking or exterior residue initially.

Table 2 Package Integrity Test Results Reported in Section P.8 for Stability Batches DP1453F2, DP1473F1, and DP1474F4 with a fill volume of 6 mL

Batch	Position	Time point (months)							
		0	1	3	6	9	12	18	24
DP1453F2	horizontal	Pass	Pass	Pass	Fail*	Pass	Fail*	Fail*	Fail*
	upright	Pass	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*
DP1473F1	horizontal	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*	Fail*
	upright	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*	Fail*
DP1474F4	horizontal	Pass	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*
	upright	Pass	Pass	Pass	Pass	Pass	Pass	Fail*	Fail*

*Failure due to observed evidence of residue or leakage. Only one unit was pulled for package integrity per time point

The observations discussed above clearly indicate that the current method (b) (4) for assessing container integrity is **not specific and sensitive enough to support the proposed product**. It is not sensitive because it cannot timely detect subtle leaks which, given time, may develop into a significant leak. It is not specific because it cannot detect leaks that do not produce residues, and for those residue-producing leaks, it cannot reliably discern the cause of the residues (i.e., filling dripping or a true leak).

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.

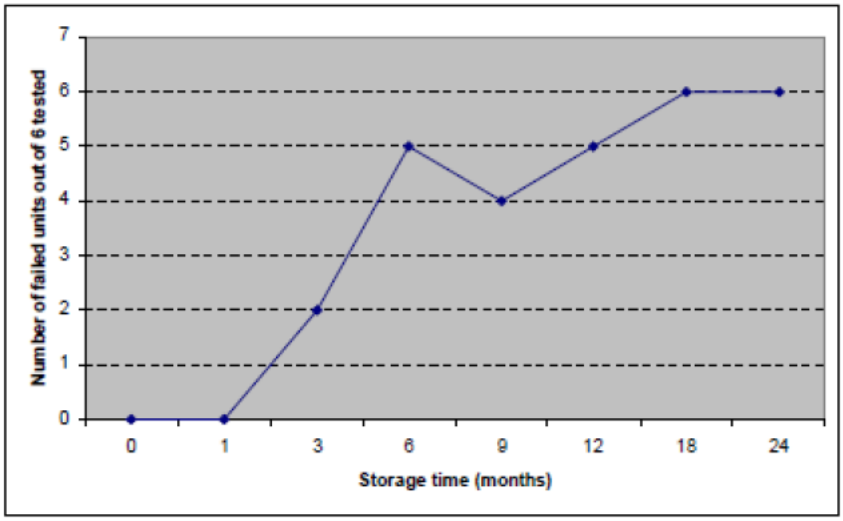
3. Inadequate integrity of the container closure system

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.

In the teleconference on 20-Mar-2013 and in the information submitted before the teleconference on 19-Mar-2013, the number of bottles with residue on the exterior surface (also referred to as "leakers") was claimed to be lower than (b)(4)% for batches made using (b)(4) . The estimate of (b)(4)% was calculated based on package integrity test results collected from Batches (b)(4) 1460 and (b)(4) 1461 over a period of 3-4 months (pages 36-37 of Report 129).

However, short term data alone are not indicative of overall package integrity failure rate for a product with a history of latent leaks as shown in Tables 1 and 2 as well as Graph 1. The data submitted to the stability section of the application indicate that leakage is more likely to be detected after 3 months of storage of drug product. Graph 2 is the presentation of the pooled data from Table 2, showing total number of failure incidence for package integrity from the initial time point through 24 months. At Time Zero and one month, no failure was noted, but after 18 months all containers tested for package integrity failed the test. Therefore, the estimated (b)(4)% leaking rate based on 3-4 months of data may likely underestimate the true leak rate for the proposed expiration dating period of (b)(4) months.

Graph 2. Package Integrity Failure Incidences Observed in Stability Batches



In the teleconference on 20-Mar-2013 you stated that the leakage issue had been fully resolved by (b)(4) We have reached conclusion and deemed that your statements are not supported by the information/data submitted to the NDA to-date based on the following reasons:

- 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 cannot discern the cause of exterior residue (i.e. filling line dripping/vibration or true leakage), and cannot detect non-residue-producing leaks.

You asserted in the 19-Mar-2013 amendment that (b) (4) . We have concluded that your argument is not valid because stability samples are randomly withdrawn from the overall pool and considered a statistical representation of the stability batch at a given time point.

4. Inadequate stability data to assure the expiration dating period

The stability data presented in Section 3.2.P.8 (stability) of the application was generated from batches manufactured using a manufacturing process which is not representative of commercial production process. As stated in Report 129, additional process improvements would need to be made in filling/capping (b) (4) operation for commercial production. Therefore, the provided data to-date in Section P.8 are not considered to be representative of stability characteristics of commercial batches which are to be produced using an improved process.

The two (b) (4) batches (b) (4) 1460 and (b) (4) 1461) presented in Section 3.2.P.2 Pharmaceutical Development (Report 129 pages 36-38) are not considered to be registration or supportive registration stability batches by the Agency. To qualify as a registration stability batch, the batch must have a full testing panel and acceptable testing intervals in addition to (b) (4) than (b) (4) of production batch size and a manufacturing process representative of commercial process. According to Section 3.2.P.2 of the application, these two (b) (4) batches were tested for one attribute only (package integrity by (b) (4)), and (b) (4) 1460 is a vehicle batch (not the to-be- marketed formulation).

5. Pending cGMP compliance evaluation of the facilities involved in this application.

6. Pending label/labeling evaluation.

INFORMATION NEEDED TO RESOLVE DEFICIENCIES

1. Regarding manufacturing process and control information

- Update Section P.3 and Master Batch Record with 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 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 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.

5. **Regarding cGMP compliance**

- Satisfactory recommendation from the Office of Compliance is needed.

6. **Regarding label/labeling**

- Satisfactory resolution of all label/labeling issues.

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 the Report 129 states that all bottles from batch DP1444 were weighed, with the acceptance criteria to be specified in the batch record. Please provide:
  - the acceptance criteria,
  - weight results (summarized in table format)

- 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. Please provide:
  - results of (b) (4) evaluation (e.g., assay, weight loss, etc.)
  - full accountability of all bottles sent to (b) (4), including those bottles sent to clinical studies experimental details

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GARY T CHIANG
04/15/2013

DAVID L KETTL
04/15/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203-567	**Applicant: Dow Pharmaceutical Sciences, Inc.**	**Stamp Date: July 26, 2012**
Drug Name: efinaconazole	**NDA/BLA Type: original submission**	**Filing Date: September 24, 2012**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD Specifications (June 2008)
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: DPSI-IDP-108-P2-01 Study Title:A Multicenter, randomized, double-blind, vehicle-controlled, parallel-group study to evaluate the safety and efficacy of a once-daily application of 5% and 10% IDP-108 relative to Vehciel in the treatment of onychomycosis of the toenail(s). Sample Size: 135 Arms: IDP-108 5%, IDP-108 10%, and Vehicle Location in submission: 5.3.5.1	X			This study was completed entirely in Mexico

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: DPSI-IDP-108-P3-01 Indication: Mild to Moderate onychomycosis of the toenails Subjects: 870 Duration: 52 weeks Pivotal Study #2: DPSI-IDP-108-P3-02 Indication: Mild to Moderate onychomycosis of the toenails Subjects: 781 Duration: 52 weeks	X			For pivotal study #1: 17.8% of subjects had complete cure at week 52 compared to 3.3% of vehicle group. For pivotal study #2: 15.2% of the subjects had complete cure at week 52 as compared to 5.5% of the vehicle group. Total exposed to IDP-108in Ph3 trials: 1236
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Primary endpoint = complete cure (no clinical involvement and negative KOH and culture) at 52 weeks
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		A request for the rationale will be made in the 74-day letter
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			AE> 1% were application site dermatitis, application site vesicles, and tinea pedis. No deaths. Clinical labs were WNL
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			A TQT waiver was granted on 4/14/10. Applicant was asked to collect routine ECGs during phase 3 trials
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA Version 12.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Applicant has requested (b) (4)
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Phase 2 (DPSI-IDP-108-P2-01) study was done in Mexico. Phase 3 trials had clinical sites in Japan, Canada, and Mexico
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			The applicant states that the clinical investigators have no significant financial interests to disclose
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Provide a rationale as to why it is acceptable to extrapolate your foreign clinical data to the general US population for the treatment of mild to moderate toenail onychomycosis.

Gary T Chiang MD, MPH — September 17, 2012
Reviewing Medical Officer — Date

David Kettl, MD — September 17, 2012
Clinical Team Leader — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GARY T CHIANG
09/17/2012

DAVID L KETTL
09/17/2012