

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218275Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

IND 064407

MEETING MINUTES

Basilea Pharmaceutica International, Ltd., Allschwil
c/o Kleinfeld Kaplan and Becker
Attn: Daniel Dwyer, US Agent
1850 M Street, NW
Washington, DC 20036

Dear Mr. Dwyer:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ceftobiprole medocartil.

We also refer to the teleconference between representatives of your firm and the FDA on October 13, 2022. The purpose of the meeting was to discuss various aspects of the planned regulatory filing for ceftobiprole medocartil in December of 2022.

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

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Peter Kim, MD, MS
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 13, 2022, from 12:00 PM to 1:00 PM, EST

Application Number: 064407
Product Name: Ceftobiprole medocaril

Indications:

- *Staphylococcus aureus* bloodstream infections (bacteremia) (SAB) in adult patients, including those with right-sided infective endocarditis (RsIE), (b) (4) caused by methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) isolates.
- Acute bacterial skin and skin structure infections (ABSSSI) in adult patients.
- Community-acquired bacterial pneumonia (CABP) in adult and pediatric patients.

Sponsor Name: Basilea Pharmaceutica International, Ltd., Allschwil

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Peter Kim, MD, MS, Division Director

Meeting Recorder: J. Christopher Davi, MS, Senior RPM

Invited CDER Participants: Division of Anti-Infectives (DAI)

*Unless otherwise noted

Peter Kim, MD, MS, Director

Dmitri Iarikov, MD, PhD, Deputy Director

Hiwot Hiruy, MD, PhD, Clinical Team Leader

Mukil Natarajan, MD Clinical Reviewer

Dorota Matecka, PhD, Product Quality (CMC) Team Leader

Katherine Windsor, PhD, Senior Pharmaceutical Quality Assessor

George Lunn, PhD, Product Quality Reviewer

Karina Zuck, PhD, Product Quality Reviewer

Dakshina Chilukuri, PhD, Clinical Pharmacology Team Leader

Cristina Miglis, PharmD, MS, Clinical Pharmacology Reviewer

Terry Miller, PhD, Pharmacology/Toxicology Supervisor

Amy Ellis, PhD, Pharmacology/Toxicology Reviewer

Avery Goodwin, PhD, Clinical Microbiology Team Leader
Jalal Sheikh, PhD, Clinical Microbiology Reviewer
Daniel Rubin, PhD, Biostatistics Team Leader
Chris Kadoorie, PhD, Biostatistics Reviewer
Abimbola Adebawale, PhD, Associate Director for Labeling
Cheryl Grandinetti, PhD, Pharmacologist, Office of Scientific Investigations, (OSI)
Hanan Ghantous, PhD, Director, Division of Pharmacology/Toxicology, Infectious Disease (DPTID)
Gregory DiBernardo, Chief, Project Management Staff
Maureen Dillon-Parker, MS, Director, Division of Regulatory Operations for Infectious Disease
J. Christopher Davi, MS, Senior Regulatory Project Manager

SPONSOR ATTENDEES (Basilea Pharmaceutica International, Ltd., Allschwil & Biomedical Advance Research and Development Authority (BARDA)):

Maziar Assadi Gehr, MD, Medical Director Anti-Infectives
Natalija Backmann, PhD, Regulatory Affairs and Publishing Manager
Farima Barmaki Rad, MD, Head of Global Drug Safety
Guillaume Bernat, Team Leader, Product Quality
Marc Engelhardt, MD, PhD, Chief Medical Officer
Karsten Goedecke, PhD, Head of Global Regulatory Affairs
Daniel Ionescu, MD, Clinical Research Physician
Mark Jones, PhD, Head of Project Management and Pre-Clinical Development
Stephen Keech, Non-Clinical Safety Head
Karine Litherland, PhD, DMPK & Clinical Pharmacology Head
Fernando Santamaria, Serna Product Operations Leader
Mikael Saulay, Data Management/Biostatistics Lead
Jennifer Smart, PhD, Group Leader Microbiology
(b) (4), MD, Consultant to Basilea
(b) (4), MD, Consultant to Basilea
Mark Albrecht, PhD, Branch Chief, Antibacterials team, BARDA
Sue Cammarata, MD, Clinical Subject Matter Expert, BARDA
Kensley Amaya, PhD, Project Officer, Antimicrobials Team, BARDA
Melissa Willens, MS, Regulatory specialist, BARDA

1.0 BACKGROUND

Basilea Pharmaceutica International, Ltd., Allschwil (Sponsor) requested a type B, pre-NDA meeting on August 15, 2022, in order to discuss with the Division of Anti-Infectives (Division) their planned regulatory filing for ceftobiprole medocaril in December of 2022. The Division granted the meeting on August 26, 2022, for an October 13, 2022, meeting and the Sponsor provided briefing materials on September 13, 2022. The Division provided preliminary meeting responses to the questions in the Sponsor's briefing package on October 11, 2022.

The Sponsor provided the Division a slide presentation on October 13, 2022, to be used at the meeting. Discussion points surrounding the preliminary responses are provided herein.

2.0 DISCUSSION

- The Sponsor initiated the discussion with a slide deck (appended) outlining the items of clarification they wished to make with regard to items 1, 6 and 14 of the FDA preliminary responses (appended). With regard to slide 3, the Office of Product Quality (OPQ) indicated that additional corrective and preventive actions (CAPA) data are not necessary with regard to the two impurities in question. The Sponsor acknowledged this.
- The Division and Sponsor discussed the plans for late submission of (b) (4) 9- and 12-month real time stability data from the restarted stability study. The Division stressed that it is important that the former be submitted by 30 days after the official receipt date of the NDA (if agreement is reached on this information as a late submission) to ensure evaluation of the data during the review cycle. The 12-month stability data should follow not later than April of 2023. The Sponsor indicated that they were aiming to meet these timeframes (assuming a December 2022 NDA submission); however, the Sponsor could not commit to submitting the 9-month data within 30 days of the original NDA submission due to remaining uncertainty regarding the actual submission date of the complete NDA. The Division acknowledged this and recommended the Sponsor provide the stability data as soon as they are available and advised the Sponsor that the information will be reviewed as internal timelines allow. The Sponsor acknowledged this.
- The Division requested that the Sponsor provide accelerated stability data to address the effect of short-term temperature excursions outside the proposed label storage conditions (i.e., from shipping or handling). The Sponsor agreed to do so.
- With regard to Question 6 (Slide 4), the Sponsor indicated that they would be providing all methods validation templates in the submission, as well as pharmacometric data and models, as specified by the Division. The Division agreed with the approach as outlined on Slide 4.
- The Division's clinical and statistical teams agreed with the Sponsor regarding all items outlined on Slide 5, as they pertain to adverse events of special interest (AESI), updating the integrated summary of safety (ISS), statistical analysis plan (SAP), and providing information on case report forms (CRFs) for serious adverse events (SAE's) and discontinuations. There were no additional questions on Slide 5.

- With regard to Slide 6, the Sponsor indicated that they would put the 12-month storage and leachables information in the dossier. The Division acknowledged this along with the other information conveyed on Slide 6 (i.e., shelf-life information, reconstitution of lyophilized product, toxicologic qualifications). There were no additional questions on Slide 6.
- The Division agreed with the general approach conveyed by the Sponsor on Slides 7, 8, and 9 and there were no further questions on these slides.
- The Sponsor wished to update the Division on the GMP certification revocation at the Nipro manufacturing facility in Japan. The Division had been made aware of this situation on October 3, 2022. The Sponsor provided a synopsis of the issue on Slide 10 and indicated that they (Sponsor) are actively working to get the license at Nipro reinstated this year. The Sponsor indicated that the integrity of their drug product has not been impacted and added that the revocation only applies to products distributed outside of Japan. The Division acknowledged these points and informed the Sponsor that the Agency is currently considering the issue internally. The Division noted that all manufacturing facilities must be identified on the 356h at the time of submission and are required to be ready for inspection at that time. The Sponsor acknowledged these points and informed the Agency that they would be submitting additional information to the IND regarding the issue in the coming weeks. The Division agreed to review this information.

3.0 OTHER IMPORTANT MEETING INFORMATION:

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. In addition to the 9- and 12-month stability data discussed above, the Sponsor was advised to provide an IND submission outlining any additional components of the NDA they wished to submit on a rolling review basis along with associated timelines for each component prior to NDA submission. The Sponsor acknowledged these points.
- The Division noted that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application. As indicated above, the Sponsor was advised that the Nipro manufacturing facility in Japan must be ready for inspection at the time of submission and specified, as required, on the FDA Form 356h.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. The Division informed the Sponsor that it is not anticipated that a REMS or Formal Communication Plan will be required for this application at this time.
- The Division noted that major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The Division agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
 - 9-month stability data.

Additional Post-Meeting Comments

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA NUMBER: LATE COMPONENT - QUALITY

In addition, we note that a chemistry pre-submission meeting was held on June 3, 2020. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information¹ and Pregnancy and Lactation Labeling Final Rule² websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

² <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.³

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁴

³ <http://www.fda.gov/ectd>

⁴ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁵ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁶.

⁵ <https://www.fda.gov/media/84223/download>

⁶ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials).

Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁷

4.0 ATTACHMENTS

- Division's preliminary meeting responses dated October 11, 2022
- Sponsor's slide presentation dated October 13, 2022

End.

⁷ <https://www.fda.gov/media/85061/download>

IND 064407

MEETING PRELIMINARY COMMENTS

Basilea Pharmaceutica International, Ltd., Allschwil
c/o Kleinfeld, Kaplan, and Becker
Attn: Daniel Dwyer, US Agent
1850 M Street, NW
Washington, DC 20036

Dear Mr. Dwyer:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ceftobiprole medocaryl powder for injection.

We also refer to your August 15, 2022, correspondence requesting a Pre-New Drug Application (NDA) meeting to discuss the planned regulatory filing for ceftobiprole medocaryl in December of 2022.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Gregory DiBernardo
Chief, Project Management Staff
Anti-Infectives Group 2
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments



PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Format: Teleconference
Date and Time: October 13, 2022, from 12:00 PM to 1:00 PM, EDT

Application Number: IND 064407
Product Name: Ceftobiprole medocaril powder for injection

Indication(s): *Staphylococcus aureus* Bacteremia (SAB), Acute Bacterial Skin and Skin Structure Infections (ABSSSI), Community-Acquired Bacterial Pneumonia (CABP)

Sponsor: Basilea Pharmaceutica International, Ltd., Allschwil

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for October 13, 2022, between Basilea Pharmaceutica International, Ltd., and the Division of Anti-Infectives. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Basilea Pharmaceutica International, Ltd., (Sponsor) requested a Type B Pre-NDA meeting on August 15, 2022, to discuss the planned submission of a marketing application for ceftobiprole medocaril in December of 2022. The Division granted the meeting on August 26, 2022, and the Sponsor provided background materials for the meeting on September 13, 2022. Preliminary responses from the Division, as they relate to the questions in the Sponsor's briefing document (*italics*) are provided herein.

2.0 QUESTIONS

Question 1: Reference is made to the July 3, 2020, pre-NDA CMC teleconference, and the discussion about drug substance manufacturers included in the planned ceftobiprole medocaril NDA. Basilea plans to include two drug substance manufacturers in the NDA:

(b) (4). (b) (4) has been an established manufacturer of ceftobiprole medocaril for more than 10 years, and drug substance from (b) (4) has been used for both the supply of the pivotal clinical studies (see also CTD Module 3.2.S.2.1), and for commercial sales outside the USA. Does the Agency agree with the inclusion of the drug substance manufacturer (b) (4) in the NDA, and with the presentation and assessment in the NDA of the available (b) (4) stability data?

Division Response: Your proposal to include the drug substance manufacturer (b) (4) in the NDA appears reasonable. However, a comparability evaluation between drug substance batches manufactured by (b) (4) and (b) (4) will be made during the NDA review, once all the data supporting both manufacturers are provided.

In the meeting background package, you state that the formal 12-month stability data for the (b) (4) drug substance will be available in April 2023. Clarify when the formal 9-month data from this restarted stability study will become available. We recommend you submit the 9-month and 12-month data from the restarted stability study as soon as they become available, with the understanding that information submitted beyond 30 days after the original NDA submission will be reviewed as internal timelines and resources allow.

The accelerated stability data from the restarted study provided for batches A9001DE, A9002DE, and A9003DE have out of specification (OOS) results. The impurity (b) (4) is OOS in the three batches after six months at accelerated conditions. In addition, the impurity (b) (4) and total impurities are also OOS after six months at accelerated conditions in batch A9001DE. We acknowledge the root cause investigation and corrective and preventive actions (CAPA) provided for the OOS results observed with the impurity (b) (4). In the NDA submission, also provide a summary of the root cause investigation and CAPA for the impurity (b) (4) OOS results observed.

Question 2: The drug substance manufacturing process at both (b) (4) and (b) (4) is essentially identical, with only minor adaptations based on the equipments used; the same drug substance specifications and methods outlined in the NDA are used at both manufacturers. Accordingly, Basilea does not plan to submit separate standalone Module 3.2.S documents for each of the two API manufacturers, and with two exceptions will present combined data for each manufacturer in the respective Modules. Basilea proposes to provide separate Modules 3.2.S.6, and 3.2.S.7.3 for each manufacturer. Does the Agency agree with this approach?

Division Response: *The approach to submit single Module 3.2.S documents containing combined data for the two API manufacturers, except for Modules 3.2.S.6, and 3.2.S.7.3 as outlined in Table 3 of the briefing document, appears reasonable. In addition, provide in the NDA submission the updated version of the drug substance process transfer report, including process changes from validation batches, and the equipment comparison for (b) (4) and (b) (4) process validation batches (Appendix 4 of the briefing package) to support the process comparability at the two sites.*

Question 3: Basilea plans to submit and discuss the nonclinical safety studies identical to those provided in previous NDA 22-132 submitted by Johnson & Johnson in 2007, for the indication complicated skin and skin structure infections (cSSSIs) at that time. As Basilea considers the existing studies to be adequate to support the submission of an NDA for ceftobiprole medocartil for the indications SAB, ABSSSI, and CABP, no additional nonclinical safety studies have been conducted. A comprehensive list of completed studies supporting the route of administration and duration of treatment for the three proposed clinical indications is provided [below](#). No SEND datasets will be provided for any nonclinical safety studies, since these were all completed before December 2016; instead, simplified TS files will be included in the eCTD (see also [Question 11](#)). Does the Agency agree that this nonclinical safety data will support filing of the NDA?

Division Response: *We anticipate that providing final reports of the nonclinical studies submitted under NDA 22132 will be adequate to support the current NDA for ceftobiprole medocartil. As these studies were completed prior to the requirement for SEND datasets, we agree that the SEND datasets are not necessary. We accept your offer to provide simplified TS files in the eCTD, but note that they are not required. If the previous nonclinical studies do not permit qualification of the current impurities (including extractables/leachables from the container/closure system) in the product to be marketed, you should be aware that it will be necessary to provide information to qualify any new impurities. This could include an additional nonclinical study if adequate information is not available from other sources.*

Question 4: Basilea plans to submit and discuss the nonclinical pharmacology and pharmacokinetics studies which are identical to those provided in previous NDA 22-132 submitted by Johnson & Johnson in 2007 for the indication cSSSI. No additional nonclinical pharmacology and pharmacokinetics studies have been conducted, with the exception of two in vitro DDI studies to comply with more recent FDA guidelines. Basilea will include reports from these two studies, which are currently ongoing, in the NDA: a cytochrome P450 induction in cultured human hepatocytes study (XT223040), and an ABC and SLC transporter inhibition and substrate potential study (XT228043). Both studies are being conducted with the active moiety ceftobiprole.

The maximum concentrations of ceftobiprole tested in the nonclinical pharmacology and pharmacokinetics studies were limited by ceftobiprole's low solubility, and reached a maximum of 84 µM (ceftobiprole C_{max}~62 µM at efficacious dose of 500 mg).

Basilea considers these studies in total to be adequate for the submission of an NDA for ceftobiprole medocaril. Does the Agency agree that these nonclinical pharmacology and pharmacokinetics data will support filing of the NDA?

Division Response: *We agree.*

Question 5: Consistent with the 2018 FDA guidance ‘Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis, and Presentation’, Basilea plans to submit a microbiology program which includes over 10 years of surveillance data, including U.S. surveillance data from 2016 to 2020 from the SENTRY surveillance program, as well as studies testing enriched collections of resistant pathogen phenotypes, mechanism of action, in vitro bactericidal, and time-kill studies, propensity for resistance studies, development of susceptibility testing methodology, and in vivo efficacy models. Basilea considers that the microbiological activity of ceftobiprole medocaril has been assessed in sufficient detail to support the proposed indications in SAB, ABSSSI, and CABP including specific labelling for *S. aureus* (MSSA and MRSA). A comprehensive, integrated summary of clinical and nonclinical microbiology data will be presented in Module 2.7.2, Section 4. A Microbiology Reviewers Guide will be provided to assist in the review of the associated clinical data files. Section 12.4 of the Proposed USPI will include a primary list of pathogens for which the efficacy of ceftobiprole has been demonstrated in clinical studies, and a secondary list of pathogens for which clinical efficacy has not been demonstrated, but against which ceftobiprole activity has been observed in vitro. Potential clinical breakpoints will be proposed for each of the pathogens in the primary pathogen list, with supporting data presented in Module 2.7.2.4. Does the Agency agree with this approach? Does the Agency have any recommendations regarding a Microbiology Reviewers Guide for these data that should be included in the NDA?

Division Response: *We agree.*

Question 6: Basilea plans to submit full CSRs for the clinical pharmacology and pharmacokinetics studies, including identical versions of all those included in the previous NDA 22-132 submitted by Johnson & Johnson in 2007 which were deemed acceptable by FDA for the indication cSSSI at that time. Datasets for these studies will be provided in CDISC format as legacy conversions of the original datasets (see also [Question 11](#)). In addition, Basilea plans to submit the reports and datasets undertaken on Basilea’s behalf by the (b) (4) as outlined in the briefing document. Does the Agency agree that this program of clinical pharmacology and pharmacokinetics studies and reports will support filing of the NDA?

Division Response: Please submit the provided method validation template for each new study that includes a PK assessment, as an MS Word document file (.doc or .docx). The following are the general expectations for submitting pharmacometric data and models:

- The 'Specification for File Format Types Using eCTD Specifications' document¹ provides a listing of many file formats, file types, and file locations for eCTD submissions used in pharmacometrics analyses. These file formats, types, and locations can be used when feasible. Sponsors can communicate with the review team about planned population pharmacokinetic and dose/exposure-response analyses for concurrence on data collection, analysis, and data submission plans. If a file format or type not on the list is planned for submission, the sponsor can discuss with the review team how to submit datasets and codes supporting pharmacometric analyses.
- Population pharmacokinetic, exposure-response, and physiologically based pharmacokinetic reports for new drug and biologic applications can be submitted in Module 5.3.3.5. All datasets used for model development and validation can be submitted as a SAS transport files (*.xpt). Datasets used for model development and validation that will be submitted to Module 5.3.3.5 can alternatively be submitted as comma delimited files (*.csv). A description of each dataset and variables within can be provided in a define file as an XML or PDF. In addition, a "reviewer.aid.pdf" file can be provided and include a listing and description of all submitted analysis scripts, the software, version, and package dependencies needed to run the analysis scripts, and a flowchart and/or table depicting input and output files for each analysis script. If analysis scripts need to be executed in a specific order, those requirements can be documented in the "reviewer.aid" file.
- We recognize there may be situations where data collected for analyses may have omitted information or information incorrectly transcribed (i.e., missing dosing times; negative infusion durations, etc.). In such cases, sponsors can attempt to reconcile such issues with the responsible sites. If issues cannot be resolved and imputation of records is needed, sponsors can provide information on rules for imputation and which records were imputed in the analysis report. Likewise, while analyzing data it is not uncommon to identify outlying values or subjects that should be excluded from the analysis. In such cases, criteria for identifying outliers and values and/or subjects excluded from the analysis should be documented in the analysis report. Any values and/or subjects that have been **excluded from the analysis** can be flagged and maintained in the datasets.

- *Model codes or control streams and output listings can be provided for all major model building steps (e.g., base structural model, covariates models, final model, and validation model). These files can be submitted as ASCII text files. It is not necessary to rename ASCII files ending in different extensions (e.g., .R, .sas, .ctl, etc.) to a file with a *.txt extension for submission.*
- *For population pharmacokinetic and exposure-response analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Reports should include a summary of clinical application of the modeling results, including how analysis results are being used to support labeling claims and dosing within the submission. Covariate assessments should include a description of how the covariate alters exposure parameters (e.g., AUC, C_{trough}) or response rate and not just the impact of the covariates on the model parameter.*

¹<https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/ucm347471.pdf>

Question 7: Basilea has received topline results from the most recent pivotal ceftobiprole medocartil study BPR-CS-009 in patients with Staphylococcus aureus bacteremia (SAB). The protocol for study BPR-CS-009, including both protocol amendments implemented during the conduct of the study, was agreed with FDA under a Special Protocol Assessment (SPA). The topline results of the study, which met all primary and secondary endpoints, are provided below. Does the Agency have any comments on the results of clinical study BPR-CS-009? Does the Agency agree that these results may support an indication in SAB?

Division Response: *The Division does not have comments on the topline results of Study BPR-CS-009 at this time. The adequacy of the study will be determined after full review upon submission of the NDA.*

Question 8: In 2019, Basilea completed pivotal ceftobiprole medocartil study BPR-CS-008 in patients with acute bacterial skin and skin structure infections (ABSSSI). The protocol for study BPR-CS-008, including the protocol amendment implemented during the conduct of the study, was agreed with FDA under an SPA. An outline of the results of the study, which met all primary and secondary endpoints (see also Briefing Document Appendix 5 prepared for the July 6, 2021 Type C guidance meeting, submitted to IND 64,407 under Serial Number 393), are provided below. Does the Agency have any comments on the results of clinical study BPR-CS-008? Does the Agency agree that these results may support an indication in ABSSSI?

Division Response: *The Division does not have comments on the results of Study BPR0CS-008 at this time. The adequacy of the study will be determined after full review upon submission of the NDA.*

Question 9: Since pivotal study CAP-3001 in adult patients with community-acquired bacterial pneumonia (CABP) was completed in 2007, Basilea will undertake a re-analysis of the primary efficacy endpoint in accordance with the current FDA CABP guidance. The results of this analysis, and associated tables, figures, and listings, are planned to be provided in an Addendum to the CAP-3001 CSR, and the new datasets will be included in the CSR datasets submitted with the NDA (see also the Briefing Book prepared for the June 24, 2014 Type C meeting, submitted to IND 64,407 under Serial Number 310). The data submitted for this study will therefore comprise:

- Original CSR with full tables, figures, and listings, appendices, and converted datasets. The information will include patient narratives for patients who died, had serious adverse events, or withdrew due to an adverse event, and CRFs for those patients who died.
- CSR Addendum 1 prepared in 2012, with the results of subgroup analyses, tables, figures, and listings
- CSR Addendum 2 prepared in 2022, with re-analysis of the primary endpoint in accordance with current FDA CABP guidance.

The CSR for study BAP248/307 in patients with hospital-acquired bacterial pneumonia (HABP) will be provided in the NDA to complete the safety information, and to support the microbiology analysis in regard to microbiological pathogen assessments. A HABP indication will not be sought in the NDA (see also [Question 12](#)). Does the Agency agree with this approach, and that the original results, combined with the re-analysis, may support an indication in CABP?

Division Response: *Your approach appears reasonable. As noted during the June 2014 meeting, Study CAP-3001 has several limitations due to its study design, reliance on post-hoc subgroup analyses, and other concerns (e.g., robustness of efficacy findings and study site integrity). As a result, Study CAP-3001 will need to be reviewed in the context of an NDA to determine whether it can support an indication for CABP. If, upon Agency review, studies BPR-CS-008 and BPR-CS-009 are deemed adequate, they may be able to be used to cross-support a CABP indication.*

Question 10: In the planned NDA, Basilea proposes to present and discuss data from:

- Twenty Phase 1 studies investigating safety, pharmacokinetics, and preliminary efficacy
- Five Phase 3 studies primarily investigating efficacy and safety to support the proposed indications (see also [Question 12](#)).

Basilea does not plan to present data in the NDA from seven legacy clinical studies: JPN-01 (Phase 1, PK in healthy Japanese adult male subjects), NOS-1002 (Phase 1, lung PK study in ventilated patients), FBN-3004 (Phase 3, treatment of fever in neutropenic patients), BAP00034 (Phase 2, cSSSIs), BAP00154 and BAP00414 (Phase 3, cSSSIs). Does the Agency agree with this proposal?

Division Response: *We agree.*

Question 11: For Module 2.7.4, the Summary of Clinical Safety, the datasets for the integrated analyses (ADaM) for the analysis described in the ISS SAP will be provided. For the population PK analysis, PK/PD efficacy analysis per indication, and target attainment analysis per indication (see [Question 12](#)), datasets for six analyses will be provided. For clinical study data, individual study datasets will be provided which are compliant with the Clinical Data Interchange Standards Consortium (CDISC) standard. An overview of the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets to be submitted in the NDA is provided below. Except for the four clinical studies completed since 2019 (BPR-CS-009, BPR-CS-008, BPR-PIP-001, BPR-PIP-002), all clinical study datasets in CDISC/SDTM format are legacy conversions.

An overview of the individual study datasets to be provided for the NDA submission, is also provided below. Pinnacle 21 will be used to check CDISC compliance for all SDTM and ADaM datasets, and any unresolved errors will be documented in the Study Data Reviewer's Guide and Analysis Data Reviewer's Guide, respectively. Data definition files will be provided in the form of define.xml and/or define.pdf for SDTM datasets, ADaM datasets, and safety datasets. Consistent with the FDA Guidance 'Providing Regulatory Submissions In Electronic Format – Standardized Study Data' Revision 2, June 2021, no SEND datasets will be provided for toxicology studies, since all toxicology studies were completed before 2016; instead, simplified TS files will be included in the eCTD. Basilea plans to undertake a test submission in Q4 2022. Does the Agency agree with the plan for presentation of these datasets in the NDA?

Division Response: *We agree with the plan for presentation of these datasets in the NDA.*

Question 12: Reference is made to the July 6, 2021 Type C pre-NDA Guidance meeting (teleconference). Basilea plans to submit an NDA for the following indications:

- *Staphylococcus aureus* bacteremia (SAB)
- Acute bacterial skin and skin structure infections (ABSSSI)
- Community-acquired bacterial pneumonia (CABP)

Reference is also made to the agreed Initial Pediatric Study Plan (iPSP). In this regard, Basilea has already conducted the following pediatric clinical investigations:

- CSI-1006 (Phase 1 single-dose PK study in patients ≥ 3 months to < 18 years)
- BPR-PIP-001 (Phase 1 single-dose PK study in neonates and infants aged up to 3 months)
- BPR-PIP-002 (Phase 3 study in patients aged from 3 months to less than 18 years with CABP or HABP requiring hospitalization)
- Pediatric population PK analysis Based on these data, Basilea proposes in the NDA submission to request approval for a pediatric indication for CABP.

Basilea will update the pediatric label on completion of the studies outlined in the iSPS for the ABSSSI and SAB indications. Details of the draft labeling language regarding the indications, product description, instructions for use, and packaging of ceftobiprole medocaril are provided below. Noting that a detailed review of the Highlights and Full Prescribing Information will only be undertaken during review of the final NDA, does the Agency have any early comments or questions regarding these selected sections of the draft USPI?

Division Response: *It is premature to comment. The wording of the product labeling will be determined during review of the NDA.*

Question 13: Basilea plans to present a separate Module 2.7.3 Summary of Clinical Efficacy for each of the proposed indications (SAB, ABSSSI, CABP), incorporating data from the respective pivotal studies, with a detailed integrated discussion of clinical microbiology data in Module 2.7.2.4 Summary of Clinical Pharmacology Studies. In view of the different indications, study populations, and endpoints, Basilea does not plan to provide a separate written Integrated Summary of Effectiveness (ISE). Does the Agency agree with this approach to presentation of efficacy data?

Division Response: *We agree.*

Question 14: Reference is made to the Integrated Summary of Safety (ISS) Statistical Analysis Plan (SAP) Version 1.0 submitted to IND 64,407 on June 1, 2022 (Serial Number 407). Basilea proposes to present a single Module 2.7.4 Summary of Clinical Safety, with the ISS SAP, tables, figures and listings and the associated datasets that support the safety analyses presented in Module 5.3.5.3. Accordingly, Basilea does not plan to provide a separate standalone written ISS in Module 5.

- (a) Does the Agency agree with this approach to presentation and summarization of clinical safety data in the NDA?

Division Response: *We agree.*

- (b) Specifically: Does the Agency agree with the proposed pooling of clinical studies for the purpose of the ISS?

Division Response: *We agree.*

- (c) Does the Agency agree with the proposed approach to AESI?

Division Response: *In addition to your plan to include convulsions, hypersensitivity reactions, and Clostridioides difficile related AEs as AESI, we recommend the following additions: hepatic enzymes increased, hyponatremia, renal failure, nausea, and vomiting.*

- (d) As described in ISS SAP Section 4.6, subgroup analyses for ISS Datasets 3 and 4 will include treatment duration, age, gender, race, renal status, and region. Does the Agency agree with these planned subgroups?

Division Response: *We agree.*

- (e) Basilea plans to include in the NDA full electronic datasets in SDTM/AdAM format for all contributing clinical studies. Adverse events are being re-coded to MedDRA Version 24.1. It is Basilea's intention to include in the NDA narratives for all subjects who died, had an SAE, or withdrew from the study due to an AE, and to provide copies of CRFs for those subjects who died, regardless of causality. Does the Agency require copies of the CRFs in the NDA for subjects who had an SAE, or withdrew due to an AE, or should these CRFs be made available on request during the review?

Division Response: *We agree with your plan to include subject narratives for all subjects who died, had an SAE, or withdrew from the study due to an AE and to provide copies of CRFs for those subjects who died, regardless of causality. Please also include in your NDA the CRFs of subjects who had an SAE or withdrew due to an AE.*

Additionally, please submit a dataset that includes all treated patients from the primary efficacy studies (i.e., the five phase 3 studies) including only variables depicting the patient ID and treatment assignment. We will take a 10% random sample of these patients and request that CRFs for these patients also be included in the NDA.

- (f) Does the Agency have any additional comments on the planned safety analyses, based on the ISS SAP?

Division Response: *See the Division's response to Question 14 (c). We do not have any additional comments on the planned safety analyses, based on the ISS SAP.*

Question 15: In clinical study BPR-CS-009, 46.5% of patients in the mITT population were enrolled in Ukraine. In clinical study BPR-CS-008, 23.9% of patients in the ITT population were enrolled in Ukraine. The NDA will include a BIMO package for this study to assist the inspectorate in planning GCP inspections.

Considering that it is unlikely that site inspections will be feasible in Ukraine, Basilea would like to discuss with the Agency possible alternative approaches, and clarify the Agency's expectations in this regard. **Will the agency make any exceptions or alternate approaches for conducting site inspections in Ukraine?**

Division Response: *FDA will review the BIMO package (subject-level data line listings, by clinical site) at the time the NDA is submitted to determine clinical trial sites to be inspected. In cases where a site is selected for inspection and an onsite inspection is not feasible, FDA may consider alternative inspection approaches. In such cases, for example, these alternative approaches may include verifying critical data and other critical clinical trial activities from certified copies of source records for these sites selected for inspection.*

Question 16: Basilea currently plans to submit an NDA in December 2022, with the timeline mainly driven by the clinical module. For the compilation of the NDA in eCTD format, Basilea expects both the nonclinical and CMC modules to be ready for submission earlier than that date, e.g., by the end of November 2022, and by mid-December 2022, respectively. Since ceftobiprole medocartil was granted QIDP designation for each of the proposed indications SAB, ABSSSI, and CABP, and due to the expected earlier availability of the nonclinical and CMC modules, Basilea would like to explore the opportunity to submit a rolling NDA for ceftobiprole medocartil, with the submission of these sets of modules as they become available. The details of the proposed timing and modules to be submitted are provided in the briefing document. Would the Agency accept a rolling NDA for ceftobiprole medocartil, with the target dates outlined above?

Division Response: *Our records indicate you were granted Fast Track designation on June 3, 2004, and as such, you are eligible to submit a rolling review request to your IND. Please note that the review clock does not begin until all modules are submitted and the complete NDA application received. A request for rolling NDA review should be submitted to the IND file, outlining the specific details for each component to be submitted and the associated timing for each component. Upon review of this submission, the Division will advise on the acceptability of your plan.*

Question 17: Does the Agency wish to have an NDA Orientation meeting?
Background information to Question 17 - Basilea is willing to have an Orientation meeting to acquaint the Agency with the location of NDA content, including application datasets. Basilea would appreciate FDA's guidance for such a meeting.

Division Response: *We do not think an application orientation meeting is necessary. If questions arise regarding data presentation after the NDA filing, we will send out information requests for clarification.*

Additional Comments:

Chemistry, Manufacturing, and Controls:

1. The NDA submission should include results from a one-time leachable study on three representative drug product batches/registration stability batches (manufactured using the proposed commercial process and packaged in the to-be-marketed container closure system) through the proposed expiry period. Both solid and reconstituted drug product samples should be evaluated. Refer to USP <1663> and <1664> for additional recommendations. Any leachable found must be adequately controlled, and those found above the applicable threshold must be adequately qualified.
2. Each vial of the reconstituted drug product solution should contain sufficient volume to permit withdrawal and administration of the labeled amount of the drug product as per USP <697> and <1151>. The NDA submission should include a deliverable volume study to demonstrate that the labeled amount of drug can be consistently withdrawn from the vial following the labeled instructions. These data should include the volume (mL) and concentration (mg/mL) of the drug product solution in the vial after reconstitution.
3. We recommend that you conduct a risk assessment for (b) (4) impurities in your API and drug product. Refer to the following Guidance for additional information: (b) (4)

Pharmacology/Toxicology:

4. In accordance with current FDA best practices and recommendations by the Product Quality Research Institute workgroup on parenteral products, we recommend you submit a comprehensive toxicological risk assessment (i.e., local toxicity, systemic toxicity, mutagenicity, carcinogenicity, reproductive toxicity, etc.) for any leachable that exceeds a daily total intake limit of 5 mcg/day.

From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity should not exceed 20 mcg/day for an indication of 1-12 months for most potentially genotoxic impurities, or be adequately qualified for mutagenicity and carcinogenicity as described in ICH Guidance M7(R1) "Assessment and Control of DNA Reactive (Mutagenic) Impurities in

Pharmaceuticals to Limit Potential Carcinogenic Risk”.¹ The overall risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

In the absence of adequate information to support the safety of the identified leachables at the levels detected in your drug product, additional nonclinical qualification studies may be recommended to qualify the leachable(s). Refer to ICH Guidance M7(R1) and ICH Guidance Q3B(R2) “Impurities in New Drug Products”², as well as USP <1663> and <1664>, for additional information on the safety qualification of impurities.

Statistics:

5. We recommend that you include a brief algorithm in the Reviewer Guide of your NDA submission which describes how results from all primary, secondary, and major safety analyses were derived (e.g., the dataset and names of variables used).

This would help to limit potential discrepancies between FDA Reviewer and Sponsor analysis results. In addition, SAS programs can be provided. Please ensure that ADaM datasets with define.xml and define.pdf will be submitted for each study. Study analysis datasets should be traceable to the tabulation datasets. If the ADaM datasets were created based on case report form (CRF) raw data, please also submit the CRF raw data as well. Note that we may need to further address issues regarding data analysis after the NDA is submitted.

The following additional comments pertain to the SAP (Version 2.0) for Protocol BPR-CS-009 (SDN 442):

6. In general, the primary and secondary efficacy analyses, supplementary, sensitivity, subgroup analyses are appropriate. However, the Sponsor should conduct subgroup analyses based on whether subjects were enrolled before or after Protocol Amendment 4 as well as consider conducting sensitivity analyses of the primary endpoint which stratify by this variable.
7. The analysis sets appear to be generally acceptable however the Sponsor should clarify how subjects with *S. aureus* resistant to daptomycin will be handled. It appears that they could be included in the mITT. If so, the Sponsor should consider conducting sensitivity analyses in which they are excluded from the mITT.

¹ <https://www.fda.gov/media/85885/download>

² <https://www.fda.gov/media/71733/download>

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DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our August 26, 2022, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VII.

Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan.

You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.³

In addition, please note the following:

- The content of a complete application will be discussed at the meeting and the agreements will be summarized in the minutes.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion will be held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

³ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

We note that a chemistry pre-submission meeting was held on June 3, 2020. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015).

As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry.

If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.⁶

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review.

Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁷

MANUFACTURING FACILITIES

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

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

⁶ <http://www.fda.gov/ectd>

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁸ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁹. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VII. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

⁸ <https://www.fda.gov/media/84223/download>

⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.¹⁰

-End.

¹⁰ <https://www.fda.gov/media/85061/download>

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/s/

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/s/

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IND 64,407

MEETING MINUTES

Basilea Pharmaceutica, Ltd.
c/o Kleinfeld Kaplan and Becker
Attention: Dan Dwyer
U.S. Agent
1140 Nineteenth Street, N.W.
Washington, DC 20036

Dear Mr. Dwyer:

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

We also refer to the meeting between representatives of your firm and the FDA on November 17, 2015. The purpose of the meeting was to discuss the Phase 3 drug development program.

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

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

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

Enclosures: Meeting Minutes
Agency's preliminary responses dated November 12, 2015
Sponsor's slide presentation



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: November 17, 2015
Meeting Location: CDER White Oak Campus

Application Number: IND 64,407
Product Name: Ceftobiprole Medocaril for Injection
Indications: Acute Bacterial Skin and Skin Structure Infections (ABSSSI)
Staphylococcus aureus Bacteremia (SAB)
Community-Acquired Bacterial Pneumonia (CABP)

Sponsor/Applicant Name: Basilea Pharmaceutica, Ltd.

Meeting Chair: Sumathi Nambiar, MD, MPH, Director, Division of Anti-Infective Products (DAIP)
Meeting Recorder: J. Christopher Davi, MS, Senior Regulatory Project Manager

FDA ATTENDEES: DAIP*

*Unless otherwise specified

John Farley, MD, MPH, Deputy Director, Office of Antimicrobial Products (OAP)
Sumathi Nambiar, MD, MPH, Director
Joseph Toerner, MD, Deputy Director for Safety
Thomas Smith, MD, Medical Team Leader
Maria Allende, MD, Medical Reviewer
Seong Jang, PhD, Clinical Pharmacology Team Leader
Zhixia (Grace) Yan, PhD, Clinical Pharmacology Reviewer
Karen Higgins, ScD, Biostatistics Team Leader
Christopher Kadoorie, PhD, Biostatistics Reviewer
Wendelyn Schmidt, PhD, Non-Clinical Pharmacology Team Leader
Kerry Snow, MS, Clinical Microbiology Team Leader
Avery Goodwin, PhD, Clinical Microbiology Reviewer
Maureen Dillon-Parker, Chief, Project Management Staff
J. Christopher Davi, MS, Senior Regulatory Project Manager

SPONSOR ATTENDEES: Basilea Pharmaceutica, Ltd.

(b) (4), MD, Medical Advisor, (b) (4)
(b) (4), MD, Medical Advisor, (b) (4)
Marc Engelhardt, MD, Head of Clinical Development
(b) (4), PhD, Regulatory Consultant, (b) (4)
Marc Jones, PhD, Head of Project Management
Achim Kaufhold, MD, Chief Medical Officer
Anne Schmitt-Hoffmann, PharmD, PhD, Head of Pharmacology
Lutz Wevelseip, PhD, Head of Global Regulatory Affairs

BACKGROUND

Basilea Pharmaceutica, Ltd., (Sponsor) requested a Type B meeting on September 4, 2015, to discuss the Phase 3 trials for ceftobiprole medocartil in the above referenced indications. The Sponsor provided a briefing document on October 16, 2015, and the Division of Anti-Infective Products (Division) provided preliminary responses (appended) to the questions in the briefing document on November 12, 2015. Discussion points generated from the preliminary responses are recorded herein.

DISCUSSION

- The Sponsor provided a slide presentation (appended) to focus the discussion around the preliminary responses for which they sought clarification. The Sponsor began the discussion asking about patients who are diagnosed with left sided infective endocarditis (LIE) after randomization and how such patients should be managed. The Sponsor did not feel it was prudent to exclude such patients but at the same time, was concerned about enrolling subjects with known LIE. The Division agreed that if patients are doing well clinically, they can remain in the trial. The Division advised the Sponsor to specify in the protocol how such patients will be managed. The Division clarified that having a few cases of LIE would not be sufficient to support an indication of LIE. The Sponsor acknowledged this.
- The Sponsor discussed the allowable window for prior antibacterial drug therapy currently recommended by the Division as 48 hours within 7 days before randomization. The Sponsor indicated that a 48-hour window will be logistically difficult from an enrollment perspective. They added that even with rapid diagnostics, a significant amount of time elapses before one can enroll a patient. The Sponsor felt that over a 4 to 6 week course of therapy, the potential impact of an additional 24 hours of therapy would be negligible.

- The Division expressed concern with the 72 hour window, as early effective therapy may have an impact on therapeutic outcome. In a noninferiority (NI) trial, it is critical to avoid factors that could confound the treatment effect. The Division recommended that the Sponsor adhere to the 48 hour timeframe and see how the trial progresses. The Division stressed that there needs to be a balance between feasibility and interpretability in a clinical trial. Any lengthening of the prior therapy time window must be considered in the context of data that describes the effect of delayed therapy as well as the impact of early therapy on final treatment outcomes. The Division stated that the discussion of their proposal needs to be data driven. The Sponsor acknowledged this.
- The Sponsor asked why an M2 of 20%, similar to what was used in the daptomycin trial, was not being considered. The Division stated that as the Sponsor is aware, there have been several recent public discussions about NI trials and the need for justification of an NI margin. The Division indicated that the M1 is large and that in their assessment, the M2 should not exceed 15% as a matter of clinical acceptability, which is larger than the 10% more commonly used. The Division indicated that this is consistent with advice given to other applicants. The Sponsor expressed concern regarding the feasibility of a trial using 15% NI margin. The Division indicated that the Sponsor could put together an argument for a 20% NI margin if they wished and it could be considered.
- With respect to data available to support prolonged treatment with ceftobiprole, the Sponsor discussed the results of animal studies of over 4 weeks duration, indicating that they wanted to present the results in more detail. The Sponsor indicated that they have data from Phase 2/3 trials that have not shown safety signals or thromboembolic events. The Sponsor asked if their comprehensive assessment of convulsions and thromboembolic events in the animal studies could be discussed in a separate meeting.
- The Division noted that in marmoset studies, deaths were encountered at all four doses, which was cause for concern. The Division asked the Sponsor if they felt they had enough of a safety margin from animal or human studies to support a 2g/day (500 mg q6) dosing regimen. The Sponsor indicated that they did not have data for 500 mg q6 but that they did have data for 2g over 8 days dosing. The Division encouraged the Sponsor to submit all data to support the safety of the higher dose and duration proposed (b) (4) as part of a Type C (written response) meeting request, and indicated that further dialogue could take place following the review of such data.
- With regard to the microbiologic cure, the Sponsor wanted to obtain guidance on how to best establish this and asked whether “presumed eradication” would be correct to use when clinical cure or improvement are observed but no specimen has been collected to confirm it. The Sponsor was referring to the Division’s suggestion of having a fixed time point for the primary endpoint at Day 70 after randomization. The Sponsor indicated that obtaining blood cultures at this time point is not consistent with general clinical practice, because if a patient is clinically improved, an additional blood culture at a later time is not generally needed to confirm clinical cure.

In addition, this would represent an inconvenience for patients (e.g., patients that are feeling better are often reluctant to have blood draws). The Division stated that if there are prior negative blood cultures while on therapy and post-therapy, that would be an alternative to the final blood draw at Day 70 if the patient is considered a clinical success. The Division encouraged the Sponsor to consider endpoint definition and data window specification carefully. Reference to Appendix A of the *Guidance for Industry – Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* may be helpful.¹

- With regard to allowing concomitant antibacterial drugs during the study, the Sponsor indicated that they would be excluding patients with nonsusceptible Gram-negative pathogens at baseline. However, if enrolled subjects are subsequently found to have nonsusceptible Gram-negative infections that need to be treated with antibacterial drugs that also have activity against methicillin-susceptible *S. aureus* (MSSA), it was unclear how they would be handled. The Sponsor acknowledged that concomitant antibacterial drugs that have activity against MSSA (carbapenems, quinolones, beta-lactam/beta-lactamase inhibitor combinations) will be permitted in patients with nonsusceptible Gram-negative co-infections in both treatment groups if ceftobiprole or aztreonam are not appropriate.
- The Sponsor will perform a separate pre-planned subgroup analysis of patients receiving concomitant Gram-negative antibacterial drugs with potential activity against MSSA. The Division instructed the Sponsor to make every effort to minimize confounding and to specify in the protocol and to describe in the CRF, specifically why a patient was prescribed a concomitant antibacterial drug.
- The Division asked the Sponsor what indication they had decided to study to initiate the program and the Sponsor indicated that this was still under consideration.

ACTION ITEMS

- Issue minutes within 30-days of meeting.

ATTACHMENTS AND HANDOUTS

Division's preliminary responses dated November 12, 2015
Sponsor's slide presentation dated November 17, 2015

¹ Available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128.pdf>

GENERAL APPLICATION INFORMATION [not part of meeting discussion]

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>.

In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards.

Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at:

<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a

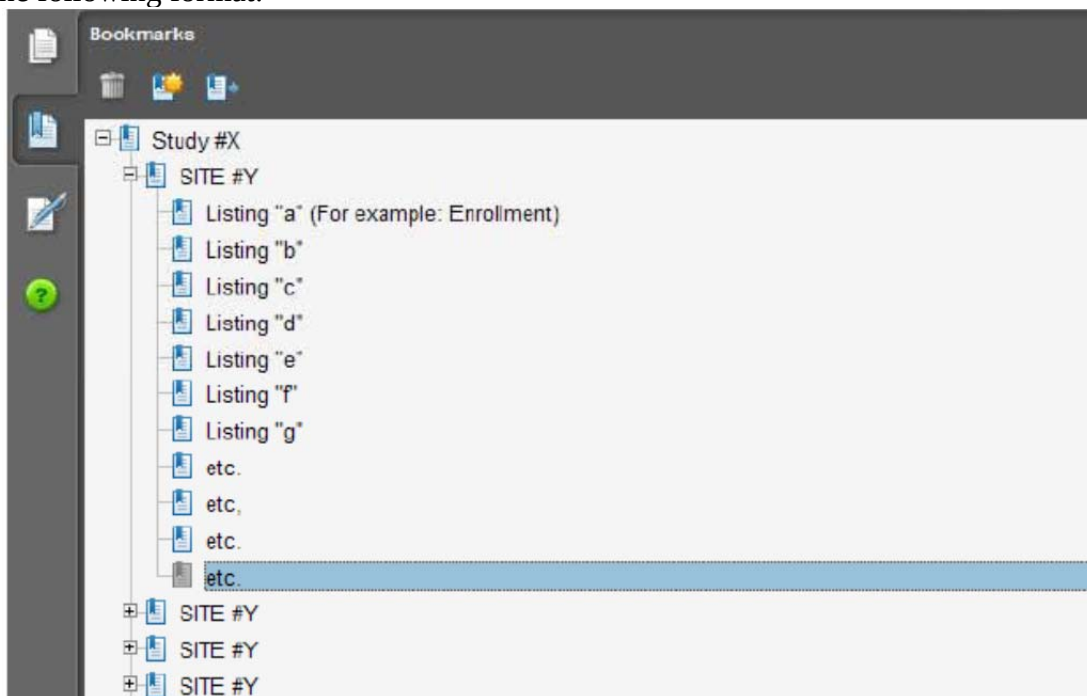
clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates

- g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ²	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

² Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

-END

Dear Dr. Wevelsiep,

In anticipation of our meeting with Basilea Pharmaceutica, Ltd., on November 17, 2015, for IND 64,407, the Division of Anti-Infective Products (DAIP) has the following responses to the questions in your briefing document dated October 16, 2015:

Question 1: *The Division previously advised the sponsor (June, 2014) that one pivotal Phase 3 study each in ABSSSI and in CABP would be sufficient to support the approval of both indications in an initial NDA. On the basis of such an approval (of ABSSSI and CABP in the initial NDA), would submission of a single adequate and well-controlled SAB study in the initial NDA, or in a later sNDA, be sufficient to expand the indication to include SAB?*

Division Response: Yes, evidence of effectiveness obtained in a single adequate and well-controlled trial of ceftobiprole for the treatment of *S. aureus* bacteremia could be sufficient to support this indication if the indications of ABSSSI and CABP are approved in an initial NDA.

Question 2: *As a variation of the submission strategy outlined in Question 1, the sponsor would consider submitting an initial NDA, which would contain the results of one ABSSSI study and one SAB study. Would this be sufficient to support an approval of both these indications? On the basis of such an approval (of ABSSSI and SAB in the initial NDA), would the subsequent submission of a single adequate and well-controlled CABP study in the initial NDA, or in a later sNDA, be sufficient to expand the indication to include CABP?*

Division Response: Yes, provided that the two adequate and well-controlled trials in ABSSSI and SAB demonstrate safety and efficacy for each of the two indications, it would be acceptable to submit them in the initial NDA and then pursue a third indication with another adequate and well-controlled study in CABP.

Question 3: *Does the Division agree with the proposed study population? The sponsor would like to clarify whether approximately 30 patients with definitive infective endocarditis (which would be a subgroup of similar size to that enrolled in the daptomycin study NCT00093067, [Fowler 2006](#)), and 30 patients with SAB undergoing chronic intermittent hemodialysis or peritoneal dialysis, would provide a sufficient basis to allow a specific wording for either of these two subgroups in the indication section of the product labelling.*

Division Response: We are in general agreement with the proposed study population. However, we note that patients with left-sided endocarditis may or may not be included depending on an interim look at the data. We do not recommend specifying inclusion/exclusion criteria in such an *ad-hoc* manner as this can lead to potential biases. We recommend that all inclusion/exclusion criteria be pre-specified and remain fixed throughout the trial for all patients. An unblinded interim analysis being conducted to alter an ongoing trial would lead to concerns regarding study integrity and type I error control.

A blinded pooled analysis of the study could possibly be considered in order to make some limited changes to the enrollment, but this should be discussed in detail in the protocol.

Treatment with potentially effective (anti-staphylococcal) systemic antibiotic for more than 48 hours within 7 days before randomization should be an exclusion criterion.

It is premature to discuss specific wording of product labeling. We might be willing to consider inclusion of infective endocarditis, depending on the quality of cases identified and outcomes in this subgroup. It is unlikely that all other subgroups of interest will be included in the indications and might be considered for inclusion in the clinical studies section.

Question 4: *Does the Division agree with the use of the proposed ‘standard of care’ regimen as a comparator?*

Division Response: The proposed standard of care is acceptable. However, we recommend that you limit the number of possible comparator treatments where possible. Sensitivity analyses should be performed to show the robustness of the overall results to the choice of the comparator treatment.

Question 5: *Does the Division agree with the proposed ceftobiprole dosing regimen?*

Division Response: We have concerns about the use of ceftobiprole for longer than 4 weeks based on the findings of convulsions and thrombi in the rat and marmoset 13 week studies, as well as thrombi and fibrin/erythrocytes/inflammatory cells clogging catheters at 4-11 weeks in the 13 week dog study. Please provide your justification for proposing treatment duration of longer than 4 weeks.

Question 6: *Does the Division agree with the protocol stipulations regarding the concomitant use of non-study antibiotics?*

Division Response: Please clarify the circumstances under which antibiotics with activity against methicillin-susceptible *S. aureus* would be permitted and whether this applies only to the comparator regimen. Your protocol stipulations regarding concomitant use of non-study antimicrobial agents are otherwise acceptable.

Question 7: *Does the division agree with the proposed primary endpoint and the definition of treatment failure?*

Division Response: We do not agree with the proposed primary efficacy endpoint. The primary efficacy endpoint should be well-defined and reliable such that it does not depend on the overall judgment of investigators regarding the necessity of additional therapy, and should be a direct measure of patient feeling, function, or survival. We recommend a primary endpoint composite based on the following major events:

- o All-cause mortality
- o Metastatic spread of infection
- o Infective endocarditis, if not present at baseline
- o Absence/presence of well-documented baseline signs/symptoms
- o Microbiological eradication

A cure would be defined as alive, no metastatic focus of infection, no evidence of endocarditis, resolution of baseline signs and symptoms and negative blood culture.

Note that the failure criteria defined should address the time period starting from 'randomization' rather than from 'first administration of study drug.' To preserve the integrity of randomization, we recommend that the evaluation time point for the primary endpoint be based on a window defined by the time from randomization rather than a window defined by the time from the end of therapy. Given that your duration of treatment can range from 28 to 42 days, we propose that your test of cure visit be around Day 70 post randomization (42 plus 28 days).

The primary analysis population should minimize post-randomization exclusions, while focusing on patients with the disease of interest.

We also have concerns regarding the open-label nature of your trial and the degree to which investigators can potentially influence the assessment made by the DRC. It is also not clear as to whether blinding of the DRC members can be properly maintained. Please address these concerns.

Question 8: *Does the Division agree with the approach for justifying a non-inferiority margin of 20% for the primary endpoint of clinical success and the proposed sample size?*

Division Response: We do not agree with this approach. In estimating a non-inferiority (NI) margin, the effect that the active control would reliably have over placebo (M1) needs to be established. M1 should be estimated using the lower limit of the 95% confidence interval of the estimated effect of the active control over placebo or no treatment. In considering the final NI margin, application of a fraction to M1 can be applied to account for various uncertainties. In addition, the acceptable margin based on clinical judgment (M2) must also be considered, where the final NI margin is the minimum of M1 and M2. Based on consideration of M2, a non-inferiority margin of 20% does not necessarily rule out an unacceptable loss of efficacy relative to the active control.

We recommend that you provide a justification of the NI margin using an approach as discussed above. We believe that the effect of antibiotics (M1) is quite large for this indication and we refer you to an article by Skinner and Keefer (Skinner, D. and Keefer, C., Significance of bacteremia caused by *Staphylococcus aureus*. *Arch. Intern. Med.* (Chic). 1941;68(5):851-875.). Note that due to the severity of this indication, an acceptable M2 will likely be no larger than 15%.

Question 9: *In the ABSSSI protocol to be submitted for a SPA, the sponsor plans to fully adhere to the relevant FDA guidance. Does the guidance in its current form fully represent the Division's thinking on ABSSSI studies? Can the Division confirm that vancomycin plus aztreonam at the proposed dosing regimen is an adequate comparator treatment?*

Division Response: The 2013 guidance represents the Division's current thinking regarding this indication. Vancomycin plus aztreonam at the proposed dosing regimen is an appropriate comparator.

Question 10: *In the CABP protocol to be submitted for a SPA, the sponsor plans to fully adhere to the relevant FDA guidance. Does the guidance in its current form fully represent the Division's current thinking on CABP studies? Can the Division confirm that ceftriaxone (with or without linezolid) at the proposed dosing regimen is an adequate comparator treatment?*

Division Response: The 2014 draft guidance represents the Division's current thinking regarding this indication. Ceftriaxone and linezolid at the proposed dosing regimen is an acceptable comparator. Given ceftobiprole's spectrum of activity, have you considered enriching enrollment of patients with pneumonia due to methicillin-resistant *S. aureus*?

We can discuss the above responses with you in more detail at our meeting on November 17, 2015. If you have questions in the interim, please contact me.

J. Christopher Davi, MS, Sr. RPM
DAIP
(301) 796-0702
christopher.davi@fda.hhs.gov

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

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

/s/

SUMATHI NAMBIAR
12/08/2015