CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209816Orig1s000
209817Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

IND 75928
IND 73431

MEETING MINUTES

Paratek Pharmaceuticals, Inc.
Attention: Randall Brenner
1000 First Avenue, Suite 200
King of Prussia, PA 19406

Dear Mr. Brenner:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for the following:

IND 75928 PTK-0796 (Omadacycline) for Injection
IND 73431 PTK-0796 (Omadacycline) Tablets

We also refer to the meeting between representatives of your firm and the FDA on Wednesday, July 26, 2017. The purpose of the meeting was to discuss the content and format of the CMC information to be included in the potential NDA submission.

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, please contact Anika Lalmansingh, Regulatory Business Process Manager at (240) 402-0356.

Sincerely,

{See appended electronic signature page}

Balajee Shanmugam, PhD
Branch Chief (Acting), Branch III
Division of New Drug Product I
Office of New Drug Products
Center for Drug Evaluation and Research Branch

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre- NDA
Meeting Date and Time:	Wednesday, July 26, 2017, 2:30pm-3:30pm
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 75928/ IND 73431
Product Name:	PTK-0796 (Omadacycline) for Injection and Tablets
Indication:	Acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP)
Sponsor/Applicant Name:	Paratek Pharmaceuticals, Inc.
Meeting Chair:	Balajee Shanmugam, PhD
Meeting Recorder:	Anika Lalmansingh, PhD

FDA ATTENDEES

Office of Pharmaceutical Quality (OPQ)

Christina Capacci-Daniel, PhD	Facility Lead (call-in)
Anika Lalmansingh, PhD	Regulatory Business Process Manager
James Laurenson, PhD	Environmental Assessment Reviewer (call-in)
Dorota Matecka, PhD	CMC Lead
Helen Ngai, PhD	Microbiology Reviewer
Erika Pfeiler, PhD	Microbiology Lead
Sateesh Sathigari, PhD	Process Reviewer
Milton Sloan, PhD	Drug Product Reviewer
Balajee Shanmugam, PhD	Drug Product Branch Chief (Acting)
Aditi Thakur, MS	Facilities Reviewer
Katherine Windsor, PhD	Drug Substance Reviewer
Yang Zhao, PhD	Biopharmaceutics Reviewer

Division of Anti-Infective Products (DAIP)

Carmen DeBellas PharmD	Chief Project Manager
Sumati Nambiar, MD, MPH	Clinical Division Director
Dmitri Iarikov	Deputy Division Director (Acting)

SPONSOR ATTENDEES

Paratek Pharmaceuticals, Inc.

Randy Brenner, MS	Senior Vice-President, Regulatory Affairs, Quality Assurance, & Technical Operations

Anita Das, PhD	Statistical Consultant
Sean Johnston, PhD	Vice President, Operations and Manufacturing
Jennifer Li	Regulatory Affairs (CMC) & Quality Assurance
Evan Loh, MD	President, Chief Operating Officer and Chief Medical Officer
Kristen Manion	Senior Director, Regulatory Affairs (CMC) & Quality Assurance
Amy Manley	Senior Director, Clinical Operations
Paul McGovern, MD	Vice President, Clinical and Medical Affairs
Mary Anne Potok	Regulatory Operations
Judith Steenbergen, PhD	Executive Director, Microbiology
Evan Tzanis	Senior Vice President, Clinical Development and Clinical Operations
Stephen Viccia	Senior Manager, Regulatory Affairs

1.0 BACKGROUND

Paratek Pharmaceuticals, Inc. (Paratek) submitted a meeting request to discuss the content and format of the CMC information to be included in the potential NDA submission.

The Office of Pharmaceutical Quality (OPQ) granted the meeting as a type B pre-NDA CMC-only meeting. Paratek also met with the OND Division of Anti-Infective Products on Wednesday, July 26, 2017 from 1:00pm – 2:00pm, to discuss non-CMC issues.

Paratek has developed Omadacycline p-Toluenesulfonate as an immediate-release, film-coated tablet and a sterilized, lyophilized powder for infusion under IND 73431 and IND 75928, respectively. The current meeting request was in reference to both INDs.

FDA sent Preliminary Comments to Paratek Pharmaceuticals, Inc. on Friday, July 21, 2017.

2.0 DISCUSSION

***Question 1:** The Sponsor intends to request categorical exclusion from submission of an environmental assessment for the New Drug Application (NDA) No. 20-9816 Omadacycline Tablets, 150mg and NDA No. 20-9817 Omadacycline IV, 100mg in accordance with 21 Code of Federal Regulations §25.31 (a). Does the Agency agree?*

FDA Response to Question 1:

The categorical exclusion that you cited, 21 CFR 25.31(a), is for actions that do not increase the use of the active moiety. The correct exclusion would appear to be 21 CFR 25.31(b), for actions that increase the use of the active moiety, but for which the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. Please provide the derivation of the expected quantity of the substance use, and the estimated introduction concentration (EIC). Also, the daily dose scenario presented is not relevant to your statement that

omadacycline is considered unlikely to represent a risk for the environment (also referred to as "extraordinary circumstances"). Please provide any readily available information on the likely impact of omadacycline on the environment. For example, given the likely similarity between the effects of omadacycline and tetracycline and other related substances, you could provide a brief description of the most recent literature that addresses the impact of these related substances, and the additional impact that omadacycline might contribute cumulatively.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): No further discussion.

***Question 2:* The Sponsor does not intend to perform a leachable and extractable study on the primary container closure for Omadacycline IV. Does the Agency agree?**

FDA Response to Question 2:
The discussions presented in the briefing document are acknowledged. Since it is possible that undesirable compounds may emanate from the stopper during prolonged storage and may become adsorbed on the powder contents, we recommend extractable and leachable study through the proposed shelf-life. We recommend that the full study report be submitted in module 3.

Paratek's Response (received 7/25/2017):
The Agency's feedback is very clear; however, Paratek would like to further discuss Question #2. Specifically, would the Agency agree to the Sponsor submitting extractable testing on our proposed stopper and leachable testing on a representative Omadacycline IV clinical batch (Batch 57501A or Batch 57502A) that has been stored through 18-24 months at the long-term stability condition (25°C/60%RH) within 2 months of submission of the NDA or submission of the final module (if rolling NDA). The leachable study would be performed as per our proposed label language; (b) (4) *. Does the Agency agree?*

For reference, batches 57501A and 57502A were manufactured at the proposed commercial manufacturing site (b) (4) *utilizing the proposed drug product composition, manufacturing process, and container closure system. The Sponsor considers the data for these batches to be representative of the proposed commercial process for Omadacycline IV.*

Table 1 Batch Details for Supportive Batch of Omadacycline IV, 100 mg Unit Dose,

	Batch Details		***Proposed Commercial Process***
Batch Number	(b) (4) *57501A*	(b) (4) *57502A*	*N/A*

	Batch Details	***Proposed Commercial Process***
Manufacturer API	(b) (4)	
Manufacturer Lyophilization cycle		
Primary container closure		
Batch size (vials)		

At this time, the Sponsor is still considering our proposed shelf life but clinical Batches 57501A and 57502A were manufactured prior to the registration batches and therefore have been stored at the long-term stability condition (25°C/60%RH) for a greater amount of time. The Sponsor would then commit to testing one representative primary registration/stability batch if the accepted shelf life is longer than the time-point for which the representative clinical batch (b) (4) 57501A or (b) (4) 57502A) were tested (e.g. 36 months, 48 months, etc . . .). This data would be generated post approval and submitted in a future annual report. Would the Agency be agreeable to this approach?

Meeting Discussion (7/26/2017): In discussing timelines for submission of the leachable study, the Sponsor indicated that they plan to submit a complete NDA by December 2017 and obtaining leachable/extractable and stability data may result in the submission of an incomplete application in December 2017. The Agency was willing to accept submission of the extractables/leachables data within 2-months of the NDA submission. The Sponsor plans to use aged clinical batches, as indicated above, to study extractables and leachables. The Agency emphasized that the chosen batches should be representative of the proposed commercial batch with regards to formulation, manufacturing process and container closure system and requested this information to be submitted in the NDA. The Sponsor indicated that these batches have been stored for 18-24 months. The Sponsor accepted the Agency's recommendation to perform leachables study of the constituted solution using vials in both upright and inverted orientations, the later representing the worst-case scenario. The Agency also agreed to review the extractable/leachable study protocol if submitted for comments via a Written Response Only (WRO) meeting request prior to conducting the study. In responding to the Agency's question on the orientations used in the long-term stability studies the sponsor indicated that the vials were not stored in inverted orientation.

Regarding the Sponsor's proposal to submit extractable/leachable data from extended time points (36, 48 months) from one representative primary registration/stability batch in

a future annual report, the Agency indicated that a determination can be made after evaluation of the stability data submitted in the NDA.

Question 3: ***As per the Agency's recommendation, the Sponsor intends to perform an in-use study for omadacyline IV and provide microbiological data*** (b) (4) ***to support the post constitution storage time of*** (b) (4) ***. Does the Agency agree?***

FDA Response to Question 3:

(b) (4) In addition to *S. epidermidis* and *S. aureus,* it is recommended to include strains as described in USP <51> including *C. albicans, A. brasiliensis, E. coli* and *P. aeruginosa* when performing the post-constitution and post-dilution storage study.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and would like to discuss this further. Upon further consideration, the Sponsor believes that evaluating Staphylococcus epidermidis and Staphylococcus aureus for our product is not warranted due to the proven potency of omadacycline against both S. epidermidis and S. aureus with MIC90 values 1.0 and 0.25 µg/mL, respectively. Considering the Agency's feedback, the Sponsor proposes to focus the microbiological testing on the 4 microorganisms as specified in USP<51> (C. albicans, A. brasiliensis, E. coli and P. aeruginosa) as these would provide the most meaningful data for omadacycline IV. Does the Agency agree?

In addition, the Sponsor is proposing to submit in-use microbiological testing (C. albicans, A. brasiliensis, E. coli and P. aeruginosa) and on a representative Omadacycline IV clinical batch (Batch 57501A or Batch 57502A) that has been stored through 18-24 months at the long-term stability condition (25°C/60%RH) within 2 months of submission of the NDA or submission of the final module (if rolling NDA). As discussed above, batches 57501A and 57502A are considered representative batches for the proposed commercial process for Omadacycline IV. Would the Agency agree?

The Sponsor would not repeat the microbiological testing on the primary registration/stability batches at a longer storage time as microbiological data would not change over time. The also Sponsor prefers to do this testing with a representative clinical batch due to constraints in the number of vials pre-determined and set aside for the primary registration/stability program. Does the Agency agree?

The chemical in-use stability study will continue as planned and be provided on the three-primary registration/stability batches beginning with the 12-month testing being

submitted within 2 months of submission of the NDA or submission of the final module (if rolling NDA). Would the Agency be agreeable to this approach?

Meeting Discussion (7/26/2017): The Agency recommended that all 5 microorganisms be tested as originally proposed. The microbiological in-use study comment with study design in provided below. In addition, the Agency agreed to the following:

1. Performing in-use microbiology studies on representative (aged) clinical batches only and not repeating the studies on the primary registration/stability batches (this only applies if clinical batches are the same formulation as proposed for commercial production).
2. Submission of in-use microbiology study data within 2 months (60 days) after submission of the NDA
3. Submission of the in-use chemical stability study data within 2 months (60 days) after the NDA submission.

***Question 4:** As per the Meeting Granted Letter issued by the FDA (dated 15May2017), the Sponsor is providing an overview of the content of NDA 20-9816 for Omadacycline Tablets, 150mg in Attachment #1 and is providing an overview of the content of NDA 20-9817 for Omadacycline IV, 150mg in Attachment #2 including a comprehensive list of the clinical sites and proposed commercial manufacturing facilities for omadacycline tosylate drug substance, omadacycline oral tablets, and omadacycline IV. The Sponsor is requesting agreement with the proposed content as provided in the two attachments and is also soliciting any general advice regarding the proposed content of the CMC section of the NDA to ensure first round approval. Does the Agency agree with the Sponsor's proposed content for the two NDA submissions and does the Agency have any general feedback to provide?*

FDA Response to Question 4:

The outlined content for the tablet and IV NDA's appears reasonable. However, adequacy of the information provided will be evaluated during review and additional information may be requested to aid in further evaluation.

It is noted that the process validation campaign is not complete. Note that all sterilization validation activities must be included in the submission, or the application will not be fileable.

An overview of the information that is required in the submission can be found in the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products:
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

Additionally, Based on the background information provided on the manufacturing processes, the Agency has the following general comments:

1. The manufacturing process flow diagram for tablets on page 16 (Figure 3) lacks in- process controls for [redacted](b) (4) process steps. The process flow diagrams in module 3.2.P.3.3 should be complete and should show all the manufacturing process steps, material flow and in-process controls.
2. Applicant should address/discuss in the tablet NDA application the impact of the manufacturing process ([redacted](b) (4)) on the polymorphic form of the drug substance in the tablet.
3. The Intravenous NDA application should include details on the lyophilization process development and scale up approach in module 3.2.P.2.2.

Regarding facilities, the agency does not have any specific comments on the information communicate with your contract manufacturers to ensure that they continue to resolve any outstanding inspectional issues. In addition, you should seek full transparency of historical inspectional issues to have a full understanding of the potential impact to your IND and intended NDA submission. Further, we remind you of your responsibility as a sponsor to ensure your clinical and commercial manufacturing is conducted in accordance with CGMPs as described in FDA Guidance: Contract Manufacturing Arrangements for Drugs: Quality Agreements available at:

https://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): No further discussion.

Question 5: ***In addition, and as per the Meeting Granted Letter issued by the FDA (dated 15May2017), the Sponsor is requesting agreement to our proposals (including any minor components to be submitted after the Sponsor's original submission) as outlined here and previously agreed upon with the Agency. The Sponsor is looking to document all previous agreements made with the Agency in the official preNDA Meeting Minutes.***

Question 5a: ***The Sponsor is intending to provide a cross reference to NDA 20-9816 for all drug substance information supporting the IV formulation for omadacycline as agreed in the Agency's Written Response (dated 03-MAR-2017). Paratek requests reconfirmation of the Agency's previous agreement here.***

FDA Response to Question 5a:
We agree with your proposal to provide a cross reference to NDA 209816 (for the oral tablet formulation) for all CMC drug substance information supporting the IV formulation for omadacycline.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): No further discussion.

Question 5b: ***The Sponsor is intending to categorize*** [redacted]**, *purchased commercially from suppliers who have submitted a Drug Master File (DMF) as the starting material for omadacycline drug substance as agreed with the Agency at the May 17, 2016 CMC Type C Meeting. Paratek requests reconfirmation of the Agency's previous agreement here.***

FDA Response to Question 5b:
We agree that any [redacted] purchased for use in your drug substance manufacturing process should be sourced from suppliers with active DMFs. We remind you that in this case the regulatory starting material is not [redacted] itself, but rather the DMF starting material(s) used to synthesize [redacted]. Therefore, all steps from the DMF starting material(s) onward should be conducted under GMP. Provide a Letter of Authorization for each [redacted] DMF in the NDA submission.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): No further discussion.

Question 5c: ***The Sponsor considers omadacycline drug substance to be adequately characterized as agreed in the Agency's preliminary feedback for the Type C CMC meeting (dated 12-MAY-2016). Paratek requests reconfirmation of the Agency's previous agreement here.***

FDA Response to Question 5c:
We agree that the drug substance has been sufficiently characterized.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): No further discussion.

Question 5d: ***The sponsor manufactured our three-primary registration/stability batches for omadacycline drug substance as follows and as agreed in the Agency's preliminary feedback for the Type C CMC meeting (dated 12-MAY-2016).***

1. ***Registration Batch 1:*** [redacted] (b) (4)
2. ***Registration Batches 2 & 3:*** [redacted] (b) (4)

Paratek requests reconfirmation of the Agency's previous agreement here.

FDA Response to Question 5d:
We agree with your proposal.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): No further discussion.

Question 5e: ***The Sponsor is soliciting any additional feedback regarding the proposed control strategy concerning omadacycline drug substance as provided and as preliminarily agreed with the Agency as part of the Agency's feedback for the Type C CMC meeting (dated 12-MAY-2016). Specifically, the Sponsor is looking for general agreement/feedback regarding the control strategy for omadacycline drug substance but is also requesting specific feedback regarding the proposed individual unspecified impurities acceptance criterion of ≤ [redacted] (b) (4) area%. Does the Agency still generally agree with the proposed control strategy for omadacycline drug substance and does the Agency still agree with the proposed individual unspecified impurities acceptance criterion of ≤ [redacted] (b) (4) area%?***

FDA Response to Question 5e:
We agree that the proposed specification appears reasonable, provided you include adequate justification for exclusion of elemental impurities testing in the NDA submission. Controlling each individual unspecified impurity at ≤ [redacted] (b) (4) area% appears acceptable. A final determination of the acceptability of the specification will be made at the time of NDA review.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): No further discussion.

Question 5f: ***The Sponsor is soliciting any additional feedback regarding the proposed control strategy concerning omadacycline tablets as provided and as preliminarily***

agreed with the Agency as part of the Agency's feedback for the Type C CMC meeting (dated 12-MAY-2016). Does the Agency still generally agree with the proposed control strategy for omadacycline tablets?

FDA Response to Question 5f:
We agree and a final determination on the acceptability of the proposed specification will be determined at the time of NDA review.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): *No further discussion.*

Question 5g: The Sponsor is intending to submit 12 months of long-term stability data for 1 registration batch for the tablets packaged in the HDPE bottle and 9 months of long-term stability data for the remaining 2 registration batches for the tablets packaged in the HDPE bottle at time of the full NDA submission with the commitment to submit the 12 months of stability data on the 2 remaining registration batches at the long-term stability condition within 2 months of the initial submission date of the NDA as agreed in the Agency's written feedback for the General Type B WRO dated 03-MAR-2017. Paratek requests reconfirmation of the Agency's previous agreement here.

FDA Response to Question 5g:
Yes, we agree with the recommendations in the WRO dated 03-March-2017 on the stability package at the time of NDA submission. We also confirm that in consideration of the potential need for your product, we accept your proposal to submit the 12-month stability update for the two batches no later than 2 months after the NDA submission.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): In response to Agency's request for clarification on the size of the HDPE bottle in the bracketing studies for stability, the Sponsor confirmed the HDPE bottles are the same size.

Question 5h: The Sponsor considers the dissolution method to be adequately developed and suitable for use for omadacycline tablets. The Sponsor does not intend to perform any additional development work (including illustrating discriminatory power) for the dissolution method as per the response from the Agency dated 14May2017. Paratek requests reconfirmation of the Agency's previous agreement here.

FDA Response to Question 5h:
Yes, the Division agrees.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): No further discussion.

Question 5i: ***The Sponsor is soliciting any additional feedback regarding the proposed control strategy concerning omadacycline IV as provided and as preliminarily agreed with the Agency as part of the Agency's feedback for the Type C CMC meeting (dated 12-MAY-2016). Does the Agency still generally agree with the proposed control strategy for omadacycline IV?***

FDA Response to Question 5i:
We agree and a final determination on the acceptability of the proposed specification will be determined at the time of NDA review

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): No further discussion.

Question 5j: ***The Sponsor is intending to submit 12 months of long-term stability data for 1 registration batch for the IV and 9 months of long-term stability data for the remaining 2 registration batches for the IV at time of the full NDA submission with the commitment to submit the 12 months of stability data on the 2 remaining registration batches at the long-term stability condition within 2 months of the initial submission date of the NDA as agreed in the Agency's written feedback for the General Type B WRO dated 03-MAR-2017. Paratek requests reconfirmation of the Agency's previous agreement here.***

In addition, the Sponsor would also like to propose submitting the 12 month in-use stability data for the 3 registration batches and the photo stability data for 1 registration batch within 2 months of the initial submission date of the NDA. Would the Agency be willing to accept this proposal?

FDA Response to Question 5j:
The proposed timelines are acceptable.

Paratek's Response (received 7/25/2017):
Paratek acknowledges FDA's response and no further discussion is warranted at this time.

Meeting Discussion (7/26/2017): *No further discussion.*

FDA and Sponsor Agreements on timelines for data submission:

The FDA inquired about the timeline for the NDA submission. The Sponsor replied that they are currently exploring the following two options,
a) Rolling submission of the NDA with Module 3 submitted in December 2017, or
b) Submission of the complete NDA in the first quarter of 2018.

The Sponsor indicated that they are likely to opt for option b but a firm decision has not been made yet. It was agreed that if the NDA will be submitted in the first quarter of 2018 it will provide complete CMC information including those agreed to be submitted within 2-months of the NDA submission planned under the rolling submission option.

The Agency was willing to accept submission of the following information within 2-months of the NDA submission if the NDA will be submitted in December 2017.

1) Results of extractables/leachables studies
2) Results of chemical and microbiological in-use stability testing
3) Submission of 12-month stability data on the 2 remaining registration batches at the long-term stability condition for both drug products.

3.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit a sponsor a sample microbiology protocol (see below)	FDA	as soon as possible

4.0 Post-Meeting Comments

Microbiology Comments

Microbiological studies in support of the post-constitution or post-dilution storage time (as stated in the proposed product labeling) should be performed. Please provide a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage (time, temperature, and diluent(s)) Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Please include a description of the test methods and results of studies that are designed using a minimum countable inoculum (<100 CFU/mL) to simulate potential microbial contamination that may occur during product constitution and/or dilution. It is generally accepted that growth is evident when the population increases more than 0.5 log10, however other evidence of growth may be significant. Please perform the test using the storage conditions (temperature and duration) and diluents specified in product labeling. Please provide justification for the selected test conditions

and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the reconstituted and/or diluted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> plus typical skin flora, species associated with nosocomial infection. Please provide a positive control that demonstrates the viability of the organisms over the duration of the test period.

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

/s/

BALAJEE SHANMUGAM
08/23/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 75,928

Paratek Pharmaceuticals, Inc.
Attention: S. Ken Tanaka, Ph.D.
Vice President, Research and Development
75 Kneeland Street
Boston, MA 02111

Dear Dr. Tanaka:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PTK 0796.

We also refer to the face-to-face meeting between representatives of your firm and the FDA on July 7, 2008. The purpose of the meeting was to discuss overall development of PTK 0796.

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

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Katherine Laessig, MD
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 7, 2008
TIME: 02:00 PM – 03:00 PM (EST)
LOCATION: White Oak Building 22, Room 1309
APPLICATION: IND 75,928
DRUG NAME: PTK 0796
TYPE OF MEETING: Type B, End-of-Phase 2

MEETING RECORDER: Kyong Hyon

FDA ATTENDEES: (FDA)
Division of Anti-Infective and Ophthalmology Products

Wiley A. Chambers, MD, Acting Director
Katherine Laessig, MD, Deputy Director
John Alexander, MD, MPH, Clinical Team Leader
Tatiana Oussova, MD, Clinical Reviewer
Wendelyn Schmidt, PhD, Pharmacology/Toxicology Team Leader
Kerry Snow, MS, Clinical Microbiology Reviewer
Rapti Madurawe, PhD, Pharmaceutical Assessment Lead, Branch IV, ONDQA
Sarah Robertson, PharmD, Clinical Pharmacology Reviewer
Thamban Valappil, PhD, Statistical Team Leader
Mushfigur Rashid, PhD, Statistical Reviewer
Kyong Hyon, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES: (Sponsor)
Paratek Pharmaceuticals, Inc.

Robert Arbeit, MD, Vice President, Clinical Development
Sean Johnston, PhD, Vice President, Operations
Stanton Ken Tanaka, PhD, Vice President, Research and Development, Clinical Microbiology
Robert McCormack, PhD, Regulatory Consultant
Dennis Molnar, PhD, Vice President, Corporate Development
Elizabeth Cannon, PhD, A.D. Preclinical and Toxicology Development
Michael Draper, PhD, Director, Anti-infective Drug Discovery

BACKGROUND: On April 11, 2008, Paratek Pharmaceuticals requested an End-of-Phase 2 meeting with the Division to discuss overall development of PTK 0796. The face-to-face meeting was granted on April 23, 2008 and scheduled to occur on July 7, 2008. The meeting package was submitted on May 29, 2008. The Division sent written response to the Sponsor's questions from the meeting package on July 1, 2008 via e-mail and U.S. mail. On July 6, 2008, the Sponsor sent power point slides of their responses and clarification questions to the Division's July 1, 2008 written response via e-mail (see attachment)

MEETING OBJECTIVES: To discuss the specific questions posed in the meeting package

DISCUSSION POINTS: The following is a summary of the minutes of the face-to-face meeting held on July 7, 2008, including prior communication. The Sponsor's initial questions are in bold followed by responses from the Division and the points discussed during the face-to-face meeting.

The meeting started with the introduction of the attendees and a brief description of the purpose of the meeting followed by discussion in the order of questions from the meeting package.

Chemistry and Manufacturing Controls

1) Based on the release profile of the 100 mg PTK 0796 tosylate tablets does FDA agree that (b) (4) **?**

Division Response (per July 1, 2008 e-mail):
This may be acceptable depending on an evaluation of the data described below, some of which has yet to be submitted.

(b) (4)

Discussion at the July 7, 2008 face-to-face meeting: No further discussion was needed as indicated in slide 2 of presentation.

Nonclinical

2) Does the FDA agree that the current nonclinical program is acceptable in supporting the Phase 3 clinical studies in cSSSI and CAP with the PTK 0796 tosylate salt?

Division Response (per July 1, 2008 e-mail):
From the pharmacology/toxicology perspective, the studies appear to be sufficient to support the clinical program. However, further issues may arise during the review of the pending studies or in light of clinical toxicities.

Discussion at the July 7, 2008 face-to-face meeting: No further discussion was needed

Clinical Microbiology:

The clinical microbiology reviewer requests that additional information be submitted to the IND prior to initiation of phase 3 studies:

1. Confirm which specific bacterial pathogens will be sought in the proposed indications.
2. Provide in vitro data describing the antimicrobial activity of PTK 0796 against recent clinical isolates of the particular pathogens sought in the proposed indication. Provide data for at least 100 recent isolates of each pathogen, and information should be included that describes the source of the isolate, the recovery date, and the geographic origin of the isolate. Isolates with specific mechanisms of resistance, as well as prominent biotypes, genotypes, and serotypes should be included in the test panel (including isolates positive for the Panton Valentine leukocidin, isolates expressing tetracycline resistance genes, etc.) The methods used for identification of isolates and the determination of minimum inhibitory concentration should be described. Quality control information for all determinations should be included. The data should be submitted both as tabulated summaries and as a line listing suitable for analysis with standard statistical software (e.g. JMP). Summarized data should include the MIC_{range}, MIC_{50}, MIC_{90} and MIC:MBC ratio.
3. Submit quality control information for the in vitro data submitted to date.
4. Include definitions, in the summary tables included in this submission, for "penicillin-resistant *S. pneumoniae*", "multi-drug-resistant *S. pneumoniae*", and other resistant phenotypes listed. Definitions should include the MIC breakpoint used to define resistance.
5. Investigate interactions between PTK 0796 and other antimicrobials (synergy, antagonism, indifference), including combinations involving bactericidal antimicrobials.
6. Present preclinical data describing patterns of antibacterial killing (e.g. time-kill studies) and pharmacodynamic data to predict inoculum effects and persistent antibiotic effects (PAE, PALE, etc.)

7. Develop provisional interpretive susceptibility breakpoints for PTK 0796.
   Refer to the following references:
   a. Attachment A regarding development, analysis, and presentation of microbiologic data for antibacterial drug products.
   b. "Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters; Approve Guideline-Second Edition", published by the Clinical Laboratory Standards Institute [CLSI].
8. Develop quality control parameters for susceptibility testing (MIC and disk diffusion) of PTK 0796. Provide the briefing material recently presented at the June 15-17 meeting of the Clinical and Laboratory Standards Institute. Comment on the testing discrepancies observed when testing Haemophilus species against PTK 0796.
9. Perform additional mechanism of resistance studies, as well as studies designed to determine the occurrence of resistance via currently understood mechanisms of tetracycline resistance. Investigate the potential for the development of heteroresistance in targeted pathogens to PTK 0796.
10. Investigate the in vitro activity of PTK in human body fluids (including plasma protein, lung surfactant, and blister fluid).
11. Perform additional studies designed to describe the mechanism of action of PTK 0796.
12. Determine the intracellular activity/concentration of PTK 0796.
13. Define the effect of culture conditions (media, surfactants, temperature, atmosphere, pH, etc.) on susceptibility testing procedures.
14. Please provide detailed microbiologic data from Phase II trials (organisms isolated, MIC values, test methodology, quality control parameters, source of data (centralized or local lab), etc.).
15. Provide the literature referenced in the summarized data included in this submission, describing in vitro activity of PTK 0796 and in vivo activity in animal models of infection.
16. Provide complete detailed procedures for all microbiologic investigations planned in Protocol PTK 0796-CSSI-0804 and Protocol PTK 0796-(b) (4), including specimen collection, shipping, Gram stain, culture, isolate identification, techniques used to determine genotype/phenotype of pathogens, and susceptibility testing. Methods should include algorithms used by the testing facility to identify which colonies are identified as pathogens (and further tested) and which are dismissed as "contaminants." Indicate which procedures will be performed at the local site and which will be referred to a central testing laboratory. Please ensure that all testing is performed by a facility that is qualified and appropriately accredited (e.g. accreditation by the College of American Pathologists). *It is preferred that susceptibility testing be performed by the central reference laboratory.*
17. Perform susceptibility testing on all pathogens collected during the proposed Phase 3 trials, including isolates from subjects considered clinical failures in either the PTK 0796 or comparator arms.
18. (b) (4)
19. Ensure that all isolates collected in Phase 3 trials are labeled and preserved for additional analysis, as needed.

REFERENCES:

NCCLS. *Development of* In Vitro *Susceptibility Testing Criteria and Quality Control Parameters*; *Approved Guideline-Second Edition*. NCCLS document M23-A2 (ISBN 1-56238-435-X). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2001.

Discussion at the July 7, 2008 face-to-face meeting:

3) In correspondence dated November 1, 2006 FDA requested that appropriate antigenicity studies be conducted. Does FDA agree that the proposed antigenicity study satisfies this request?

Division Response (per July 1, 2008 e-mail):
The proposed study may be excessive, as some of the answers could be obtained by adding observations to the proposed 3 month toxicology studies (e.g., adding a Coombs test to help investigate the drop in RBC numbers seen in 28-day studies). Please see Guidance for Industry – Immunotoxicology Evaluation of Investigational New Drugs (October 2002) available at http://www fda.gov/cder

Discussion at the July 7, 2008 face-to-face meeting: The Sponsor agreed to perform Coombs tests during 3 month toxicology studies and no further discussion was needed.

4) Does the FDA agree that a Segment III reproductive toxicology study does not need to be performed to support the filing of the NDA?

Division Response (per July 1, 2008 e-mail):
A segment III reproductive toxicity study will not be required as there is existing class labeling and human data for other tetracyclines.

Discussion at the July 7, 2008 face-to-face meeting: No further discussion was needed.

5) Does the FDA agree that carcinogenicity studies do not need to be performed to support the filing of the NDA?

Division Response(per July 1, 2008 e-mail):
Yes. Carcinogenicity studies are not required for this duration of use.

Discussion at the July 7, 2008 face-to-face meeting: No further discussion was needed.

6) Does FDA agree that the anticipated overall nonclinical program is acceptable to potentially support approval of an NDA for PTK 0796 tosylate salt as an intravenous and an oral formulation?

Division Response (per July 1, 2008 e-mail):
Yes. See Pharmacology/Toxicology comments for question 2.

Discussion at the July 7, 2008 face-to-face meeting: No further discussion was needed.

Clinical

7) Does the FDA agree that the results from Phase 1 clinical pharmacology and bioequivalence studies and from the Phase 2 study in cSSSI support proceeding to Phase 3 trials in cSSSI with the PTK 0796 tosylate salt?

Division Response (per July 1, 2008 e-mail):
Additional information needs to be generated before proceeding with phase 3 study for cSSSI indication (see microbiology comments in question #2 and clinical pharmacology comments below).

Providing us with additional data from the cSSSI Phase 2 study would help us to better understand the drug's safety profile. Since the drug has a dose-related potential to prolong QT interval, ECG data from Phase 2 study should be reviewed in full. We are particularly interested to know whether there were any patients with evidence of possible liver toxicity. Therefore, provide all available data for transaminases, bilirubin, and alkaline phosphatase. Also, provide a table with the exposure data from the phase 2 study.

If a new oral formulation of PTK 0796 is developed, the bioavailability of the oral formulation should be assessed using IV PTK 0796 as a reference. A bioequivalence (BE) study comparing the new oral formulation to the previous freebase capsule is not necessary as long as the final, to-be-marketed formulation is used in the Phase 3 efficacy trials. If the final formulation is not used in the Phase 3 trials, then a BE study will need to be conducted in which both oral formulations are administered under fasted conditions. In addition to evaluating $AUC_{0-\infty}$, the BE study should also evaluate AUC_{0-t} and Cmax with respect to the pre-specified statistical criteria for the purposes of establishing bioequivalence. In addition, the effect of food on the bioavailability of the new formulation should be assessed. All food effect, BE and bioavailability studies should utilize a crossover design in which all subjects receive both the test and reference treatments with a sufficiently long washout period.

Discussion at the July 7, 2008 face-to-face meeting:

- In slides 3-9, the Sponsor reviewed the previously submitted QT related data in their IND to demonstrate that there was no evidence of dose related QT interval prolongation although the dose related heart rate acceleration was observed; they observed the increased heart rate with high dose. The Sponsor proposed to conduct a formal QT study during Phase 3. The Division advised the Sponsor of the Agency's recommendation that the formal QTc study be conducted prior to Phase 3 studies, in accordance with the E14 Guidance document. The Division stated that without results from a QTc study additional monitoring may be necessary during Phase 3. The Sponsor acknowledged this point and agreed to discuss the timing of their QTc study internally.
- The Sponsor agreed that if a new oral dosage form is developed prior to Phase 3, the bioavailability will be assessed relative to IV PTK 0796, as will the effect of food, using a crossover design (slide 10). The Division also commented that the effect of antacids on oral bioavailability may need to be assessed in the future.
- (b) (4)

Other Clinical Pharmacology comments for the Sponsor (per July 1, 2008 e-mail):

1. Clarify whether the urinary excretion of PTK 0796 has been assessed in humans.
2. Describe the stability of PTK 0796 in human liver microsomes, as well as the characterization of any circulating metabolites in human plasma and urine.
3. A renal impairment study may need to be conducted depending on the extent to which PTK 0796 is excreted unchanged in the urine. It is encouraged that the study be conducted prior to commencing with the Phase 3 studies, such that appropriate doses may be identified for renally impaired patients, thus allowing enrollment of individuals with severe renal impairment.
4. Given that > 20% of systemic PTK 0796 is likely eliminated by hepatic metabolism and/or excretion, a hepatic impairment study should be conducted. It is preferable the study be conducted prior to conducting any Phase 3 studies, such that appropriate doses may be identified, thereby allowing enrollment of individuals with hepatic impairment.
5. (b) (4)
6. What is the magnitude of the PK/PD target (AUC/MIC) identified for PTK 0796? Please justify the doses selected for evaluation in the Phase 3 studies based on what is known about the PK/PD.
7. Please provide justification for the exclusion of elderly subjects > 80 years of age from the Phase 3 trials.
8. Sparse PK samples should be collected in all Phase 3 clinical trials in order to provide data for an exposure-response analysis for efficacy and safety.
9. A formal QT study should be performed before proceeding with Phase 3 studies.

Discussion at the July 7, 2008 face-to-face meeting:

- In slide 11, the Sponsor indicated that information regarding PTK 0796 inhibition of human liver P450 isoenzyemes had previously been submitted.
- The Sponsor agreed to submit the following prior to Phase 3 as indicated in slide 12:
  - Phase 2 safety data, including LFTs, exposure to study drug by subject
  - Stability of PTK 0796 in human liver microsomes
  - PK/PD target and dose justification
  - Removal of age exclusion (> 80 years) from Phase 3; this will be submitted in the revised protocol.
- The Sponsor agreed to submit the following during Phase 3 as indicated in slide 13:
  - Renal impairment study
  - Hepatic impairment study
  - Protocol amendment to permit enrollment of these patient populations

- The Sponsor agreed to submit the following with the NDA as indicated in slide 14:
  - Urinary excretion studies (validated bioanalytic assay in development)
  - Characterization of circulating metabolites in human plasma and urine
  - Exposure-response analysis of Phase 3 studies based on sparse PK

8) Does the FDA agree that the design of the Phase 3 clinical studies for cSSSI, including the justification for the delta in establishing non-inferiority, is acceptable to potentially support NDA approval in this indication?

Division Response (per July 1, 2008 e-mail):

(b) (4)

Discussion at the July 7, 2008 face-to-face meeting:

(b) (4)

9) Paratek is planning to submit an initial NDA containing both the cSSSI and CAP indications. However in the event the CAP Phase 3 trials take longer to complete the sponsor may want to submit the initial NDA with just the cSSSI indication. If this is the case does FDA agree that the planned overall safety database is acceptable to potentially support NDA approval in the cSSSI indication?

Division Response (per July 1, 2008 e-mail):
We would prefer to see both cSSSI and CAP indications submitted at the same time to assure an adequate safety database. If you submit cSSSI as a single indication, we would prefer to see a larger database than the one proposed to provide safety information from a larger number of subjects. We recommend increasing patient numbers by approximately 200 patients per study (approximately 100 patients per arm) for the cSSSI trials. If significant toxicities are identified, additional data might be required.

Discussion at the July 7, 2008 face-to-face meeting:

- In slides 17-18, the Sponsor proposed safety database for NDA which will include greater than 1400 subjects in PTK population. The Division stated that this number is acceptable as long as there would be no significant toxicities are identified in phase 3 study.

- (b) (4)

10) Does FDA agree that the pediatric development plan is acceptable for filing the NDA?

Division Response (per July 1, 2008 e-mail):
There are safety concerns about the use of tetracycline group drugs in children less than 8 years of age, however we see no reason to exclude children aged 8-13 from pediatric studies. A complete pediatric development plan should be submitted to include outlines and timelines for completing multiple dose safety and efficacy studies for the proposed indications, as well as the single dose PK study.

We encourage you to start collecting PK data in children while doing phase 3 studies in the adult population.

Discussion at the July 7, 2008 face-to-face meeting:

- In slide 19, the Sponsor agreed to conduct followings in phase 3:
  - (b) (4)
  -
- The Sponsor would submit a complete pediatric program with detailed timelines for efficacy studies with NDA. The Division stated that these would be acceptable.

11) Does the FDA agree that the results from Phase 1 clinical pharmacology and bioequivalence studies and from the Phase 2 study in cSSSI support proceeding to Phase 3 trials in CAP with the PTK 0796 tosylate salt?

Division Response (per July 1, 2008 e-mail):
The CAP study may be initiated after pre-clinical requirements are satisfied (see comments to #7). We recommend obtaining data documenting lung penetration in humans (e.g. ELF concentrations) prior to proceeding with Phase 3 trial.

Discussion at the July 7, 2008 face-to-face meeting:

- In slide 20, the Sponsor agreed to conduct and submit the data of the followings:
  - *In vitro* activity in surfactant prior to phase 3 CAP
  - *In vivo* ELF concentration study will be submitted with the NDA

- The Division was concerned over conducting phase 3 study of CAP without the human ELF study and recommended that an ELF study be conducted prior to phase 3 study. The Sponsor responded that it is difficult to do ELF study on human, but there are the microbiological data, *in vivo* activity, and the history of the tetracycline class in treating pneumonia to support phase 3 study of CAP. The Sponsor stated they will submit this reason to the Division for review.

12) Does the FDA agree that the design of the Phase 3 clinical study for CAP, including the justification for the delta in establishing non-inferiority, is acceptable to potentially support approval of this indication?

Division Response (per July 1, 2008 e-mail):
Two adequate, double-blind and well-controlled studies, each convincing on its own, to establish the efficacy of a drug should be conducted for CAP indication. Because microbial resistance patterns differ by location, we prefer that at least one of two studies is conducted totally in the US and/or Canada.

The justification for the dose selection for CAP studies should be provided.

We have recently had a joint workshop with the Infectious Disease Society of America and an Anti-infective Drugs Advisory Committee meeting to discuss clinical trial design for CAP products, and are working on updating the guidance. Our current advice regarding CAP study design is provided below. We expect to be able to provide you additional comments when you submit your final protocol for review. The following outlines the main criteria for the pivotal study in CAP patients.

Study population and Inclusion/Exclusion Criteria

The Pneumonia Severity Index (PSI) or Pneumonia Patient Outcomes Research Team (PORT) classification system is recommended as an enrollment criterion. The criteria that were used to calculate the PORT score and determine the risk class for each patient should be included in the case report form and in the datasets.

All patients being enrolled in studies of intravenous antibacterials should have PORT scores of ≥II. No more than 25% of the enrolled population should have PORT score of II and at least 25% of the population should have PORT scores ≥IV.

The diagnosis of CAP should be based on the clinical, radiographic, and microbiologic criteria listed below:

(a) Clinical Findings

As part of the clinical picture of CAP, a patient should have at least three of the following symptoms and signs:

- Cough with production of purulent sputum or a change in the character of sputum
- Dyspnea or tachypnea, particularly if progressive in nature
- Chest pain
- Fever, defined as body temperature >38°C (100.4°F) taken orally; >38.5°C (101.2°F) tympanically; or >39°C (102.2°F) rectally

Note: Some patients, especially elderly and others who have risk factors such as alcoholism, malnutrition, and other comorbid illnesses, develop hypothermia, defined as core body temperature of <35°C (95°F) as a sign of infection.

Additional criteria that may be helpful but are not a requirement for inclusion are as follows:

- Auscultatory findings of rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)
- Hypoxemia with a PO_2 < 60mm Hg while patient is breathing room air
- An elevated total white blood cell count or leukopenia, or elevated immature neutrophils (bands)

(b) Radiographic Findings

The chest radiograph should show the presence of a new infiltrate(s) in a lobar or multilobar distribution characteristic of bacterial pneumonia. The final full report of the pretreatment and subsequent chest radiograph(s) by the radiologist should be included in the case report form.

(c) Microbiologic Criteria

At the time of enrollment, an adequate specimen of respiratory secretions should be obtained in all patients and sent to the laboratory for Gram stain, culture and antibacterial susceptibility. Microscopic examination of the Gram-stained respiratory secretions (10-20 oil fields) should show the presence of microorganisms and <10 squamous epithelial cells and >25 polymorphonuclear cells per field at 100X magnification (low-power, 10X objective) for suitability of culture. In addition, the Gram stain morphology of the bacteria seen under high power magnification (1000x) should be recorded. The Gram stain should be performed and the specimen plated for culture within 2 hours

from the collection time, if the specimen is kept at room temperature. Alternatively, these tests may be performed within 24 hours of collection if the specimen is stored at 4^0 C before processing.

The specimen of respiratory secretions may be obtained by any of the following means:

Deep expectoration
Endotracheal aspiration in intubated patients
Bronchoscopy with bronchoalveolar lavage or protected-brush sampling

Exclusion criteria:

- Atypical pneumonia
- Viral pneumonia
- Aspiration pneumonia
- Hospital acquired pneumonia, including VAP
- Receipt of prior antibiotics
- Patients with known bronchial obstruction or a history of postobstructive pneumonia. (This does not exclude patients who have chronic obstructive pulmonary disease.)
- Patients with primary or metastatic lung cancer
- Patients with cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis.

We would prefer that microbiological confirmation of the etiologic agent (typical bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *S. aureus* and *Moraxella catarrhalis* and excluding *Legionella, Mycoplasma*, or *Chlamydophila*) should be provided in a reasonable proportion (30-40%) of enrolled patients.

Study design

Patients should be randomized for receipt of study drugs at enrollment. All studies should be double-blind unless there is a clearly compelling reason for unblinding.

Stratification by age (< 50 years, ≥50 years) and PORT scores is recommended.

Since PK data indicates the differences between IV and oral formulation, it is unclear whether the proposed studies would support approval of both (IV and oral) formulations. Given the lower bioavailability of the oral formulation compared to IV, additional oral studies may be needed.

Objective criteria that allow for oral switch should be specified in the protocol and captured on the case report form. Clinical assessment must be performed at the time of IV to oral switch.

Definitions of clinical success and failure should be as follows:

- ***Clinical success.*** Clinical success is defined as, patient is alive with resolution of disease-specific signs and symptoms present at enrollment and the absence of new symptoms or complications attributable to CAP.
- ***Clinical failure.*** Patients designated as clinical failures at an early time point should be designated as clinical failures for all subsequent follow-up visits. Patients who experience clinical improvement without complete resolution of symptoms should also be considered clinical failures. Clinical failure is defined as follows:

- All-cause mortality within 30 days of start of study medication
- Lack of resolution of baseline CAP-specific signs and symptoms at the test of cure visit
- Progression or development of new symptoms attributable to CAP at any time point after enrollment
- Development of complications of CAP such as empyema or lung abscesss
- Rescue therapy with non-study antibacterial drugs

The primary analysis population is a clinical mITT population where 10% non-inferiority (NI) margins would be acceptable. In addition, a 15% NI margins is expected to be achieved in a co-primary population of MITT patients with documented baseline bacterial infection. However, consistency of the results will also be evaluated in the CE/PP, and ME populations.

Appropriate sample size should be estimated using a two-sided α =0.05, and the studies should have sufficient statistical power of at least 80% to detect the treatment difference based on the mITT population.

Discussion at the July 7, 2008 face-to-face meeting:

- The Sponsor responded to the Division's above comments for CAP studies and proposal of CAP study plan in slides 21-25. The Sponsor agreed to submit a revised CAP protocol as a Special Protocol Assessment and that the exclusion of atypical pathogen and prior antibiotic therapy would be addressed as part of the assessment for Division review.
- The Sponsor agreed to accept Division's recommendation of using 15% NI margin in a co-primary population of MITT patients with documented baseline bacterial infection.
- In slide 26, the Sponsor presented the list of items that they would submit prior to phase 3.
- In slide 27, the Sponsor presented the list of items that they would submit in the NDA.

Discussion at the July 7, 2008 face-to-face meeting on CMC issues:

- The Division recommended that as (b) (4), DMF should be referenced in NDA, and a letter of authorization for the DMF for the referenced DMF should be included. [Post-meeting note: This is because (b) (4) is not acceptable as a starting material for the drug substance synthesis; and so complete details on its preparation should either be included directly in the NDA or in a referenced DMF]
- The Division was concerned about possible genotoxic impurities resulting from the tosylate salt, particularly (b) (4). A strategy for controlling these impurities, and test data on representative lots should be submitted in the NDA.

ATTACHMENTS/HANDOUTS: Slides from Paratek

28 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Linked Applications	Sponsor Name	Drug Name
IND 75928	PARATEK PHARMACEUTICALS	PTK 0796

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

/s/

KATHERINE A LAESSIG
08/07/2008