CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208562Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208562 SUPPL # HFD # 520

Trade Name None

Generic Name Voriconazole for Injection

Applicant Name Xellia Pharmaceuticals Inc.

Approval Date, If Known PDUFA goal date May 24, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Not a supplemental NDA

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 021267 VFEND® (voriconazole) for injection

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved

the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Naseya Minor
Title: Regulatory Project Manager
Date: May 23, 2016

Name of Office/Division Director signing form: Sumathi Nambiar
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

NASEYA N MINOR
05/23/2016

SUMATHI NAMBIAR
05/23/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 208562	NDA Supplement #:	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Voriconazole for Injection Dosage Form: Lyophilized powder for solution for injection Strengths: 200 mg		
Applicant: Xeilla Pharmaceuticals, ApS		
Date of Receipt: January 9, 2017		
PDUFA Goal Date: March 9, 2017	Action Goal Date (if different):	
RPM: Naseya Minor		
Proposed Indication(s): invasive aspergillosis; candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds; serious infections caused by Scedosporium apiospermum and Fusarium species including Fusarium solani, in patients intolerant of, or refractory to other therapy		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 021267 VFEND® (voriconazole)	FDA's previous findings of safety and effectiveness
NDA 20966 Sporonax® (Itraconazole)	FDA's previous findings of safety and effectiveness

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The applicant is relying on the Agency's findings of safety and effectiveness for the listed drug VFEND (voriconazole) for injection (NDA 21267). The proposed product is bridged to the listed drug VFEND per 21 CFR 320.24(b)(5). The proposed commercial formulation of the applicant's drug product was evaluated in the *in vitro* studies that compared its physicochemical properties (i.e., pH, osmolality), release kinetics, and antifungal activities to those of the Listed Drug (VFEND) and was found to be acceptable.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
VFEND (voriconazole) for injection	021267	Y
Sporonax® (Itraconazole)	20966	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Sporanox

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in the inactive ingredient from Sulfobutyl ether ßcyclodextrin (SBEβCD) to Hydroxypropyl ßcyclodextrin (HPβCD). The active ingredient, indication, route of administration, dosage form and strength are the same as those of the reference listed drug.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): NDA 021267 VFEND (voriconazole) for injection, 200 mg

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☒

*If this application relies only on non product-specific published literature, answer **"N/A"***

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):
NDA 021267 VFEND (voriconazole) 200mg
Patent number 5567817 Exp. May 24, 2016
Patent number 6632803 Exp. June 2, 2018

NDA 20966 Sporanox (Itraconazole)
Patent number 6407079 Exp. June 18, 2019

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph

III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
NDA 021267 VFEND Patent number 5567817
NDA 021267 VFEND Patent number 6632803
NDA 20966 Sporanox Patent number 6407079

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *October 26, 2015, October 27, 2015, and May 23, 2016*

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☒ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

NASEYA N MINOR
03/17/2017

Minor, Naseya

From: Holovac, Mary Ann
Sent: Tuesday, February 28, 2017 11:34 AM
Minor, Naseya
Schumann, Katherine; Sharma, Khushboo; Goldstein, Beth A (Duvall); Holovac, Mary Ann
Subject: NDA 208562 - voriconazole - cleared for action

Naseya,

We discussed the subject application at Monday's 505(b)(2) clearance meeting. The application is **~ cleared for action ~** from a 505(b)(2) perspective.

Please make the following changes to the draft assessment before archiving in DARRTS, assuming you are heading towards an approval. If you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the resubmission arrives so that we can add it anew to our clearance queue.

- *Q2: add Sporanox NDA 20966 to the list of sources of information relied upon in this application.*
- *Q3:* ***Please include info from 2/21/17 email NM to MAH your responses to this question.***
  ~The applicant is relying on the Agency's findings of safety and effectiveness for the listed drug VFEND (voriconazole) for injection (NDA 21267). The proposed product is bridged to the listed drug VFEND per 21 CFR 320.24(b)(5). The proposed commercial formulation of the applicant's drug product was evaluated in the in vitro studies that compared its physicochemical properties (i.e., pH, osmolality), release kinetics, and antifungal activities to those of the Listed Drug (VFEND) and was found to be acceptable.
  AND
  ~Xellia intends to rely primarily on the safety of HPβCD as approved by the FDA for use in intravenous itraconazole (Sporanox®, NDA 020966); a product with similar HPβCD content and a similar patient population and duration of treatment as the proposed Voriconazole product by Xellia.
- *Q4: Response to 'a' should be 'yes'; 'b' should be 'no'*
- *Q6: add Sporanox NDA 20966*
- *Q8d: response should be 'yes' since Sporanox is in the DC section of the Orange Book. Assuming it was not DC for reasons of s/e, check 'no' under 8di and make sure this determination is documented in a review.*
- *Q11a: Please check YES*
- *Q11b: check indications (MAH)*
- *Q11c: Please check NO list PAs at the end of the question*
- *Q12: Add patent 6407079 (the Sporanox patent) at its expiration date to the list of unexpired patents.*
- *Q15e:* ***Change 15e to YES****. [A lawsuit was filed and dismissed.]*

Please let me know if you have any questions.

Mary Ann

From: Minor, Naseya
Sent: Tuesday, February 21, 2017 3:29 PM
To: Holovac, Mary Ann
Cc: Schumann, Katherine
Subject: RE: Voriconazole inj. NDA 208562 - voriconazole

.. Mary Ann,

Please see my responses below in red.

Thanks,

Naseya

From: Holovac, Mary Ann
Sent: Friday, February 17, 2017 10:12 AM
To: Minor, Naseya
Cc: Schumann, Katherine
Subject: Voriconazole inj. NDA 208562 - voriconazole

Hi Naseya,
I am working on the subject 505(b)(2) NDA resubmission today and have a couple of questions for you.

1. Can you provide an updated response to question 3 as was requested when the NDA was cleared for TA (see email below)? Although the application was cleared for TA, I am not sure we have complete information with respect to the Vfend bridge and the committee had questions about it in the prior cycle. **The applicant is relying on the Agency's findings of safety and effectiveness for the listed drug VFEND (voriconazole) for injection (NDA 21267). The proposed product is bridged to the listed drug VFEND per 21 CFR 320.24(b)(5). The proposed commercial formulation of the applicant's drug product was evaluated in the *in vitro* studies that compared its physicochemical properties (i.e., pH, osmolality), release kinetics, and antifungal activities to those of the Listed Drug (VFEND) and was found to be acceptable.**

2. Additionally, as the application is now also relying upon Sporanox a bridge will needed to reflect how the applicant bridged to Sporanox in addition to Vfend. Can the division provide the scientific rationale for reliance on Sporanox? Katie Schumann has provided what the applicant proposed with respect to how they will 'bridge' which will not be a bridge in the traditional due to the active ingredient differences. Katie has agreed to help you revise the assessment as needed for committee review. **Xellia intends to rely primarily on the safety of HPβCD as approved by the FDA for use in intravenous itraconazole (Sporanox®, NDA 020966); a product with similar HPβCD content and a similar patient population and duration of treatment as the proposed Voriconazole product by Xellia.**

3. Please advise me when the applicant submits a patent cert or verification as related to the new MMA amendment requirements. **The applicant responded via email today (2-21-17) and will submit the patent verification electronically tomorrow**

Thank you and please let me know if you have any questions. Copied below is the TA clearance email for reference.
Mary Ann

From: Goldstein, Beth A (Duvall)
Sent: Tuesday, May 24, 2016 1:04 PM
To: Schumann, Katherine; Minor, Naseya
Cc: Nambiar, Sumathi; Holovac, Mary Ann
Subject: Voriconazole inj. NDA 208562 - cleared for TA

Naseya,

Since I'll be tied up in meetings the rest of the day, I wanted to send you the clearance email now. As previously discussed, please tighten up your response to Q3 of the 505(b)(2) assessment as described below and include the following language in your TA letter:

From:	Minor, Naseya
To:	"Edward Eichmann"
Subject:	NDA 208562 Information Request
Date:	Thursday, May 12, 2016 1:48:00 PM

Hi Edward,

As a follow up to our teleconference here is the information request for NDA 208562:

In your May 5, 2016 response to the Division's information requests of May 3 and May 4, 2016, you provided the following information in support of Section 12.3 of the proposed prescribing information.

Itraconazole (Sporanox) Clinical Pharmacology and Biopharmaceutics review (NDA 20,966) submitted to FDA on April 27, 1998
Kurkov et al, 2012. The Effect of Parenterally Administered Cyclodextrins on the Pharmacokinetics of Coadministered Drugs. Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci. 101: 4402-4408.
Mohr JF et al, 2004. Pharmacokinetics of Intravenous Itraconazole in Stable Hemodialysis Patients. Antimicrob. Agents Chemother. 48(8): 3151-3153.

Additionally, in the toxicology written summary (2.6.6) provided in NDA 208562, you state:

Xellia intends to rely primarily on the safety of HPβCD as approved by the FDA for use in intravenous itraconazole (Sporanox®, NDA 020966); a product with similar HPβCD content and a similar patient population and duration of treatment as the proposed Voriconazole product by Xellia.

You may not rely on information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries to support a 505(b)(2) application; however you may rely on labeling of the listed drug. You may alternatively be able to rely on published literature. However, if the published literature describes a specific listed drug, you are required to submit an appropriate patent certification or statement with respect to any relevant patents that claim the listed drug.

Taking the above into consideration, your 505(b)(2) application appears to rely upon the Agency's finding of safety for NDA 20966 for Sporanox (itraconazole). Please provide a revised Form FDA 356h specifying reliance on NDA 20966 for Sporanox (itraconazole) as a listed drug that is the basis of your 505(b)(2) application, in addition to VFEND. Please also provide an appropriate patent certification or statement with respect to any relevant patents that claim the listed drug, NDA 20966 for Sporanox (itraconazole), and that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug according to 21 CFR 314.54(a)(1)(vi).

Please let me know if you have any additional questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
05/12/2016

From: Minor, Naseya
To: "Edward Eichmann"
Subject: NDA 208562 Information Request
Date: Tuesday, May 03, 2016 2:01:00 PM
Importance: High

Hi Edward,

We have an information request for NDA 208562

In reviewing your PI we noticed the following statement was included in your 10/28/15 labeling amendment. Please submit the data source (eg. literature reference) that supports the highlighted statement below as well as Table 2.7.1-7 Mean Pharmacokinetic Parameters for HPβCD in Renally Impaired Patients Intravenously Administered 200 mg of Itraconazole and 8g of HPβCD in the Biopharmaceutics Summary.

> (b) (4)
> In patients with normal renal function, the pharmacokinetic profile of hydroxypropylbetacyclodextrin (HPβCD), an ingredient of Voriconazole for injection , has a short half-life of 1 to 2 hours, and demonstrates no accumulation following successive daily doses. In healthy subjects and in patients with mild to severe renal insufficiency, the majority (>85 %) of an 8 g dose of HPβCD is eliminated in the urine. In a study investigating another antifungal drug, itraconazole, following a single intravenous 200 mg dose, clearance of hydroxypropyl-ß-cyclodextrin was reduced in subjects with renal impairment, resulting in higher exposure to hydroxypropyl-ß-cyclodextrin. In subjects with mild, moderate, and severe renal impairment, half-life values were increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of HPβCD until steady state is reached. HPβCD is removed by hemodialysis, (b) (4)

Please submit a response as soon as possible by email and to the NDA.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
05/10/2016

Minor, Naseya

From: Edward Eichmann <Edward.Eichmann@xellia.com>
Sent: Tuesday, May 10, 2016 11:02 AM
To: Higgins, Janet
Cc: Minor, Naseya
Subject: Re: Information Request regarding Proposed proprietary name review for NDA 208562

Good morning,

This communication is to advise / confirm that Xellia is not submitting a proposed proprietary name for this product. Please confirm receipt of this email and advise if any further action on this subject is required.

Thank you and have a nice day

Ed Eichmann

xellia
Edward Eichmann
US Regulatory Affairs Director
Xellia Pharmaceuticals USA, LLC
8900 Capital Blvd
Raleigh NC USA 27616
t+1 919-327-5504 **f**+1 919-871-0309 **m**+1 919-437-7832
edward.eichmann@xellia.com
www.xellia.com

From: "Higgins, Janet" <Janet.Higgins@fda.hhs.gov>
To: "'edward.eichmann@xellia.com'" <edward.eichmann@xellia.com>
Cc: "Minor, Naseya" <Naseya.Minor@fda.hhs.gov>, "Higgins, Janet" <Janet.Higgins@fda.hhs.gov>
Date: 05/09/2016 10:00 AM
Subject: Information Request regarding Proposed proprietary name review for NDA 208562

Dear Mr. Eichmann:

Please refer to your New Drug Application (NDA) dated July 24, 2015, received July 24, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for voriconazole injection.

Please let me know if you plan on submitting a proposed proprietary name for your product.

If you do plan on submitting a proposed proprietary name, we recommend you submit a request for a proposed proprietary name review as soon as possible. Refer to the guidance for industry, *Contents of a Complete Submission for the Evaluation of Proprietary*

Names, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf.

If you have any questions regarding the contents of this email or any other aspects of the proprietary name review process, contact me in the Office of Surveillance and Epidemiology. For any other information regarding this application, contact Naseya Minor, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-0756.

Please confirm receipt of this email. Please respond via email by **May 16, 2016** to me followed by an official submission to your application.

Sincerely,

Janet

Janet G. Higgins
Senior Regulatory Health Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 4345
Silver Spring, MD 20903

(240) 402-0330 (phone)

From:	Higgins, Janet
To:	"edward.eichmann@xellia.com"
Cc:	Minor, Naseya; Higgins, Janet
Subject:	Information Request regarding Proposed proprietary name review for NDA 208562
Date:	Monday, May 09, 2016 10:00:22 AM

Dear Mr. Eichmann:

Please refer to your New Drug Application (NDA) dated July 24, 2015, received July 24, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for voriconazole injection.

Please let me know if you plan on submitting a proposed proprietary name for your product.

If you do plan on submitting a proposed proprietary name, we recommend you submit a request for a proposed proprietary name review as soon as possible. Refer to the guidance for industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf .

If you have any questions regarding the contents of this email or any other aspects of the proprietary name review process, contact me in the Office of Surveillance and Epidemiology. For any other information regarding this application, contact Naseya Minor, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-0756.

Please confirm receipt of this email. Please respond via email by **May 16, 2016** to me followed by an official submission to your application.

Sincerely,

Janet

Janet G. Higgins
Senior Regulatory Health Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 4345
Silver Spring, MD 20903

(240) 402-0330 (phone)

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/s/

JANET G HIGGINS
05/09/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208562

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Xeilla Pharmaceuticals ApS
Attention: David Vogt
US Agent for Xellia Pharmaceuticals ApS
8900 Capital Boulevard
Raleigh, NC 27616

Dear Mr. Vogt:

Please refer to your New Drug Application (NDA) dated July 24, 2015, received July 24, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Voriconazole for Injection, 200mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 24, 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- 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 in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 30, 2015. The resubmitted labeling will be used for further labeling discussions.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Naseya Minor, Regulatory Project Manager, at (301) 796-0756

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

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/s/

SUMATHI NAMBIAR
10/07/2015

From:Minor, Naseya
Sent:Friday, April 24, 2015 12:22 PM
To: (b) (4)
Subject:PreNDA 124450 Preliminary Meeting Responses

Hi (b) (4),

Below are the responses to the questions included in the meeting briefing package for your PreNDA meeting to discuss a 505(b)(2) NDA submission Voriconzaole for injection.

Please be advised that any new information or data not contained in your meeting package and presented in response to these comments will not be considered for official comment. The information may be very briefly presented, but must be provided as a submission to the application subsequent to this meeting to allow an opportunity for appropriate review and comment.

If you wish to cancel this teleconference, the following responses will become part of the administrative record. Please let me know if you have any additional questions.

Regulatory

1.The proposed Table of Contents for the NDA will be provided in the briefing package to demonstrate those sections of the application that Xellia believes are applicable to their product. Does the FDA agree with the planned contents?
FDA Response: From a regulatory standpoint the proposed TOC looks adequate.
2. The proposed 505(b)(2) NDA will rely on the Agency's prior finding of safety and efficacy of VFEND for injection (NDA #021267). Xellia intends to modify the label language for VFEND to reflect the substitution of HP?CD for SBECD in the label sections that refer to the cyclodextrin excipient. Does the Agency agree with this approach?
FDA Response: Yes we agree with this approach.
3.Xellia understands that VFEND was approved without a REMS program and does not intend to include this in the proposed 505(b)(2) new drug application. Does the FDA agree?
FDA Response: At this time a REMS is not required. If a safety signal arises during our review, a REMS may be required.
4.With respect to the need for complying with PREA, in the FDA responses to the PIND meeting questions, the FDA stated:
"If upon review it is determined that this voriconazole formulation does not result in changes in PK/PD parameters compared to VFEND® and BA/BE studies can be waived, then this product would not represent a change in active ingredient, dosage form, dosing regimen, route of administration or new indication. Therefore, PREA requirements would not apply. If upon review it is determined that this formulation results in changes in PK/PD parameters that would lead to changes in dosing regimen, pediatric studies would be required under PREA. Any requests for waiver of such studies should be submitted in the NDA and will be discussed with the Pediatric Review Committee."
Xellia believes they meet the requirements for a biowaiver (refer to Question 11) which will be submitted in their NDA. Xellia does not intend to submit an iPSP or a waiver request in the NDA since this provision does not apply to their product. Does the FDA agree with this approach?

FDA Response: If your application does not include a new active ingredient, indication, dosage form, dosing regimen, or route of administration, then PREA does not apply, and you are not required to submit an iPSP or waiver request.

CMC

5.Xellia has prepared an exhaustive comparability summary report for their voriconazole product when compared to the RLD (VFEND) that demonstrates the comparability between the two products. For ease of review, Xellia plans to include this comparability summary in the Module 2.3 (Quality Overall Summary- QOS) in addition to the required QOS information for this section of the NDA. Does FDA agree to this approach?

FDA Response: Yes, the report can be included in Module 2.

6.The API manufacturer, (b) (4) has an active and current DMF on file at the FDA. A Letter of Authorization (LOA) will be included in the NDA file. As such Xellia plans to refer solely to the DMF in the following Module 3.2.S sections; 3.2.S.2, 3.2.S.3.1, 3.2.S.6 and 3.2.S.7. Xellia will however include pertinent information in the remaining 3.2.S.sections (3.2.S.1, 3.2.S.3.2, 3.2.S.4, and 3.2.S.5) as required for the NDA. Does FDA agree to Xellia's proposal?

FDA Response: Yes, the proposed plan is reasonable.

Nonclinical

7.Xellia intends to seek approval for the same (b) (4), dosing regimen, and patient population as VFEND for injection and has conducted no nonclinical studies of the drug substance, voriconazole, to support their planned 505(b)(2) NDA for voriconazole for injection. Xellia intends to rely on the FDA's prior approval of VFEND for injection to support the safety of the active ingredient. With respect to the extent of background information provided in the NDA, Xellia intends only to provide information in the nonclinical sections (2.4 and 2.6 and applicable sections of Module 4) to support product-specific impurities in the drug substance and drug product, excipients, and any extractables of concern. Does the FDA agree that a summary of publicly available nonclinical studies of voriconazole is not required to support the planned NDA?

FDA Response: Yes, we agree.

8.Xellia believes that a hemolysis study to demonstrate the tolerability of the proposed voriconazole formulation is not necessary. The components of the formulation (voriconazole, HP?CD, and water for injection) are utilized in the Xellia formulation at levels that result in intravenous exposures that are either identical to or are lower than those found in similar FDA-approved intravenous products for comparable patient populations. Does the FDA agree that a hemolysis study of Xellia's formulation is not needed?

FDA Response: Yes, we agree.

9.With respect to the excipient, HP?CD, the FDA indicated in their Pre-IND responses agreement with the conclusion that "the safety of hydroxypropyl ?-cyclodextrin may be supported based on the FDA approval and history of safe use of injectable Sporanox® which provides similar levels of exposure to hydroxypropyl ?-cyclodextrin" and that "no additional nonclinical testing of hydroxypropyl ?-cyclodextrin would be required for the proposed Xellia product." For the planned NDA submission, Xellia intends to rely solely on the FDA approval and history of safe use of injectable Sporanox to support the safety of the use of HP?CD in the Xellia product. Xellia does not believe that a detailed discussion of the safety

of HP?CD is needed. Does the FDA agree this approach is sufficient to support the proposed NDA?

FDA Response: An abbreviated discussion of the safety of HP?CD will suffice.

10.Xellia intends to rely on compliance with USP <381> and USP <87> tests for extractables and leachables from the proposed (b) (4) stoppers as the product is a lyophilized cake that is reconstituted immediately before use and further transferred to a suitable infusion diluent bag for administration. Does the FDA agree with this approach?

FDA Response: Testing per USP <381> and USP <87> is reasonable.
Additionally, compatibility of the stopper with the drug product should be demonstrated. Please provide a risk assessment of the potential for (b) (4) of the Type 1 glass vials as result of the manufacture and storage of the drug product.

Clinical

11.Xellia intends to seek approval for the same (b) (4) dosing regimen, and patient population as VFEND for injection and has conducted no clinical studies of the drug substance or drug product to support their planned 505(b)(2) NDA for voriconazole for injection. Xellia intends to rely on the FDA's prior approval of VFEND for injection to support the safety and efficacy of their product. Xellia intends to limit the clinical sections (2.5, 2.7, and applicable sections of Module 5) to a discussion of the appropriateness of a biowaiver for the product.

a.Xellia has not performed any clinical efficacy studies, and intends to request a waiver for preparing the Module 5 ISE. Does the FDA agree?

b.The safety sections of the VFEND for injection label were updated on January 30, 2015. Given the recent update of the VFEND safety information, Xellia believes that an update to the safety of voriconazole for injection would provide no new information and Xellia intends to request a waiver for the Module 5 (ISS). Does the FDA agree?

FDA Response: You do not need to submit an ISE or ISS. We recommend that you perform a search of the scientific literature to assess if there are any new safety findings reported with voriconazole that are not included in the current VFEND label. If you identify any safety concerns that need to be included in labeling, please provide a justification along with your proposed revision(s) to labeling.

12.In order to demonstrate pharmaceutical equivalence and bioequivalence with VFEND, Xellia has conducted a series of in vitro comparability studies according to the FDA recommendations to the Pre-IND meeting question regarding the biowaiver:

"We recommend that, in your NDA submission, you provide adequate scientific information/data supporting the bridging of your proposed product to the reference product with a side by side summary table comparing your proposed product vs. the reference product (including description, formulation, pH, osmolality, drug concentration, indication, etc.). For any difference(s) between your proposed product and the reference product, justify why this difference(s) would not affect the safety and/or effectiveness of your proposed product."

Does the Agency agree that the executed testing strategy is adequate for supporting evidence

of therapeutic equivalence of Xellia's product to VFEND, and consequently the applicant could be waived the requirement for submission of in vivo bioequivalence data?

FDA Response: Your approach to submit a biowaiver request in your NDA appears appropriate. We refer to our previous recommendation provided in response to the Pre-IND meeting question regarding the biowaiver. All supporting information and justification should be provided in the NDA. The final decision regarding the biowaiver request will be made during review of the NDA. Please note that products covered under 505(b)(2) are not normally assigned a Therapeutic Equivalence (TE) Code. However, some 505(b)(2) products may be assigned a TE Code (e.g., some injectable products that receive a biowaiver). If you would like for your product to be considered for a TE Code in the Orange Book, submit a general correspondence to your NDA after approval of your NDA. Your correspondence should provide details of your request and justification. You should also email a courtesy copy of that request to the Orange Book general inbox at drugproducts@cder.fda.gov. For further information on how these evaluations are made, refer to the Preface of the Orange Book, Section 1.2.:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf

Naseya Minor, MPH
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/s/

NASEYA N MINOR
04/24/2015