

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208901Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



IND 78675

**MEETING MINUTES**

Mayne Pharma International Pty Ltd  
c/o Mayne Pharma LLC  
Attention: Terri Nataline  
Vice President, Regulatory Affairs  
1240 Sugg Parkway  
Greenville, NC 27834

Dear Ms. Nataline:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SUBA-itraconazole Capsules, (b) (4) 65 mg.

We also refer to the teleconference between representatives of your firm and the FDA on November 28, 2017. The purpose of the meeting was to discuss the resubmission of NDA 208901.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH  
Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** November 28, 2017, 3:00 PM – 4:00 PM  
**Meeting Location:** Teleconference

**Application Number:** IND 78675  
**Product Name:** SUBA-itraconazole Capsules, (b) (4) 65 mg

**Indication:** Treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:  
1) Blastomycosis, pulmonary and extrapulmonary,  
2) Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis,  
3) Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of, or refractory to, Amphotericin B therapy

**Sponsor/Applicant Name:** Mayne Pharma LLC

**Meeting Chair:** Sumathi Nambiar, MD, MPH  
**Meeting Recorder:** Alison Rodgers

**FDA ATTENDEES**

**Division of Anti-Infective Products**

Dakshina Chilukuri, PhD, Clinical Pharmacology Reviewer  
Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader  
Maureen Dillon-Parker, Chief, Project Management Staff  
Avery Goodwin, PhD, Acting Clinical Microbiology Team Leader  
Yang He, PhD, Clinical Pharmacology Reviewer  
Karen Higgins, ScD, Statistics Team Leader  
Dmitri Iarikov, MD, PhD, Acting Deputy Director  
John Lazor, PharmD, Director, Division of Clinical Pharmacology IV  
Fang Li, PhD, Pharmacometrics Reviewer  
Chao Liu, PhD, Pharmacometrics Team Leader  
Dorota Matecka, PhD, Product Quality Team Leader  
Owen McMaster, PhD, Pharmacology and Toxicology Reviewer  
Terry Miller, PhD, Pharmacology and Toxicology Team Leader  
Sumathi Nambiar, MD, MPH, Director  
Elizabeth O'Shaughnessy, MD, Medical Officer

Alison Rodgers, Regulatory Project Manager  
Anh-Thy Ly, PharmD, Regulatory Business Process Manager  
Joseph Toerner, MD, MPH, Deputy Director for Safety  
Yuliya Yasinskaya, MD, Clinical Team Leader

**Division of Medication Errors and Prevention**

Janet Higgins, Project Manager  
Sevan Kolejian, PharmD, Reviewer

**SPONSOR ATTENDEES**

**Mayne Pharma International Pty Ltd**

Stuart Mudge, PhD, Vice President Scientific Affairs, Mayne Pharma  
Ilana Stancovski, PhD, Executive Vice President and Chief Scientific Officer, Mayne Pharma  
(b) (4) Consultant to Mayne Pharma

**BACKGROUND**

The Sponsor submitted IND 78675 on May 9, 2008. Following an End-of-Phase 2 meeting, a Pre-NDA meeting, and two other guidance meetings, the Sponsor submitted NDA 208901 for Itraconazole Capsules, (b) (4) 65 mg, on November 30, 2015. The Agency issued a Refuse-to-File (RTF) letter on January 29, 2016. A Type A meeting was held on April 4, 2016, to discuss the RTF issues identified in the letter. On September 14, 2017, the Sponsor submitted a request for a Pre-NDA meeting. A briefing package was submitted on October 26, 2017. The Division sent Preliminary Comments to the Sponsor on November 22, 2017 (appended). The Sponsor submitted a request for clarification of the Division's response to Question #1 on November 24, 2017.

On November 27, 2017, the Division communicated to the Sponsor that it would not be able to respond to the Sponsor's request for clarification prior to the meeting, but would provide a written response within a few days after the meeting.

At the time of the meeting, the Division stated that it was prepared to discuss the Sponsor's request for clarification and would include a written response in the meeting minutes [See Post-Meeting Comments].

The Division's preliminary comments, Sponsor's responses to the comments, and meeting discussion are provided below.

**DISCUSSION**

The Sponsor opened the meeting by thanking the Division for its responses and for sending them well in advance of the meeting. The Division stated that it is prepared to respond to the Sponsor's request for clarification of the Division's response to question #1.

**Question 1:** With reference to the draft label highlights provided in Annex 8, does the Division consider that the results from the comparative pharmacokinetic studies, summarized in Annex 1, constitute a sufficient exposure bridge to the RLD to allow the re-filing of NDA 208901?

**Division Response:**

Yes, we agree that you can re-submit NDA 208901. Note that determination of a sufficient exposure bridge to the RLD will be determined during the review of your NDA.

In addition, please provide the following in your resubmission:

1. Safety and/or tolerability data for SUBA-itraconazole 65 mg capsules as it relates to any potential relationship(s) between systemic PK exposure to both itraconazole and hydroxy-itraconazole and incidence of adverse events observed from all human PK studies that you have conducted with your product. In addition, any relationship(s) between safety / tolerability with either the dose and/or systemic PK exposure to both itraconazole and hydroxy-itraconazole following administration of other itraconazole products (e.g., Sporanox), as described in the literature.
2. The full clinical study reports of all the clinical pharmacology studies you have conducted, including bioanalytical methods, bioanalytical validation and bioanalytical performance reports.
3. An updated Population PK (Pop PK) study report using available PK data from all clinical pharmacology studies you have performed to date in healthy subjects to evaluate the impact of formulation (e.g., SUBA-itraconazole vs. Sporanox), effect of food, drug-drug interactions (e.g., omeprazole), and other relevant factors on the concentration vs. time profile and PK parameters of itraconazole and the active metabolite, hydroxy-itraconazole. This should include PK data derived from administration of (b) (4) the 65 mg (b) (4) SUBA-itraconazole capsules, and Sporanox 100 mg capsules.
  - In the updated Pop PK model, the absorption process could be described by distinct functions based on the formulation (SUBA-itraconazole vs. Sporanox). The other PK characteristics (e.g., distribution, metabolism/excretion) of itraconazole and hydroxy-itraconazole should be described by the same set of functions for both SUBA-itraconazole and Sporanox.
  - In the updated Pop PK model, please estimate the relative bioavailability for SUBA-itraconazole as compared with Sporanox under fed conditions as a fixed effect. If the data support it, you may assess the effect of food on the bioavailability and/or the absorption rate of SUBA-itraconazole separately from that of Sporanox, i.e., assess

separate fixed effects on each of the respective products.

- Assess and compare if intrinsic/extrinsic factors observed across all the clinical pharmacology studies you have performed to date may potentially impact the PK profile of itraconazole and hydroxy-itraconazole, especially at the absorption phase for SUBA-itraconazole and Sporanox.
- Compare the AUC,  $C_{max}$ , and  $C_{min}$  of itraconazole and hydroxy-itraconazole between SUBA-itraconazole capsules and Sporanox capsules using the updated Pop PK model; PK parameter uncertainty also needs to be considered. The following dosing conditions should also be considered: 1) fed vs. fasting; 2) single dose vs. steady-state; 3) with vs. without PPI inhibitors.
- The datasets for all the clinical pharmacology/PK studies and Pop PK analyses should be provided in a SAS transport file (\*.xpt) format. Include the USUBJID (unique subject ID) column to all the Pop PK datasets to facilitate our review. Note that data points and/or subjects that have been excluded from the analyses should be flagged and maintained in the datasets; the flag for exclusion should be clearly explained in the define.pdf file.
- Submit the NONMEM control streams of the base and final models and the output files in the Pop PK analyses. Submit codes (e.g., R, SAS, etc.) for all modeling and simulation analyses.

**Sponsor's Request for Clarification of the Division's Responses to Question 1 (sent to the Division via email on November 24, 2017)**

Since the original submission of NDA 208901, the population pharmacokinetic model of itraconazole supporting the application has been further developed as part of a substantial academic program resulting in a PhD thesis and several important publications. The continued development of the model included:

1. Addition of a pH-dependent dissolution model for the Sporanox and SUBA- formulations of itraconazole to allow *in vitro* - *in vivo* correlation of pH-dependent dissolution and oral absorption rates.  
(Abuhelwa AY, Mudge S, Hayes D, Upton RN, Foster DJ. Population in vitro-in vivo correlation model linking gastrointestinal transit time, pH, and pharmacokinetics: itraconazole as a model drug. Pharm Res. 2016; 33: 1782-94.).

2. Meta-analysis of gastric and intestinal pH values and transit times and their variability in a population to inform *in vitro* dissolution rates of SUBA-itraconazole and Sporanox Capsules.

(Abuhelwa AY, Foster DJ, Upton RN. A quantitative review and meta-models of the variability and factors affecting oral drug absorption-part I: gastrointestinal pH. AAPS J. 2016; 18: 1309-21; Abuhelwa AY, Foster DJ, Upton RN. A quantitative review and meta-models of the variability and factors affecting oral drug absorption-part II: gastrointestinal transit time. AAPS J. 2016; 18: 1322-33)

3. Addition of a first-pass metabolism model and revision of non-linear kinetics incorporating literature data for intravenously administered itraconazole. Itraconazole clearance was described using a mixed inhibition model that allowed hydroxy-itraconazole concentrations to inhibit the clearance of parent drug. Hydroxy-itraconazole clearance was adequately described by Michaelis-Menten elimination kinetics.

(Abuhelwa AY, Mudge S, Upton RN, Foster DJ. Development of Population In Vitro-In Vivo Pharmacokinetic Model with Representation of First-pass Metabolism— Itraconazole and Hydroxy-itraconazole. Journal of Pharmacokinetics and Pharmacodynamics 2017; in press).

The model described above was based on data including [REDACTED] (b) (4) [REDACTED] single dose 65 mg SUBA-itraconazole Capsule data (Studies MPG009, HGN007, HGN008, 10850702, 10850703, 10850705 and 10850706). The model was a good description of these data and the literature data for intravenously administered itraconazole.

In support of the refiling of NDA 208901, additional clinical data has become available for comparison with the current model:

- MPG012 - Compared the rate and extent of absorption SUBA-itraconazole 65mg [2 X 65mg once per day] with Sporanox 100mg [2 X 100mg once per day] in fed conditions at steady-state.
- MPG015 - Compared the rate and extent of absorption SUBA-itraconazole 65mg [2 X 65mg twice per day] with Sporanox 100mg [2 X 100mg twice per day] in fed conditions at steady-state.
- MPG016 - Compared the rate and extent of absorption SUBA-itraconazole 65mg [2 X 65mg single dose] with and without 40 mg omeprazole.
- MPG017 - Compare the rate and extent of absorption SUBA-itraconazole 65mg [2 X 65mg twice a day] in the fasted versus the fed state at steady state.

These new data were compared to the predictions of the model by means of visual predictive checks and the calculation of prediction errors. There was substantial agreement between the model and the new data, suggesting that the current model is a good description of:

1. The accumulation and non-linear kinetics of itraconazole for multi-dose 65 mg SUBA-itraconazole and Sporanox Capsules
2. The effect of fed status on the rate and extent of 65 mg SUBA-itraconazole Capsule absorption.
3. The important role gastric and intestinal pH play in the absorption of itraconazole, including the limited role that gastric pH plays in the absorption of 65 mg SUBA-itraconazole unlike with Sporanox Capsules.

**Question:** Given there was substantial agreement between the model and the new data, would supplying the above papers, model code and model evaluation results be sufficient to demonstrate to the Division that the population modelling in support of the NDA has achieved a substantial mechanistic and quantitative understanding of the kinetics of itraconazole and the differences between the 65 mg SUBA-itraconazole and Sporanox Capsule formulations?

**Discussion:**

- The Sponsor summarized their request for clarification (above), and asked if the Division considers the body of evidence described in the request for clarification sufficient to address the issues raised in the Division's response to Question #1. The Division stated that adequacy of the Population pharmacokinetic (PK) modelling and analyses will be determined during review of the NDA. The Division stated that it is critical that the Population PK model be revised to include all PK data generated from recent studies (i.e., Studies 012, 013, 015, 016, 017), and that the model needs to be further refined to enhance predictive PK capability. Furthermore, the revised Population PK model with inclusion of the new PK data will better discern the effect of food and the effect of drugs that alter the pH of the gastrointestinal tract (e.g., omeprazole) on the bioavailability of SUBA-itraconazole.
- The Division explained that the Sponsor should update the PK model so that it makes more biological sense. For example, the model should be developed so that it more adequately characterizes the relative bioavailability due to drug-drug interactions, as well as the shared PK features post absorption between SUBA-itraconazole and Sporanox drug formulations. The Division stated that it does not think that the model submitted in the original NDA will address such questions. The Sponsor responded that the model that will be included in the resubmission will include dissolution models and a meta-analysis regarding the expected variability of gastric pH in healthy volunteers. The Sponsor expects that the model will meet the Division's requirements as described in its response to Question #1. The Division commented that it is important to have a robust model, but assessing exposure with the model is equally important.
- The Division stated that there are inconsistencies in the overall results of AUCs, C<sub>max</sub>, or both, as reported in Annex 1 of the briefing package for the newer PK studies that have been performed, and this is why incorporating these new data in the PK model will help improve PK predictability. The Sponsor asked if the Division could give an example of the inconsistencies between studies. The Division responded that in Studies MPG012 and MPG015, the dose is 130 mg twice daily for 15 days, and in both studies, the drug is given under fed conditions. In Study MPG012, the 90% confidence intervals are

inconsistent for C<sub>max</sub> and AUC versus the 90% confidence intervals in Study MPG015. The Sponsor explained that the dose is once daily in Study MPG012 and twice daily in Study MPG015. The Division acknowledged the correction and stated that there are discrepancies between the Clinical Study Report and the Annex. The Sponsor acknowledged the comment and apologized for the discrepancy.

- The Sponsor stated that at the time of the RTF, they thought that modelling was not as important as clinical studies, but now understands that the model needs to be as strong as possible. The Division explained that modelling and individual studies are supportive of each other. The Division wanted the Sponsor to conduct the studies at steady state across dosing as this information is very important. The Division cannot say if Population PK is more important than individual study data. The Sponsor stated that it understands that not having the 65 mg data in the model undermines the model. The Sponsor will update the model with the full 65 mg dataset.
- The Division reiterated the importance of the safety and/or tolerability data requested in the Division's first response to Question #1. The Sponsor acknowledged the request and stated that the information will be submitted in the NDA.
- The Sponsor stated that they plan to resubmit the NDA toward the end of January 2018.

#### **ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

#### **ACTION ITEMS**

- The Sponsor will update the Population PK model with the full 65 mg dataset.
- The Sponsor will resubmit the NDA toward the end of January 2018.

Post-Meeting Comments:

**Division's Written Response to Sponsor's Request for Clarification of Division's Response to Question #1 (submitted via email on November 24, 2017):**

**Sponsor Question:** Given there was substantial agreement between the model and the new data, would supplying the above papers, model code and model evaluation results be sufficient to demonstrate to the Division that the population modelling in support of the NDA has achieved a substantial mechanistic and quantitative understanding of the kinetics of itraconazole and the differences between the 65 mg SUBA-itraconazole and Sporanox Capsule formulations?

#### **FDA Response:**

We cannot answer your question at this time, since determination of the sufficiency of the Pop PK modelling and analyses is a review issue once the NDA has been re-submitted.

However, we reiterate our most recent requests dated 22 Nov 2017 and highly recommend that you revise the Pop PK modelling and analyses to include all PK data generated from the recently

completed studies, i.e., Studies 012, 013, 015, 016, 017. We believe inclusion of these PK data is important and the revised Pop PK model and analyses will serve to:

- More adequately refine the Pop PK model in terms of the associated predictive PK capability, PK variance including analyses of PK variability between studies, and/or potential PK covariates, especially with SUBA-itraconazole 65 mg capsules when given as repeated doses at 130 mg, 260 mg, and 390 mg.
- More adequately characterize the effect of food on the bioavailability (BA) of SUBA-itraconazole 65 mg capsules relative to that of Sporanox 100 mg capsules.
- More adequately characterize the effect of drugs that alter the pH of the gastrointestinal tract (e.g., omeprazole) and the effect on the BA of SUBA-itraconazole 65 mg capsules.

## **ADDITIONAL IMPORTANT APPLICATION INFORMATION**

### **PREA REQUIREMENTS**

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

Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

### **505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

**PRELIMINARY COMMENTS SENT TO SPONSOR ON NOVEMBER 22, 2017**

**Question 1:** With reference to the draft label highlights provided in Annex 8, does the Division consider that the results from the comparative pharmacokinetic studies, summarized in Annex 1, constitute a sufficient exposure bridge to the RLD to allow the re-filing of NDA 208901?

**Division Response:**

Yes, we agree that you can re-submit NDA 208901. Note that determination of a sufficient exposure bridge to the RLD will be determined during the review of your NDA.

In addition, please provide the following in your resubmission:

4. Safety and/or tolerability data for SUBA-itraconazole 65 mg capsules as it relates to any potential relationship(s) between systemic PK exposure to both itraconazole and hydroxy-itraconazole and incidence of adverse events observed from all human PK studies that you have conducted with your product. In addition, any relationship(s) between safety / tolerability with either the dose and/or systemic PK exposure to both

itraconazole and hydroxy-itraconazole following administration of other itraconazole products (e.g., Sporanox), as described in the literature.

5. The full clinical study reports of all the clinical pharmacology studies you have conducted, including bioanalytical methods, bioanalytical validation and bioanalytical performance reports.
  6. An updated Population PK (Pop PK) study report using available PK data from all clinical pharmacology studies you have performed to date in healthy subjects to evaluate the impact of formulation (e.g., SUBA-itraconazole vs. Sporanox), effect of food, drug-drug interactions (e.g., omeprazole), and other relevant factors on the concentration vs. time profile and PK parameters of itraconazole and the active metabolite, hydroxy-itraconazole. This should include PK data derived from administration of (b) (4) the 65 mg (b) (4) SUBA-itraconazole capsules, and Sporanox 100 mg capsules.
- In the updated Pop PK model, the absorption process could be described by distinct functions based on the formulation (SUBA-itraconazole vs. Sporanox). The other PK characteristics (e.g., distribution, metabolism/excretion) of itraconazole and hydroxy-itraconazole should be described by the same set of functions for both SUBA-itraconazole and Sporanox.
    - In the updated Pop PK model, please estimate the relative bioavailability for SUBA-itraconazole as compared with Sporanox under fed conditions as a fixed effect. If the data support it, you may assess the effect of food on the bioavailability and/or the absorption rate of SUBA-itraconazole separately from that of Sporanox, i.e., assess separate fixed effects on each of the respective products.
    - Assess and compare if intrinsic/extrinsic factors observed across all the clinical pharmacology studies you have performed to date may potentially impact the PK profile of itraconazole and hydroxy-itraconazole, especially at the absorption phase for SUBA-itraconazole and Sporanox.
    - Compare the AUC,  $C_{max}$ , and  $C_{min}$  of itraconazole and hydroxy-itraconazole between SUBA-itraconazole capsules and Sporanox capsules using the updated Pop PK model; PK parameter uncertainty also needs to be considered. The following dosing conditions should also be considered: 1) fed vs. fasting; 2) single dose vs. steady-state; 3) with vs. without PPI inhibitors.

- The datasets for all the clinical pharmacology/PK studies and Pop PK analyses should be provided in a SAS transport file (\*.xpt) format. Include the USUBJID (unique subject ID) column to all the Pop PK datasets to facilitate our review. Note that data points and/or subjects that have been excluded from the analyses should be flagged and maintained in the datasets; the flag for exclusion should be clearly explained in the define.pdf file.
- Submit the NONMEM control streams of the base and final models and the output files in the Pop PK analyses. Submit codes (e.g., R, SAS, etc.) for all modeling and simulation analyses.

**Question 2:** Does the Division agree it is important that the clinical pharmacology section explains why a 65 mg SUBA-itraconazole Capsule is comparable in exposure to a 100 mg RLD capsule, (b) (4)

**Division Response:**

It is premature to discuss labeling. The content of the label for SUBA-itraconazole 65 mg capsule will be determined during the NDA review.

**Question 3:** The results of Study MPG016 demonstrate that the  $AUC_{0-\infty}$  and  $C_{max}$  from SUBA-itraconazole 65 mg Capsules is increased by 22% and 31%, respectively, when co-administered with omeprazole (refer to [Annex 1](#) and [Annex 6](#)).

Mayne Pharma considers that this increase in exposure when co-administered with omeprazole is not clinically significant:

- Unlike for the RLD, the results from MPG016 demonstrate that the exposure to itraconazole from SUBA-itraconazole 65 mg Capsules is *increased* rather than decreased by omeprazole; as such, unlike for the RLD, there is no increased risk of lack of efficacy when co-administered with gastric acid reducers/inhibitors.

- From a safety perspective, the increase in exposure observed is within the range of variation observed for the RLD; therefore, while it is important that the prescribing physician is aware of the likely increase in exposure, there is no need for any additional mitigation measures above those already employed within the RLD label (i.e., therapeutic monitoring, liver function tests etc.).

Does the Division agree that the results from Study MPG016 allows co-administration of SUBA-itraconazole with drugs that reduce gastric acidity and that the proposed labelling in [Annex 8](#) provides sufficient guidance for any co-administration?

**Division Response:**

The results from Study MPG016 will be reviewed during the NDA review, and a decision on whether co-administration of SUBA-itraconazole with drugs that reduce gastric acidity is acceptable will be determined at the time of the review.

**Question 4:** With reference to the proposed labelling in Annex 8 the results from Study MPG017 (see Annex 7), does the Division concur with the following conclusions from Study MPG017 with respect to any food effect on SUBA-itraconazole 65 mg Capsules:

(i) As the point estimate and 90% confidence interval of the ratio of Test fed versus Test fasted is within the 80-125% range, there is no food effect on  $C_{\text{trough}}$ , which is the key pharmacokinetic parameter when predicting efficacy of itraconazole

(ii) As the Division stated in its minutes of the type B meeting on 06 December 2012, “The rate of exposure ( $C_{\text{max}}$ ) may be considered a clinically relevant parameter for safety.” Study MPG017 showed that the  $C_{\text{max ss}}$  is reduced by 27% with food, but this does not pose a safety or efficacy risk so is not considered clinically significant.

(iii) While the  $C_{\text{max ss}}$  for SUBA-itraconazole 65 mg Capsules is 27% higher in the fasted state compared to the fed, the geometric mean of 1.9 ug/ml is comparable to the 2.0 ug/ml listed in the RLD label for the  $C_{\text{max ss}}$ ; that is, the  $C_{\text{max ss}}$  for SUBA-itraconazole 65 mg Capsules in Study MPG017 is within the normal range reported for itraconazole and therefore also does not pose a safety concern.

(b) (4)

#### Division Response:

It is premature to discuss the results of Study MPG017. The effect of food intake on the systemic bioavailability of SUBA-itraconazole 65 mg capsules will be determined upon review of all relevant data in the NDA.

**Question 5:** Does the Division concur that the OSI requests are not relevant to the proposed NDA 208901 as the dossier will not include any phase 2/3 pivotal trials?

#### Division Response:

We agree that OSI inspections are not relevant to the proposed NDA. However, inspections of the bioanalytical site(s)/laboratory(ies) may be needed and this will be determined during the review of the NDA.

**Question 6:** Does the Division concur that the proposed commercial packs are adequately bracketed by available stability data?

#### Division Response:

Your approach to bracketing of available stability data in support of the proposed drug product (itraconazole capsules, 65 mg) commercial packs, as described in the meeting background

package appears reasonable. Please provide in the NDA a detailed justification for the bracketing approach and include details such as description of the container closure systems and a risk assessment of any differences between the supportive and commercial packaging configurations (taking into consideration factors that may potentially affect the stability of the proposed drug product, e.g., head space, moisture permeability, etc.).

**Question 7:** Does the Division concur that the stability of the commercial packs can be verified by the proposed post-approval stability commitments, with the data being provided in subsequent annual reports until the commitment has been met?

**Division Response:**

We agree that the stability of the proposed drug product commercial packs should be verified via post-approval stability study commitments with data reported in subsequent post-approval annual reports. Please note that details of the proposed post-approval stability commitments (e.g., the number of batches, testing conditions, etc.) will be assessed during the review of the overall stability information submitted in the NDA.

**Question 8:** Does the Division concur that, the re-filed NDA 208901 is exempt from the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)?

**Division Response:** We concur that the re-filed NDA 208901 is exempt from the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c).

**Additional Comments:**

We note the use of a product name, SUBA, in the Briefing Document for IND 78675. If you intend to have a proprietary name for your product, we recommend you submit your request for FDA review of the proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

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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.**  
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/s/  
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SUMATHI NAMBIAR  
12/18/2017



NDA 208901

**REFUSAL TO FILE**

Mayne Pharma International Pty Ltd  
c/o Mayne Pharma Inc.  
Attention: Susan Canady  
Regulatory Affairs Specialist  
1240 Sugg Parkway  
Greenville, NC 27834

Dear Ms. Canady:

Please refer to your New Drug Application (NDA) dated November 30, 2015, received November 30, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Itraconazole Capsules, (b)(4) 65 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. There are no data to adequately bridge the systemic exposure of itraconazole following administration of SUBA Itraconazole capsules to the systemic exposure of itraconazole following the administration of Sporanox capsules (i.e., the Reference Listed Drug) for the SUBA Itraconazole doses proposed for the indications of Blastomycosis, Histoplasmosis, and Aspergillosis. Specifically, no clinical efficacy / safety studies were submitted in the NDA for these indications. Therefore, an exposure bridge is necessary to justify reliance on the Agency's previous findings of safety and effectiveness for Sporanox capsules for the indications of Blastomycosis, Histoplasmosis, and Aspergillosis proposed in the package insert for SUBA Itraconazole capsules.

We remind you that the need for this information was communicated to you during the August 22, 2011, End-of-Phase 2, and November 6, 2012, Pre-NDA, meetings, as well as at the meetings held on December 5, 2013, and February 19, 2014.

2. The proposed dose regimens of SUBA Itraconazole capsules for Blastomycosis, Histoplasmosis, and Aspergillosis range from 130 mg to 260 mg once daily; and for Life Threatening Situations include use of a SUBA Itraconazole loading dose regimen of 390 mg/day for the first 3 days of treatment. Because itraconazole exhibits non-linear pharmacokinetics, the exposure data submitted in the NDA for the (b)(4) [redacted] single-dose administration of the 65 mg SUBA Itraconazole capsule, cannot be used to predict systemic exposures of itraconazole following the administration

of SUBA Itraconazole at the proposed doses ranging from 130 mg (2x 65 mg) to 390 mg (6 x 65 mg).

3.

4.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

1. Population Pharmacokinetic (Pop PK) report and analyses:

- Datasets and modeling codes are missing.
- The PK data used for the Pop PK analyses only include that obtained from studies conducted [REDACTED] PK data for the 65 mg capsule strength were not included.
- There are inconsistencies between the Pop PK report and the Summary of Clinical Studies in the description of the Pop PK analyses.

2. With regard to Section 8 of the proposed package insert, we recommend that you conduct a review of human data from published literature, post-marketing reports, or other sources for effects of itraconazole on pregnancy, lactation, and fertility. These data should be used to support the Risk Summary statements for pregnancy and lactation. Data sources may include controlled clinical trials, ongoing or completed pregnancy exposure registries, other epidemiological or surveillance studies, or case series.

Please refer to the FDA Guidance on Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>

3. Stability data for the proposed drug product, itraconazole capsules, [REDACTED] 65 mg, packaged in the proposed physician's sample packs should be provided.

## PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

### Highlights (HL)

#### HIGHLIGHTS GENERAL FORMAT

- White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval.

#### HIGHLIGHTS DETAILS

##### Highlights Limitation Statement

- The name of drug product should appear in UPPER CASE letters in the HL Limitation Statement. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**”

##### Boxed Warning (BW) in Highlights

- The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.
- The BW in the HL should include a summary of the BW in the **Full Prescribing Information (FPI)**.

## Dosage Forms and Strengths in Highlights

- For drug products other than vaccines, the verbatim **bolded** statement must be present: **“To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”**

## Contents: Table of Contents (TOC)

- The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
- In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

## Full Prescribing Information (FPI)

### FULL PRESCRIBING INFORMATION – GENERAL FORMAT

- The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

### Boxed Warning Section in the FPI

- All text in the BW should be **bolded**.
- The BW must have a title in UPPER CASE, following the word **“WARNING”** and other words to identify the subject of the warning. (Even if there is more than one warning, the term, **“WARNING”** and not **“WARNINGS”** should be used.) For example: **“WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”**. If there is more than one warning in the BW title, the word **“and”** in lower case can separate the warnings.

### Patient Counseling Information Section in the FPI

- The patient labeling was included as a subsection under Section 17. Provide a separate FDA-approved patient labeling. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues at the time of NDA resubmission. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

**PROPOSED PROPRIETARY NAME**

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at [OSECONSULTS@cder.fda.gov](mailto:OSECONSULTS@cder.fda.gov).

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely yours,

*{See appended electronic signature page*

Sumathi Nambiar, MD, MPH  
Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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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.**  
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/s/  
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SUMATHI NAMBIAR  
01/29/2016



IND 78675

**MEETING MINUTES**

Mayne Pharma Group Limited

(b) (6)

Dear Ms. Janulis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (itraconazole) capsules.

We also refer to the meeting between representatives of your firm and the FDA on November 6, 2012. The purpose of the meeting was to reach agreement on the clinical development plan that will support the filing of a 505(b)(2) New Drug Application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

*{See appended electronic signature page}*

John Farley, MD, MPH  
Acting Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** November 6, 2012, 11:00 AM – 12:00 PM  
**Meeting Location:** 10903 New Hampshire Avenue, Building 22, Room 1419,  
Silver Spring, MD 20903

**Application Number:** 78675  
**Product Name:** (b) (4) (itraconazole) Capsules  
**Indication:** Treatment of fungal infections in immunocompromised and  
non-immunocompromised patients with blastomycosis,  
histoplasmosis, and aspergillosis  
**Sponsor/Applicant Name:** Mayne Pharma Group Limited

**Meeting Chair:** John Farley, MD, MPH  
**Meeting Recorder:** Alison Rodgers

### FDA ATTENDEES

#### Division of Anti-Infective Products

John Alexander, MD, MPH, Clinical Team Leader  
Kimberly Bergman, PharmD, Clinical Pharmacology Team Leader  
Cheryl Dixon, PhD, Statistical Reviewer  
John Farley, MD, MPH, Acting Director  
Seong Jang, PhD, Clinical Pharmacology Reviewer  
Katherine Laessig, MD, Deputy Director  
Frederic Marsik, PhD, ABMM, Clinical Microbiology Reviewer  
Sumathi Nambiar, MD, MPH, Deputy Director for Safety  
Elizabeth O'Shaughnessy, MD, Medical Officer  
Shrikant Pagay, PhD, CMC Reviewer  
Alison Rodgers, Regulatory Project Manager  
Wendelyn Schmidt, PhD, Pharmacology and Toxicology Team Leader

### SPONSOR ATTENDEES

#### Mayne Pharma Group Limited

Stuart Mudge, Regulatory and Clinical Director

(b) (4)

## BACKGROUND

An End-of-Phase 2 meeting was held with Mayne Pharma Group, Ltd, (Mayne) on August 22, 2011. On July 27, 2012, Mayne requested a Pre-NDA meeting to discuss their plans for submission of a 505(b)(2) application. A briefing package was submitted on October 8, 2012. The Division provided responses to the questions outlined in the briefing package on November 5, 2012, via email. The meeting served to clarify the responses.

The sponsor's original questions and the Division's responses are appended at the end of this document for completeness.

## DISCUSSION

Mayne acknowledged the Division's response to question #3 and understands that further evidence is required in order to justify the proposed pharmacodynamic target parameter for itraconazole (i.e., AUC/MIC ratio of greater than 25). The Division stated that it is necessary for Mayne to provide data to support the correlation between the proposed pharmacodynamic target parameter and clinical outcome for itraconazole. Mayne also suggested they would provide CLSI breakpoints data for itraconazole. The Division requested that Mayne submit the CLSI breakpoints data with clinical outcomes at the individual patient level. Mayne agreed with the Division's request. The Division agreed to review the data and discuss it via teleconference.

Regarding the Division's response to question #3, the Division explained that dosing recommendations with regards to food is a labeling issue and not a filing issue. (b) (4)

Mayne discussed the possibility of using  $C_{min}$  as a potential target endpoint for (b) (4) noting that the therapeutic drug monitoring for Sporanox is empirically practiced in hospitals with a target  $C_{min}$  of 500 ng/ml. The Division acknowledged the clinical practice of therapeutic drug monitoring for Sporanox. However, the Division explained that additional clinical data would be required in order to justify a  $C_{min}$  of 500 ng/mL as a target endpoint for (b) (4)

Mayne requested clarification of the Division's response to question #5. The Division stated that if they (Mayne) pursue development of a 65 mg capsule, then Study 10850703 (703) would need to be repeated using the 65 mg capsule. Additionally they would need to conduct traditional bioequivalence comparisons and include data regarding Sporanox administration under both fasted and fed conditions.

The Division requested that Mayne repeat Study 703 with the 65 mg capsule due to the discrepant results regarding the effect of food on itraconazole. The Division stated that, based on the physical and chemical properties of Sporanox, food intake should increase the absorption of Sporanox as described in the Sporanox labeling. However, Mayne's studies showed the opposite of what was expected. Re-evaluation of the food effect on the absorption of Sporanox would be

essential for approval of (b) (4) because it is critical to determine in which condition (i.e., fed or fasted) the exposure of Sporanox should be compared with (b) (4). The Division also requested that Mayne compare the itraconazole exposure results (i.e., AUC and  $C_{max}$ ) following Sporanox from their studies with literature reports and historical data with Sporanox, as well as with the FDA-approved Sporanox labeling. Mayne agreed.

The Division acknowledged that the traditional bioequivalence criteria may not be applied for itraconazole because itraconazole may be considered a “highly variable” drug and bioequivalence is a possibility. The Division stated that it is acceptable to use methods other than the traditional bioequivalence criteria to support (b) (4) compared to Sporanox (e.g., comparing the distribution range of exposure data of (b) (4) compared to Sporanox). Mayne asked the Division if  $AUC_{last}$  (i.e., AUC from time 0 to last sampling time) rather than  $AUC_{inf}$  can be used to evaluate the itraconazole exposure between (b) (4) and Sporanox. The Division answered that it is acceptable as long as the contribution of AUC after the last sampling time to  $AUC_{inf}$  is not significant (e.g., <5%). The Division recommended that Mayne should evaluate all PK parameters when conducting its analysis.

The Division noted that Mayne could submit a draft protocol of Study 2 described in question #5 for review as a Special Protocol Assessment (SPA). The Division would like to review all pharmacokinetic results including Study 1 described in question #5 prior to submission of an SPA. After reviewing the results, the Division would determine whether or not Study 2 would be designed appropriately in terms of food intake.

If Mayne evaluates drug interactions with proton pump inhibitors (PPIs), the Division confirmed that this information may be applicable to labeling. If comparability is demonstrated between Mayne’s formulation and SPORANOX, a clinical trial in patients with invasive aspergillosis would not be necessary.

If Mayne’s data for the 65 mg capsule meets the agreed upon criteria for comparison to SPORANOX, (b) (4).

The formulation for the 65 mg capsule (b) (4)

The Division confirmed that a Phase 3 trial would not be required if studies with 65 mg capsules provide sufficient scientific evidence to rely on the innovator product.

Mayne acknowledged the Division’s responses to questions 1, 2, and 4, and had no need for further discussion.

## **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

## **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

## **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

## **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**ISSUES REQUIRING FURTHER DISCUSSION**

- The Division needs to see the correlation between the pharmacodynamic target parameter of AUC/MIC ratio of greater than 25 and clinical outcome. The Division agreed to review the data and discuss it via teleconference.
- Mayne agreed to submit for Agency review and discuss the in vitro and clinical study data related to the CLSI breakpoints via a meeting or teleconference prior to submission of an NDA.

**ACTION ITEMS**

- The Division will issue meeting minutes within 30 days.
- Mayne has the data to support their proposed CLSI breakpoints and will provide it.

**ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting minutes.

## SPONSOR'S ORIGINAL QUESTIONS AND DIVISION'S RESPONSES

### REGULATORY

#### Question 1

Mayne Pharma intends to prepare a 505(b)(2) filing for the Test product using a combination of scientific literature, pharmacokinetic, clinical and quality data it has generated on its own and references to the Sporanox 100 mg Capsules NDA, as appropriate. A detailed overview of Mayne Pharma's proposed strategy for its future NDA submission for the Test product is outlined in **Appendix I**.

A draft of the proposed label for [REDACTED] (b) (4) Capsules, taking into account the current data available for an NDA filing, is included in **Appendix II**.

**Question 1: Does the DAIP have any comments on the proposed regulatory strategy for the 505(b)(2) NDA, described in Appendix I, including the sufficiency of proposed "bridge" between [REDACTED] (b) (4) Capsules and the RLD?**

#### **FDA Response:**

*While we agree with the proposed regulatory strategy for the 505(b)(2) NDA, we do not agree that the proposed "bridge" for the [REDACTED] (b) (4) capsules and Sporanox 100-mg capsules is sufficient. We recommend that you conduct studies of 65mg capsules (see responses to Question 5).*

### MEDICAL/CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

#### Question 2



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(b) (4)

Review of the scientific literature demonstrates that there are *in vitro* and *in vivo* models which could be utilized to compare the relative performance of the Test and RLD. Results from animal model studies have correlated well with human data making such *in vivo* examination of pharmacodynamic targets critically important to designing optimal dosing of antimicrobial agents {Andes, 2003 #4;Andes, 2003 #71;Andes, 2005 #72;Andes, 2004 #74;Andes, 2003 #76;Andes, 2003 #77;Andes, 1999 #80;Baddley, 2008 #83;Pfaller, 2008 #87;Pfaller, 2006 #88}. In particular, *in vivo* animal model studies in disseminated candidiasis and invasive pulmonary aspergillosis have been useful for demonstrating the effectiveness of itraconazole {Van Cutsem, 1987 #90;Van Cutsem, 1984 #93;Van t Wout, 1989 #91}.

Accordingly, Mayne Pharma proposes to conduct the *in vivo* animal model studies outlined in Appendix VI. Mayne Pharma contends that such investigations will provide valuable insights into the relative performance of the Test and the RLD and add further weight to claims that the Test formulation is at worst therapeutically equivalent to the RLD.

(b) (4)

**FDA Response:**

No.

(b) (4)

*We understand the challenges associated with performing clinical studies with an oral formulation of an antifungal drug in an invasive fungal infection, therefore, we recommend that you conduct the two (single-dose and multiple-dose) pharmacokinetic studies that you propose with a 65 mg capsule of SUBA-itraconazole. Please see our responses to Question 5.*

*Once the results of these two studies outlined in Question 5 are available for our review, requirements, if any, for additional studies can be discussed in more detail.*

**Question 5**

(b) (4)

Accordingly, if the Agency requires a more similar extent of exposure to the RLD at the population level, Mayne Pharma proposes to perform the following studies with a SUBA-itraconazole capsule containing up to 65 mg of drug substance:

- Study 1: A randomised, open-label, two-treatment, four-period, two-sequence, replicate-design, crossover, bioequivalence study comparing single oral doses of SUBA-itraconazole 65 mg capsules (Mayne Pharma International Pty Ltd, Australia) with Sporanox (itraconazole) 100 mg capsules (Janssen-Cilag Ltd, USA), in healthy adult male and female subjects, under fed conditions.
- Study 2: A two-way crossover multiple-dose steady-state bioavailability study comparing 130 mg SUBA-itraconazole (2 x 65 mg itraconazole capsules) given twice a day under fasted conditions to 200 mg of Sporanox® (2 x 100 mg itraconazole capsules) given twice a day under fed conditions in healthy volunteers. (b) (4)

with a SUBA-itraconazole 65 mg Capsule and the Test formulation will be taken in the fasted state. Acceptance Criteria: the  $C_{\min}$  Test/Reference ratio within 0.80 – 1.25 range.

Draft protocol synopses for each study are provided in **Appendix VII**.

(b) (4)

(b) (4)

**As such, Mayne Pharma's preference would be to repeat Study HGN008 (replicate-design) and compare the US RLD with a 65 mg SUBA-itraconazole capsule. Does the Agency concur with this approach?**

**5b) Would Study 1b (replicate design) and Study 2 support approval of a 505(b)(2) NDA for the proposed SUBA-itraconazole 65 mg Capsules?**

**5c) Given the pharmacological properties of the triazole class of drug, does the Agency concur that the extent of exposure (AUC) is the relevant parameter and the rate of exposure ( $C_{max}$ ) is not clinically relevant?**

**FDA Response:**

5a) [REDACTED] <sup>(b) (4)</sup> with the proposed 65mg SUBA-itraconazole capsule in order to re-evaluate the food effect on both Sporanox and SUBA-itraconazole capsules. As stated previously, we recognize that the approved and proposed formulations of itraconazole may be considered “highly variable” drugs and bioequivalence is a possibility. As you state above, SUBA-itraconazole 65 mg capsules are more likely to be bioequivalent to the RLD. Please submit a study protocol for review and comment that includes traditional statistical methods for determining bioequivalence. We also recommend you submit the summary of the results of this study before you proceed with the proposed Study 2 for review and comment.

5b) Study 1, as recommended in the FDA response to Question 5a, and Study 2 appear to support the filing of a 505(b)(2) NDA for the proposed SUBA-itraconazole 65 mg capsules. However, please provide further rationale to support the proposed acceptance criteria for Study 2 (i.e., the  $C_{min}$  Test/Reference ratio within [REDACTED] <sup>(b) (4)</sup> range).

5c) We concur that AUC is the relevant parameter for efficacy. The rate of exposure ( $C_{max}$ ) may be considered a clinically relevant parameter for safety.

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/s/  
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JOHN J FARLEY  
12/06/2012



IND 78675

(b) (4)

**MEETING MINUTES**

Mayne Pharma Group, Ltd.

(b) (4)

Dear Ms. Janulis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (itraconazole) (b) (4) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on August 22, 2011. The purpose of this End-of-Phase 2 meeting was to discuss plans for submission of an NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

*{See appended electronic signature page}*

John Farley, MD, MPH  
Acting Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

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/s/  
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JOHN J FARLEY  
09/16/2011