CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208912Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105562

MEETING MINUTES

Icon Bioscience, Inc.
Attention: Luana Staiger
Regulatory Representative
1253 Reamwood Avenue
Sunnyvale, CA 94089

Dear Ms. Staiger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IBI-10090 IBI-10090 (dexamethasone intraocular injection).

The purpose of the July 20, 2015, meeting was to discuss your dexamethasone product. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jacquelyn Smith, M.A., Senior Regulatory Project Manager at 301 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley Chambers, M.D.
Deputy Director
Division Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 20, 2015

Meeting Time: 1:00 PM-2:00 PM EST

Meeting Location: White Oak Campus, Bldg. 22, Room 1311
10903 New Hampshire Avenue
Silver Spring, MD 20903

Meeting Type: Type B, Pre-NDA

Application: IND 105562

Drug: IBI-10090 (dexamethasone intraocular injection)

Indication: Treatment of postoperative inflammation

Sponsor: Icon Bioscience, Inc.

FDA Participants:

Wiley Chambers, MD	Deputy Director, DTOP
William Boyd, MD	Clinical Team Leader, DTOP
Sonal Wadhwa, MD	Clinical Reviewer, DTOP
Rhea Lloyd, MD	Clinical Reviewer, DTOP
Martin Nevitt, MD	Clinical Reviewer, DTOP
Philip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader, OTS/OCP/DCPIV
Abel Eshete, PhD	Statistics Reviewer, OTS/OB/DBIV
Yan Wang, PhD	Statistics Team Leader, OTS/OB/DBIV
Roy Blay, PhD	Reviewer, OC/OSI/DCCE/GCPAB
Jacquelyn Smith, MA	Senior Regulatory Project Manager, DTOP

Sponsor Participants:

David Tierney, MD	President and CEO, Icon Bioscience, Inc.
Howard Franklin, MD, MBA	Vice President Clinical and Medical, Icon Bioscience, Inc.

(b) (6) Consulting Ophthalmologist
Regulatory Consultant

Background:

On July 20, 2015, representatives from Icon Bioscience met with the FDA Division of Transplant and Ophthalmology Products (DTOP) to discuss the dexamethasone product. Icon Bioscience stated in the meeting that no discussion was needed for questions, 1, 2, 5, 6, 7 and 8. The meeting focused on responses to questions 3 and 4. The questions outlined in the meeting package (dated June 17, 2015) are presented in bold font, FDA responses are presented in italic format and the meeting discussion is in normal font.

Preliminary Comments:

1. **The proposed indication is consistent with the results from the clinical studies and with the clinical need for treatment of patients following cataract surgery. Does the Division agree with the proposed indications for use:** (b) (4) **is intended for the treatment of postoperative inflammation?"**

Agency Response: The indication is potentially acceptable; however final labeling is a review issue requiring submission and review of a new drug application.

NO DISCUSSION NEEDED

2. **Based on the results of study C13-04, both the 342 µg and 517 µg treatment groups showed statistically significant improvement in the primary endpoint of ACC clearing at day 8 versus placebo, with no significant differences in safety profile between the two active groups. As the 517 µg treatment group showed a more rapid onset of effect, with a statistically significant decrease in inflammation by post-operative day (POD) 1, Icon proposes to select the 517 µg dose to go forward for commercial development. Does the Division agree?**

Agency Response: Your proposal is acceptable, but see our response to Question #4.

NO DISCUSSION NEEDED

3. **The efficacy analysis from study C13-04 showed a statistically significant difference between both treatment groups compared to placebo, with a marked improvement in clearing of anterior chamber cells by day 1 for the 517 µg treatment group,** (b) (4) **The safety analysis from pivotal studies C11-01 and C13-04 showed a low**

occurrence of adverse events in patients treated with IBI-10090, and no major difference in safety profile between the placebo and IBI-10090 treatment groups for any of the key parameters. Does the Division have any comment on the description of these results in the draft package insert?

Agency Response: Final labeling, including clinical trial results, is a review issue requiring submission and review of a new drug application.

(b) (4)

If you haven't done so, please perform the analysis of the primary efficacy endpoint after treating subjects who required rescue therapy as treatment failures.

Meeting Discussion:
Icon clarified that in the analysis of the primary endpoint, patients who received rescue therapy prior to Day 8 were treated as treatment failures in the primary analysis. Icon further clarified that this was incorporated in the final Statistical Analysis Plan for study C13-04 submitted to the IND on August 26, 2014.

4. (b) (4)

Agency Response: No. There is insufficient information provided to answer this question.

(b) (4)

A new drug application review will be required to fully answer this question.

Meeting Discussion:
Icon acknowledged the Agency's concern regarding the findings observed in the development of IBI-10090 and further stated the NDA will include detailed information on the corneal injuries observed in clinical studies. Icon is proposing to conduct a follow-up clinical safety study to address these concerns. Icon shared that the study would be a multi-center study in approximately 180 patients who are scheduled to undergo cataract surgery and the patients would be randomized to

either a single injection of IBI-10090 or prednisolone acetate ophthalmic suspension 1% drops administered 4 times a day for 3 weeks, allowing a direct comparison of IBI-10090 to standard eye drop therapy. Icon stated that patients would be followed for up to 90 days for safety assessments. Icon shared the brief protocol synopsis that outlined the study design and key safety outcomes that would be measured. Icon further stated that the full protocol will be submitted.

The Agency stated that before a determination is made regarding the needed for another study, the full study reports for the completed trials needs to be submitted and reviewed by the Agency. An additional trial may not be necessary to answer the Agency's concern over endothelial cell density.

5. **Icon proposes that the NDA will provide the Summary of Clinical Efficacy and the Clinical Summary of Safety in Module 2, and the Integrated Summary of Safety in Module 5. A separate Integrated Summary of Efficacy is not planned. Does the Division agree with the proposed plan for the summaries of efficacy and safety that will be provided in the NDA?**

Agency Response: Acceptable.

NO DISCUSSION NEEDED

6. **Electronic datasets and supporting documentation will be provided for all clinical studies. Does the Division have any comment on the proposal for submission of the data and documentation that will be provided with the NDA?**

Agency Response:

- *You are encouraged to submit standardized datasets following the CDISC guidelines for SDTM and ADaM datasets (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm).*
- *Provide all raw datasets, as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report. Please also provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.*
- *Include the programs used for creating efficacy analysis datasets from the raw datasets and the programs used for all efficacy and safety analyses together with a document that explains what each program is used for.*
- *Provide the analysis datasets (with definition file) and programs (with documentation) used to generate the inferential analyses results in the ISS reports.*

NO DISCUSSION NEEDED

7. Case Report Forms will be provided in accordance with ICH E3. Does the Division agree that the NDA will include those Case Report Forms for any patient in Study C10-01, C11-01 and C13-04 who reported a Serious Adverse Event or withdrew from the study due to an adverse event?

Agency Response: The NDA should also contain the CRFs for any patient withdrawal, regardless of the reason.

NO DISCUSSION NEEDED

8. Based on the overall safety of the product, and the history of safe use of drug and biologic product used for intraocular injection, Icon does not believe a Risk Evaluation and Mitigation Strategy (REMS) is necessary for IBI-10090. Does the Division agree?

Agency Response: Concur, provided review of the application reveals no unexpected safety concerns with this product. See response to Question #4.

NO DISCUSSION NEEDED

Additional Comments:
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*

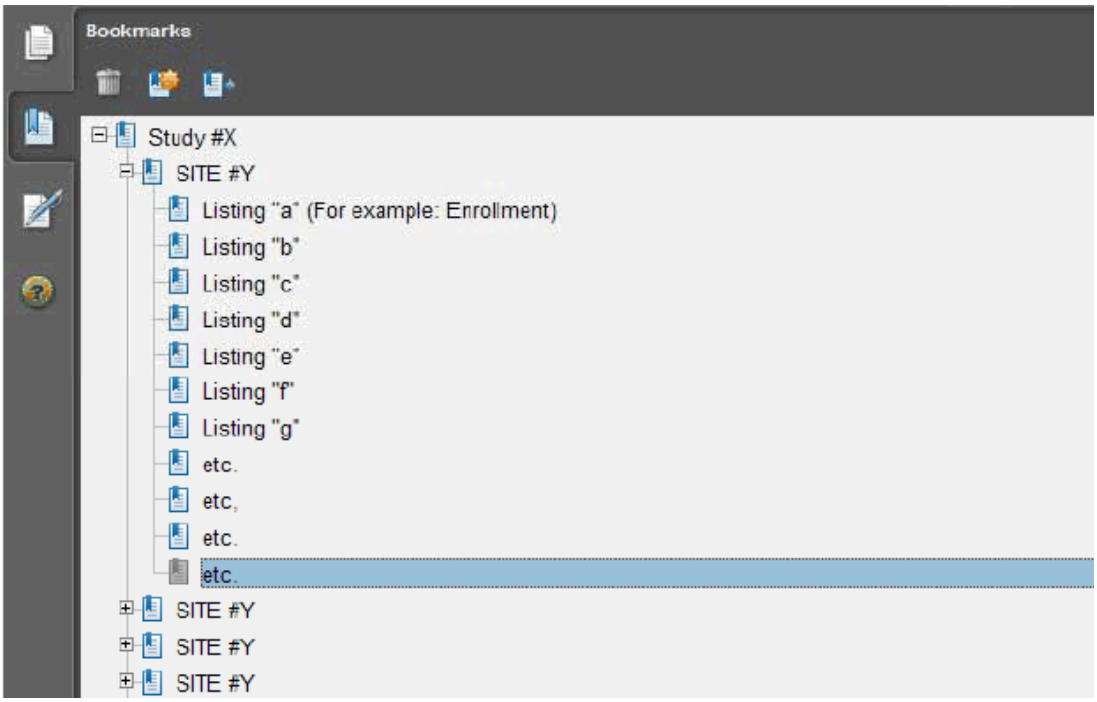
   e. *By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)*

   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.*

2. *We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:*



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

NO DISCUSSION NEEDED

Minutes Preparer: Jacquelyn Smith, M.A., Senior Regulatory Project Manager, DTOP
Chair Concurrence: Wiley Chambers, M.D., Deputy Director, DTOP

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

/s/

WILEY A CHAMBERS
07/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105562

MEETING MINUTES

Icon Bioscience Inc.
Attention: Luana Staiger, Regulatory Consultant for Icon Bioscience
499 Seaport Court
Suite 200
Redwood City, CA 94063

Dear Ms. Staiger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IBI-10090 (dexamethasone, USP (b) (4) (b) (4) acetyl triethyl citrate) for intraocular injection.

We also refer to the meeting between representatives of your firm and the FDA on December 3, 2013. The purpose of the meeting was to discuss the CMC program for IBI-10090 as Icon Bioscience initiates its Phase3 clinical study and to discuss the overall strategy for the continued CMC development and NDA filing of IBI-10090.

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 questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	EOP2
Meeting Date and Time:	December 3, 2013 1:00 – 2:00 pm, EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 105562
Product Name:	IBI-10090 (dexamethasone, USP [redacted (b) (4)] acetyl triethyl citrate)
Indication:	Treatment of post-cataract surgery inflammation
Sponsor/Applicant Name:	Icon Biosciences Inc.
Meeting Chair:	Rapti D. Madurawe, Ph.D.
Meeting Recorder:	Navdeep Bhandari, Pharm.D.

FDA ATTENDEES

Rapti D. Madurawe, Ph.D.	Branch Chief
Bala Shanmugam, Ph.D.	CMC Lead
Neal Sweeney, Ph.D.	Microbiology Reviewer
Okpo Eradiri, Ph.D.	Biopharmaceutics Reviewer
William Boyd, M.D.	Lead Medical Officer
Wiley Chambers, M.D.	Supervisory Medical Officer
Renata Albrecht, M.D.	Supervisory Medical Officer
Linda Ng, Ph.D.	Senior Policy Advisor: Compliance
Mahesh Ramanadham,Pharm.D.	Team Leader (acting): Compliance
Navdeep Bhandari, Pharm.D	Regulatory Project Manager

SPONSOR ATTENDEES

William S. White	CEO Icon Bioscience, Inc.
Vernon G. Wong, M.D.,	Chief Scientific Officer, Icon Bioscience, Inc.
Mae Hu, PhD,	Head of CMC, Icon Bioscience, Inc.
Glenn Huang, MS,	Head of Formulations, Icon Bioscience, Inc.
[redacted (b) (6)]	Manufacturing Consultant
	CMC Consultant
	Regulatory Consultant

1.0 BACKGROUND

IBI-10090 (dexamethasone, USP (b) (4) acetyl triethyl citrate) for intraocular injection is being developed for the treatment of patients with inflammation associated with ocular surgery.

This meeting is a follow up meeting that Icon had with the Division on July 22, 2013 that discussed the clinical, non-clinical and regulatory development of IBI-10090. At the close of the meeting the FDA stated that they would be willing to meet separately with Icon to discuss specific CMC issues.

2.0 DISCUSSION

This meeting's focus was to provide an update to the Division on the CMC program for IBI-10090 as Icon Bioscience initiates its Phase 3 clinical study and to discuss the overall strategy for the continued CMC development and NDA filing of IBI-10090.

The Agency sent preliminary responses on November 29, 2013 to the Sponsor. The Sponsor asked to focus on questions 3, 4, and 5.

3.0 Questions

Degradant Specification:

1. The specifications for IBI-10090 for use in the upcoming Phase 3 study include testing for appearance, identity, purity/assay, impurities, in-vitro drug release, content uniformity/potency, endotoxin and sterility and are the same as used for batches used in previous clinical studies conducted under this IND. At the time of the NDA, Icon Biosciences will review the manufacturing data and propose specifications appropriate for use in manufacturing of commercial material. **Does the Agency concur that the specifications will be suitable for the proposed clinical supplies and that the final specifications proposed for manufacturing of commercial supplies will be based on data from stability and scale up activities?**

Agency Response:

The tests included in the proposed drug product specification appear reasonable for Phase 3 studies. Adequacy of the acceptable limits is a review issue. Additional comments and recommendations are given below.

a. We note that (b) (4) is used as a test for identity. (b) (4) Institute either one specific identity method or two non-specific tests. For example, two

chromatographic procedures, where separation is based on different principles, or a combination of tests into a single procedure, such as HPLC/UV diode array, is generally acceptable. Please see ICH Q6A.

b. Report degradants according to the ICH Q3B (R2) guidelines (i.e., specified identified, specified unidentified, unidentified and total degradation product).

c. The proposed specification does not provide acceptance values for several quality attributes. Please assign values for those and as more manufacturing experience is gained, these values can be revised as appropriate. Based on the data obtained, additional quality tests (such as redispersibility) may be required.

d. Note that your proposed in-vitro drug release specifications will be assessed during NDA review based on the totality of the dissolution data of the selected formulation for commercialization. Dissolution data for the clinical and primary stability batches should be included.

e. Bacterial endotoxin limits were not included (listed as "run and report") in the IBI-10090 product specifications. Bacterial endotoxin limits should be established for both the clinical and commercial supplies. The reported <(b) (4) EU/mL (or <(b) (4) EU/dose) endotoxin testing results obtained from batch analysis of clinical lots 0090-001-09A001, 0090-002-09A001, 0090-002-10E001, and 0090-005-10E001 (stored up to 24 months at 25ºC/60%RH) would generally be considered acceptable for the proposed 5.0 µL intraocular dose.

f. We recommend establishing bioburden acceptance criteria for drug substance, excipients container/closure components, and/or filled containers, especially if a bioburden approach will be utilized to (b) (4)

Discussion: The Sponsor will amend the IND to incorporate the recommended changes including endotoxin limits.

2. The drug product is a suspension, and according to USP<788>, particulate matter testing is not applicable. **Does the Agency concur that IBI-10090 Suspension is exempt from USP<788>?**

Agency Response:

A test for particulate matter can be exempted but we expect particle size distribution in the drug product to be controlled.

Discussion: There was no specific discussion on this question.

3. Stability testing on the drug product intended for the Phase 3 study will follow the recommendations in ICH Q1A. Studies on drug product manufactured to date indicate that the product is stable at 25°±2°C/60±5% RH for 24 months. To support the submission of the NDA, Icon Bioscience is intending to manufacture three batches of drug product at the intended commercial manufacturing site. At the time of the NDA filing, it is expected that (b) (4) of stability data will be available on these primary stability batches, with data up to (b) (4) to be submitted promptly during the NDA review. **Does the Agency concur that the NDA can be submitted with (b) (4) months data on the primary stability lots of IBI-10090 Suspension?**

Agency Response:

No, the NDA at the time of submission should include 12-months long-term and 6-months accelerated stability data for three registration stability batches. Any data submitted during review may or may not be reviewed depending on resources available. Additionally, we note that the testing schedule does not include testing for some quality attributes (particle size, osmolality, pH and viscosity) at all time points. These attributes should be tested at all time points in the stability program to establish shelf-life quality of the drug product.

Discussion: (b) (4) **The Agency indicated this is necessitated due to several factors including timely completion of review and to enable a favorable action in the first cycle. The sponsor acknowledged Agency's position.**

In response to Agency's question on the commercial manufacturer, the sponsor indicated that AMRI was the manufacturer and that stability batches will also be manufactured at the same facility. Furthermore, the Sponsor indicated that the stability lots will also be tested for particle size, pH, osmolality and viscosity.

4. The clinical supplies of IBI-10090 intended for the Phase 3 study are being manufactured using the identical procedures as those previously submitted to the IND and used for the completed Phase 2 study. Manufacturing is done at (b) (4) under sterile conditions using a (b) (4) operation. For commercial supplies, Icon is planning on using a commercial manufacturing site who will utilize (b) (4) of vials. Comparability between the clinical and commercial supplies will be done using physical/chemical comparison between the lots to demonstrate that the commercial supplies meet all specifications. The company intends to use the same vial packaging

and injection components in the Phase 3 clinical trial and commercially. **Does the Agency concur that the comparability between the clinical and commercial supplies can be done using physical/chemical comparison,** (b) (4)

Agency Response:

Per SUPAC-MR, the proposed manufacturing site change corresponds to a Level 3 change that requires a bridging in vivo bioequivalence study. We advised you in the July 22, 2013 Type C meeting to measure dexamethasone systemic exposure levels in a sub-population of patients during the Phase 3 trial. If that study demonstrates that the dexamethasone levels are below the limit of quantitation of the assay making the in vivo BE study impractical, then the bridging can be supported by conducting comparative multipoint dissolution testing in at least 3 different media; the dissolution profiles of the commercial and clinical lots should be demonstrated to be similar by using an appropriate statistical test such as the f2 similarity factor.

In addition to the proposed comparison of physical and chemical attributes, provide a side by side comparison of the manufacturing process, equipment details, and process parameters to establish similarity of drug product manufactured at the different sites.

Discussion: The Sponsor stated that they do not expect to see high systemic dexamethasone exposure in patients and asked what the next step to would be to show comparability of the clinical and commercial products. A study in rabbits as an alternative to a human study was also suggested by the Sponsor. The Agency agreed with the Sponsor that the potential for significant systemic exposure in the patients is low but the decision on the need for an in-vivo bioequivalence study should be data driven. The results of the dexamethasone plasma level measurements in a group of patients in the Phase 3 trial will be submitted as an IND amendment; FDA will assess the data and give further guidance to the Sponsor. The Sponsor plans to investigate systemic exposure in 10 patients per group.

In addition, the Sponsor sought clarification on additional physiologically relevant dissolution media that may be used for in-vitro release characterization in addition to the proposed regulatory medium. The Agency stated that the narrow pH range of the eye may pose a challenge in performing dissolution testing over a wide pH-range. The Sponsor was advised to vary the dissolution medium within the pH range in the eye and justify the use of a limited number of media should that become necessary.

5. For the clinical studies, IBI-10090 is provided as a kit with all accessories needed for injection into the patient, including a needle for withdrawal of drug from the vial, a syringe fitted with a (b) (4) ring to position the plunger rod in the barrel of the syringe, a (b) (4) guide to allow delivery of the 5 µL dose, and a cannula for administration into the (b) (4) chamber of the eye. All of the accessory components are currently sterilized (b) (4). A similar configuration is planned for the commercial supplies. **Does the Agency concur with this plan to provide injection components as a kit?**

Agency Response:

Sterility and bacterial endotoxin specifications should be established (or referenced) for the product/patient-contact components of the injection kit components for the clinical and commercial supplies. From an informational perspective it would helpful to know why the copackaged kit is not pre-assembled.

Discussion: The Sponsor brought a physical prototype to demonstrate the assembly of the injection kit. (b) (4)

6. Under 21 CFR 3.2(e), the product will be considered a combination product. As IBI-10090 has been developed as a drug with therapeutic claims, and that (b) (4) no specific submission to CDRH is anticipated for any of the components. **Does the Agency agree that IBI-10090 will continue to be regulated as a drug and that no submission to CDRH is required for any of the kit components?**

Agency Response:

As long as the commercial configuration contains the delivery system co-packaged with the drug product, a separate regulatory submission for the syringe and its components to CDRH is not required. All relevant information for the container closure and its components may either provided in the NDA or referenced to DMFs and letter of authorization from the respective DMF holders be provided.

Discussion: **There was no specific discussion on this question.**

7. [redacted] **Does the agency agree that this strategy will fulfill the requirements for product validation?**

Agency Response:

The proposal for [redacted] **seems reasonable as long as these studies to support** [redacted] **are performed at the commercial facility. In general, it is the company's responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product. CDER does not approve process validation plans, protocols, or specific batches used in process validation studies. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection.**

FDA requires that drug manufacturers have an adequately designed manufacturing process [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process.

For the device constituent parts of the finished combination product, process validation requirements as described in 21 CFR 820.75 are satisfied with adequate compliance with 21 CFR 211.100(a) and 211.110(a). An evaluation of the elements that incorporate the process validation of the device constituent parts of the finished combination product will also take place during an inspection.

Please find more information in the Guidance for Industry, *Process Validation: General Principles and Practices* (January 2011).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Discussion: **The Agency asked if the Sponsor could summarize the proposal for scale up and process validation. The Sponsor responded that they are in the process of working with AMRI to develop validation and process for commercial manufacture and that the Sponsor understood the response provided and has no further questions at this time.**

ADDITIONAL BIOPHARMACEUTICS COMMENTS

We have the following comments regarding the dissolution information that should be provided in your NDA.

1) **Dissolution Test:** Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

    a. Solubility data for the drug substance over the physiologic pH range.

    b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;

    c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*)

    d. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables); and

    e. Include the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

2) **Dissolution Acceptance Criteria:** For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

   a) The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).

   b) Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).

   c) Based on the in-vitro release profile of your proposed product in the briefing document, a minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be the time point where at least 80% of drug is released. If the maximum amount released is less than 80%, the last time point should be the time when the plateau of the release profile has been reached.

   Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

   Discussion: There was no specific discussion on these additional comments.

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/s/

RAPTI D MADURAWE
12/20/2013