CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761279Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 125444

MEETING PRELIMINARY COMMENTS

Eli Lilly and Company
Attention: Conrad Wong, Ph.D.
Advisor, Global Regulatory Affairs - US
Lilly Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wong:

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

We also refer to your correspondence, dated and received November 3, 2021, requesting a meeting to discuss the safety and efficacy results from the phase 3 maintenance study (AMBG) and whether the safety and efficacy results from the induction (AMAN) and maintenance (AMBG) trials are sufficient to support your planned BLA submission.

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 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-4276 or email me at kelly.richards@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Kelly Richards, RN, MSN, RAC
Senior Regulatory Health Project Manager
Gastroenterology
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FDA U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: January 26, 2022 from 3:00-4:00 pm ET
Meeting Location: Teleconference

Application Number: 125444
Product Name: LY3074828 (mirikizumab)
Indication: Moderately to severely active ulcerative colitis
Sponsor Name: Eli Lilly and Company
Regulatory Pathway: 351(a) of the Public Health Service Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 26, 2022 from 3:00-4:00 pm ET via teleconference between Eli Lilly and Company and the Division of Gastroenterology. 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

LY3074828 (mirikizumab) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody against the p19 subunit of IL-23 that is being developed for the treatment of moderately to severely active ulcerative colitis (UC) in adult (b) (4)

Mirikizumab was granted Orphan Designation for pediatric ulcerative colitis on June 15, 2017.

With this meeting request, the Sponsor is seeking to obtain agreement from FDA that the data from the phase 3 induction and maintenance studies, listed below, are

sufficient to support submission and review of an original BLA to be submitted in Q2 of 2022 for mirikizumab to support the proposed indication statement, “for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).”

Study and Description
I6T-MC-AMAN (AMAN)
Randomized, double-blind, placebo-controlled induction study to evaluate the efficacy and safety of mirikizumab in “conventional-failed” and biologic-failed patients with moderately-to-severely active UC. Primary endpoint (clinical remission) is measured at Week 12.

I6T-MC-AMBG (AMBG)
Randomized, double-blind, placebo-controlled maintenance study to evaluate the efficacy and safety of mirikizumab in patients with moderately-to-severely active UC who have completed Study AMAN. Primary endpoint (clinical remission among clinical responders at the end of Study AMAN) is measured at Week 40.

I6T-MC-AMAP(AMAP)
Open-label extension study to evaluate the long-term efficacy and safety of mirikizumab in patients with moderately-to-severely active UC who have participated in Study AMAC (a Phase 2 study) or both Studies AMAN and AMBG.

2.0 DISCUSSION

Question 1: Does FDA agree that results from Studies AMAN and AMBG are sufficient to support a fileable BLA for mirikizumab for the treatment of adult patients with moderately to severely active UC?

FDA Response to Question 1:
It is premature to agree that results from a single induction study (AMAN), in addition to the maintenance study (AMBG), is sufficient to support the filing of a future BLA submission for mirikizumab for the treatment of adult patients with moderately to severely active UC. However, given that your induction study (AMAN) used a two-sided alpha level of 0.00125 to define statistical significance, your approach may be reasonable.

The final determination of the acceptability of your proposal will be made upon our review of the BLA submission. For additional information on circumstances where reliance on a single adequate and well-controlled trial may be acceptable to establish substantial evidence of effectiveness, refer to the draft guidance for

industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.[1]

Question 2: Does FDA agree that a Risk Evaluation and Mitigation Strategy is not required?

FDA Response to Question 2:
It is premature to agree that a Risk Evaluation and Mitigation Strategy (REMS) is not required for your proposed future BLA submission. You should include a justification of your proposed post-marketing risk management plan to support that a REMS is not necessary. The final determination of the requirement for a REMS will be made upon our review of the BLA submission.

Question 3: Does FDA agree with the scope of content planned for Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods?

FDA Response to Question 3:
The proposed scope of content for Module 2.7.1 appears reasonable. However, the adequacy of the available information to support the to-be-marketed formulation and labeling, will be determined upon our review of the BLA submission.

We recommend including a tabulated summary of bioanalytical assay methods for both your product and anti-drug antibody for each study. Refer to the draft guidance for industry: Bioanalytical Methods Templates Guidance for Industry Technical Specifications Document[2] **for further information.**

Question 4: Does FDA anticipate that an Advisory Committee meeting will be needed for this BLA?

FDA Response to Question 4:
At this time, we do not anticipate an Advisory Committee meeting will be needed for this BLA application. However, the final determination will be made upon our review of the BLA submission.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents
[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

FDA ADDITIONAL COMMENTS

Clinical

1. **We acknowledge your commitment to provide additional safety analyses and plots to assess for potential hepatic injury with your BLA submission as recommended in our written responses dated August 3, 2021.**

2. **We acknowledge that you define moderately to severely active UC as a modified Mayo score (MMS) of 4 to 9 with an endoscopic subscore of at least 2; however, we recommend that moderately to severely active UC be defined as an MMS of 5 to 9, with an endoscopic subscore of at least 2. We are concerned that your definition may allow for patients with only mild signs and symptoms of UC (i.e., rectal bleeding and stool frequency) to enroll in your study (e.g., an MMS of 4 with an endoscopic subscore of 2, a rectal bleeding subscore of 1, and a stool frequency subscore of 1). Therefore, we recommend you perform a sensitivity analysis of your primary endpoint and multiplicity-controlled secondary endpoints that excludes patients with an MMS of 4 for both study AMAN and AMBG.**

CMC

To facilitate the Agency's assessment of the BLA submission, provide the information in tables as requested below. The requested tables should summarize information from Module 3 and be submitted in Module 3.2.R. These tables do not replace other sections of Module 3 or impact the nature or amount of information included in those sections of Module 3.

3. **Provide the following information in a completed table such as the one below for all drug master files (DMFs) referenced in the BLA:**

DMF #	DMF Type	DMF Holder	Item referenced	Link to Letter of Authorization	Comments (if needed)

4. **To facilitate the Agency's assessment of the mirikizumab drug substance (DS) and drug product (DP) manufacturing process, provide the information for each process parameter and in-process control, as applicable, in the tabular format provided below. Provide a separate table for each unit operation of the DS and DP manufacturing process, as described below.**

Title: Unit Operation for Mirikizumab DS Manufacturing Process

Process parameter/ In-process control (IPC)[1]	Proposed range for commercial manufacturing process[2]	Criticality classification [3]	Characterized range from process development[2]	Historical range from clinical DS batches[2] (min-max[4]), n=?[5]	Process validation range from DS PPQ batches[2] (min-max[4]), n=?[5]	Justification of the proposed commercial acceptable range[6] (or link to eCTD)

1. Terminology should be adapted to the one used by the manufacturing site(s).
2. As applicable.
3. For example, critical process parameter, key process parameter, non-critical process parameter, IPC, as described in Module 3.
4. Provide mean ± 2 (or 3) SD as optional.
5. Indicate the total number of batches used for calculating minimum-maximum range for each unit operation and list the batch numbers in the footnote if applicable. If not all batches indicated are included for calculation, provide justification in the footnote or insert a hyperlink to eCTD.
6. This could be a brief verbal description (e.g., "development range", "validation range", or "platform experience").

Title: Unit Operation for Mirikizumab DP Manufacturing Process

Process parameter/ In-process control (IPC)[1]	Proposed range for commercial manufacturing process[2]	Criticality classification [3]	Characterized range from process development[2]	Historical range from clinical DP lots[2] (min-max[4]), n=?[5]	Process validation range from DP PPQ lots[2] (min-max[4]), n=?[5]	Justification of the proposed commercial acceptable range[6] (or link to eCTD)

1. Terminology should be adapted to the one used by the manufacturing site(s).
2. As applicable.
3. For example, critical process parameter, key process parameter, non-critical process parameter, IPC, as described in Module 3.
4. Provide mean ± 2 (or 3) SD as optional.
5. Indicate the total number of lots used for calculating minimum-maximum range for each unit operation and list the lot numbers in the footnote if applicable. If not all lots indicated are included for calculation, provide justification in the footnote or insert a hyperlink to eCTD.
6. This could be a brief verbal description (e.g., "development range", "validation range", or "platform experience").

5. To facilitate the Agency's assessment of the control strategy for mirikizumab, provide information for quality attributes and process and product related impurities for DS and DP in the following tabular format. Provide a separate table for the DS and DP.

Quality Attributes (including process and product related impurities for DS and DP)	Criticality classification[1]	Impact[2]	Source[3]	Analytical method[4]	Proposed control strategy[5]	Justification of the proposed control strategy[6]

1. Indicate if it is a CQA or not.
2. What is the impact of the attribute (e.g., contributes to potency, immunogenicity, safety, efficacy, etc.)?
3. What is the source of the attribute or impurity (e.g., intrinsic to the molecule, fermentation, purification column, etc.)?
4. List all methods used to test an attribute in-process, at release, and/or on stability. For example, if two methods are used to test identity, list both methods for that attribute.
5. List all strategies by which the attribute is controlled (e.g., in-process testing, validated removal, release testing, stability testing, etc.).
6. This could be a brief verbal description or links to the appropriate section of the eCTD.

6. To facilitate the Agency's assessment of the adequacy of the proposed commercial release specifications of mirikizumab DS and DP, provide information for each release specification in the tabular format provided below. Please provide a separate table for DS and DP, as described below. Use footnotes for each column of grouped results to indicate the lots used for each calculation of the minimum-maximum range, and provide the number of lots (n=?) in the table.

Release Specification for Mirikizumab Drug Substance							
Attribute	Analytical Method	Proposed commercial release acceptance criteria	Release results from developmental and nonclinical batches (n=?) (min-max)	Release results from clinical DS batches (n=?) (min-max)	Release results from DS PPQ batches (n=?) (min-max)	Release results from all DS batches[a] manufactured using the commercial process (n=?) (min-max)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

a. Include all batches with available release data that were manufactured following the proposed commercial process, including those prior to PPQ campaign. Provide a list of batches included in the analysis as a footnote in the table.

Release Specification for Mirikizumab Drug Product							
Attribute	Analytical Method	Proposed Commercial Release acceptance criteria	Release results from developmental and nonclinical DP lots (n=?) (min-max)	Release results from clinical DP lots[a] (n=?) (min-max)	Release results from DP PPQ lots (n=?) (min-max)	Release results from all DP lots[b] manufactured using the commercial process (n=?) (min-max)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

a. Include all lots used in any clinical testing, regardless of scale, process, or manufacturing location, etc. List all lots as a footnote in the table.
b. Include all lots with available release data that were manufactured following the proposed commercial process. Provide a list of lots included in analysis as a footnote in the table.

7. To facilitate the Agency's assessment of the adequacy of the stability specifications of mirikizumab DS and DP, provide stability information for storage at recommended condition for each stability specification in the tabular format provided below. Please provide a separate table for DS and DP, as described below. If any stability acceptance criteria are different from the corresponding release acceptance criteria for which the same analytical method is used, provide justification as to why different acceptance criteria are proposed for release and stability. Include footnotes in the tables to list all batches that were used in each assessment. The assessment should consider data from all stability time points, not limited to the release and end of proposed shelf-life time points.

If a lot has not completed stability testing to the end of proposed shelf-life, include data from all time points that are currently available.

Stability Specification for Mirikizumab Drug Substance				
Attribute	**Analytical Method**	**Stability acceptance criteria**	**Stability results for batches stored at recommended long-term storage condition (n=?) Min – Max (Range for all data from time 0 to proposed end of shelf life or currently available time points)**	**Justification of specification (e.g., clinical experience, manufacturing capability, etc.)**

Stability Specification for Mirikizumab Drug Product				
Attribute	**Analytical Method**	**Stability acceptance criteria**	**Stability results for batches stored at recommended long-term storage condition (n=?) Min – Max (Range for all data from time 0 to the proposed end of shelf life or currently available time points)**	**Justification of specification (e.g., clinical experience, manufacturing capability, etc.)**

8. **To facilitate the Agency's assessment of the suitability of the analytical methods for release and stability testing of mirikizumab DS and DP and for in-process test methods, provide summarized results of method validation in the tabular format provided below. Provide a separate table for each analytical method. Each parameter (e.g., specificity, precision, accuracy, etc.) should be described in a separate row. Add additional rows for additional parameters as needed. Study design should include a brief description of the testing material (such as batch information), the number of tests (e.g., the number of replicates, runs, plates, analysts, etc., if applicable), design of the experiment, approach of data reporting, and other important overview information regarding the validation of that parameter, as needed. Indicate in the table title the name of the method and all applicable programs where it is used (e.g., DS release/stability, DP release/stability, and in-process testing).**

Summary of Validation Results for XXX (Method) (Used for DS/DP release/stability, in-process testing, etc.)			
Location of testing site:		**Location where method was validated:**	
System Suitability Acceptance Criteria:			
Parameter	**Study Design**	**Acceptance Criteria**	**Validation Results**

9. **Regarding the immunogenicity testing in the BLA submission, we recommend you provide an Integrated Summary of Immunogenicity (ISI) in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This ISI should include: (1) Immunogenicity Risk Assessment, (2) Tiered Bioanalytical Strategy and Assay Validation Summaries, (3) Clinical Study Design and Detailed Immunogenicity Sampling Plans, and (4) Clinical Immunogenicity Data Analysis. For more information, refer to 2019 FDA Guidance for Industry: "*Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection*".**

Microbiology

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

10. **All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the [antibody intermediate, the] drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.**

11. **Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.**

    a. **The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to, the following:**

        - **Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).**
        - **Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).**
        - **Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin**

limits provided (3.2.S.2.5).

- **Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).**
- **Information and summary results from the shipping validation studies (3.2.S.2.5).**
- **Drug substance bioburden and endotoxin release specifications (3.2.S.4).**
- **Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).**

b. The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

12. The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- **Identification of the manufacturing areas and type of fill line (e.g., open, RABS, isolator), including area classifications.**
- **Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.**
- **Parameters for filling and plunger placement for the pre-filled syringes.**
- **Parameters for filling and capping for the vials.**
- **A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.**

- **Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.**
- **Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.**

13. **The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:**
    - **Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.**
    - **Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.**
    - **In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.**
    - **Isolator decontamination summary data and information, if applicable.**
    - **Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.**
    - **Information and summary results from shipping validation studies. [For prefilled syringes</autoinjectors>, the effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled syringe plunger movement during air transportation does not impact product sterility.]**
    - **Validation of capping parameters, using a container closure integrity test.**

14. **The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:**
    - **Container closure integrity testing. System integrity should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the**

assembly of the pre-filled syringe and autoinjector should be included. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry.

- **Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.**
- **Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b). [A request to waive the Rabbit Pyrogen Test may be made for insulin products by providing a scientifically justifiable rationale.]**
- **Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> Bacterial Endotoxin Test (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.**
- **Microbiological studies in support of the post-reconstitution and/or post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended reconstitution solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> Antimicrobial Effectiveness Testing, plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the <post-reconstitution and/or post-dilution> storage period is not more than 4 hours.**

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] 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

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

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 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. 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]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming*

[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
[7] https://www.fda.gov/media/85061/download

of Biological Products, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D RICHARDS
01/21/2022 09:53:16 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125444

MEETING MINUTES

Eli Lilly and Company
Attention: Helen Sile, M.D.
Advisor, Consultant Global Regulatory Affairs – US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Sile:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LY3074828 (mirikizumab).

We also refer to the meeting between representatives of your firm and the FDA on May 23, 2018. The purpose of the meeting was to End-of-Phase 2 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 me at (240) 402-4276.

Sincerely,

{See appended electronic signature page}

Kelly Richards, MSN, RN
Captain, U.S. Public Health Service
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	May 23, 2018 from 12:00-1:00 PM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	125444
Product Name:	LY3074828 (mirikizumab)
Indication:	Ulcerative colitis
Sponsor/Applicant Name:	Eli Lilly and Company
Meeting Chair:	Anil Rajpal
Meeting Recorder:	Kelly Richards

FDA ATTENDEES

Jessica J. Lee, M.D., M.M.Sc., Associate Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Anil Rajpal, M.D., Medical Team Leader, DGIEP
Marjorie Dannis, M.D., Medical Officer, DGIEP
Kelly Richards, R.N., M.S.N., Senior Regulatory Project Manager, DGIEP
Tamal Chakraborti, Ph.D., Pharmacologist, DGIEP *(via telephone)*
Jie Wang, Ph.D., Team Leader, Office of Clinical Pharmacology (OCP), Division of Pharmacology 3 (DCP3)
Anand Balakrishnan, Ph.D., Clinical Pharmacology Reviewer, OCP, DCP3
George Kordzakhia, Ph.D., Statistical Team Leader, Office of Biostatistics, (OB), Division of Biostatistics III (DBIII)
Shahla Farr, M.S., Statistical Reviewer, OB, DBIII
Ram Sihag, Ph.D., Product Quality Reviewer, Office of Biotechnology Products (OBP)
Florencia T. Wilson, R.N., B.S.N., CCRN, Nurse Consultant, Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices (DAGRID) *(via telephone)*

SPONSOR ATTENDEES
Ruth M. Belin, MD, MPH, Global Brand Development Leader, Clinical/Medical
Catherine Milch, MD, Senior Director, Immunology, Clinical/Medical
Vipin Arora, PhD, Senior Research Advisor, Statistics
Michelle Lytle, Global Regulatory Affairs (GRA)-Chemistry Manufacturing Controls (CMC)
Stuart Friedrich, PhD, Senior Research Advisor, Global PK/PD and Pharmacometrics
Susan Moriarty, MD, Senior Advisor, Global Patient Safety
Robin Pitts-Wojcieszek, RPh, Senior Director-GRA
(b) (4) Advisor, GRA
(b) (4) Consultant, GRA
Michael Hodsdon, MD, PhD, Medical Fellow, Laboratory for Experimental Medicine (LEM)
Daniel A. Peterson MD, PhD, Sr. Medical Advisor, LEM-Clinical Implementation
Allison S. Kennington, PhD, Senior Director, GRA-CMC Biotechnology
Melissa F Veenhuizen, DVM, MS, Sr. Director, Global Patient Safety

1.0 BACKGROUND

The Sponsor is seeking feedback on the proposed phase 3 development plan and submission for LY3074828 as a treatment for adult patients with moderately to severely active UC. LY3074828 is a humanized immunoglobulin G4 (IgG4) monoclonal antibody. Specifically, the Sponsor is seeking feedback on the following areas:

- Dose selection for the phase 3 induction and maintenance UC studies
- Bridging data from the planned psoriasis program with respect to the phase 1/2 and phase 3 formulations and presentations to the to-be marketed formulations and presentations
- Safety monitoring and the estimated number of patient exposures for the durations specified to support a marketing application
- Proposed drug-drug interaction study

1.0 DISCUSSION

Question 1: Does the FDA agree in principle that the single, global, multicenter, double-blind induction study could be sufficient to support an effectiveness claim for induction, and that the overall program is appropriately designed to assess the efficacy and safety of mirikizumab and to support a BLA submission for the proposed UC indication?
FDA Response:

We are responding to each of your two questions (under Question 1) separately below.

(a) Does the FDA agree in principle that the single, global, multicenter, double-blind induction study could be sufficient to support an effectiveness claim for induction?

FDA Response to Question 1a:

We generally require two adequate and well controlled trials to support the induction indication in IBD. However, the adequacy of a single trial to support approval (b) (4)

induction (b) (4) indication will be determined by its ability to support the efficacy claim based on the strength of the results. In general, internal consistency across study subsets, evidence of an effect on multiple endpoints, and statistically very persuasive efficacy results will be considered in the evaluation. For additional information on circumstances where reliance on a single adequate and well-controlled trial might be acceptable to establish effectiveness, see "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products."

(b) Does FDA agree that the overall program is appropriately designed to assess the efficacy and safety of mirikizumab and to support a BLA submission for the proposed UC indication?

FDA Response to Question 1b:

Your proposed phase 3 program includes the following studies:

- **one 12-week induction study (AMAN, with a mixed population [biologic-failed and conventional-failed] and tested at a 2-sided significance level of 0.00125 for the analysis of the primary and major secondary endpoints)**
- **one 40-week (for a total of 52 weeks of treatment) maintenance study (AMBG), and**
- **one open-label extension study (I6T-MC-AMAP [AMAP])**

If you are able to demonstrate substantial evidence of effectiveness to support the induction indication through a single trial (see response to Question 1a above), then a single adequate and well-controlled maintenance trial in UC could be sufficient to support a BLA submission. However, the final determination of acceptability for demonstration of efficacy will depend on our final review after the BLA is submitted.

Please see the device-related comments in FDA's Additional Comments regarding the requirements for the device constituent of the delivery device you intend to use for the phase 3 clinical study and propose to submit under a future BLA.

See response to Question 3 regarding the acceptability of the safety database.

Question 2: Does the FDA have any comments on the selected doses and dose regimens for the Phase 3 induction (I6T-MC-AMAN [AMAN]) and maintenance (I6T-MC-AMBG [AMBG]) studies?

FDA Response:

You have proposed the following dosing regimens for the phase 3 induction and maintenance studies:

Induction dose of 300 mg IV at Weeks 0, 4, and 8
Maintenance dose of 200 mg SC every 4 weeks (Q4W)

You have indicated that these doses were chosen based on the results from the phase 2 dose-ranging study that evaluated doses of 50, 200 and 600 mg IV Q4W for the induction phase and 200 mg SC Q4W and 200 mg SC Q12W for the maintenance phase.

Results from your phase 2 study at Week 12 showed that the maximum efficacy was observed in the 200 mg cohort, while lower efficacy was observed in the 600 mg cohort compared to 200 mg cohort. Your exposure-response analysis of the phase 2 efficacy results did not demonstrate that higher exposure was associated with better efficacy. It was observed that the drug exposures in patients who have achieved clinical remission were similar to those in patients who have not achieved clinical remission within each of the three dose cohorts (Figures AMAC.20 and AMAC.21 in your briefing document). Furthermore, your analysis of the exposure-response relationship based on the modified Mayo score (MMS) score at Week 12 did not provide compelling evidence in support of a clear exposure-response relationship. Based on these observations, you have hypothesized that the dose-/exposure-response for efficacy in the phase 2 study is "bell-shaped" or plateaued between the 200 mg and 600 mg doses.

Because your phase 2 efficacy results have not demonstrated a clear dose-/exposure-response relationship for efficacy, the selection of the 300 mg IV induction dose for phase 3 is not well justified. You have indicated that other unknown factors may have confounded the low rates of clinical response in the 600 mg cohort. Therefore, we recommend that you include an additional higher dose cohort in the induction phase of the phase 3 study to further explore the dose-response of your drug product for the treatment of UC.

For the maintenance phase of the phase 3 study, you have proposed to evaluate 200 mg SC Q4W based on a comparison of efficacy results between 200 mg Q4W and 200 mg Q12W in your phase 2 study. Your interim analysis of the efficacy results at Week 52 appear to support the selection of 200 mg Q4W relative to Q12W.

Meeting Discussion: The sponsor provided a response (see attached document) as to why based on the assessment that doses higher than the proposed 300 mg would be unlikely to result in a clinically meaningful difference in efficacy, their proposal does not include a higher induction dose.

FDA stated that the rationale for the proposal for the higher induction or more frequent dosing regimens was due to the uncertainty surrounding the dose/exposure response (U-shaped or plateau).

Question 3: Assuming no unanticipated safety signals emerge during Phase 3 development, does the FDA agree in principle that the estimated patient exposures to mirikizumab at the time of data cutoff for the UC BLA, including the estimated number of patients who will have been exposed for at least 6 months and at least 1 year, would be adequate to support a BLA submission for the proposed indication?

FDA Response:
According to the briefing document submitted for this meeting, you estimate that at least 731 patients with UC will have been treated with mirikizumab at the to-be-marketed doses for ≥6 months and at least 418 patients will have been treated for ≥12 months at the time of BLA submission We emphasize that these exposures MUST occur at the dose(s) for intended use.

At this time, we are not aware of safety information that causes us to recommend larger numbers or longer duration of exposure than you have proposed. However, this recommendation could change over time, depending on evolving safety data from the following sources: studies of your product, studies of other products in the same class (anti-IL23), and postmarketing data for Tremfya (guselkumab) and Ilumya (tildrakizumab) (approved drugs which are both in the same class).

Question 4: Based on the Phase 2 data submitted in this briefing document, does FDA have any comments about Lilly's previously proposed safety monitoring plan included in the Type C meeting briefing document (SN 0044), and whether this plan is adequate to characterize the safety profile of LY3074828 and to support submission of a BLA for the proposed indication?

FDA Response:

We are responding to each of your questions separately below.

Question 4a: Based on the Phase 2 data submitted in this briefing document, does FDA have any comments about Lilly's previously proposed safety monitoring plan included in the Type C meeting briefing document (SN 0044)?

FDA Response to Question 4a:

Based on the phase 2 data you provided in the meeting package, we do not have any additional comments regarding your previously proposed safety monitoring plan (see also response to Question C4a in WRO dated November 21, 2017).

Question 4b: Based on the Phase 2 data submitted in this briefing document, does FDA have any comments on whether the proposed safety monitoring plan is adequate to characterize the safety profile of LY3074828 and to support submission of a BLA for the proposed indication?

FDA Response to Question 4b:

Your proposed safety monitoring plan appears to be reasonable to characterize the clinical safety profile of LY3074828 and to support submission of a BLA for the proposed indication barring any new safety concerns that may be identified (see also the response to Question 3).

However, we note that you reported two incidents of anaphylaxis and provided proposed updates to informed consent forms and situational treatment in response. Please describe your plans, if any, for assessing the etiology of the anaphylactic responses.

Meeting Discussion: The sponsor stated that the informed consent forms (ICFs) for UC phase 3 trials (AMAN, AMBG, and AMAP) were updated and submitted to the IND on 07 May 2018.

The sponsor stated they have analyzed the 2 anaphylaxis events and submitted responses to FDA's Advice/Information Request letter dated 24 April 2018 on 18 May 2018 (b) (4) ***to the UC indication under IND 125444. The sponsor also provided a summary of their plan (see the attached slides) as follows:***

> ***Communicating an immediate and required change to the pharmacy manual via a letter to all investigators included with the updated pharmacy manual. In addition, a training that incorporates this additional instruction on the updated infusion rate requirements and 1-hour observation period post IV infusion administration for hypersensitivity events has been implemented. This training is mandatory for investigators and site personnel involved in performing study procedures. Additionally, to be consistent with other protocols with mirikizumab that include IV administration, appropriate infusion duration and observation time will be added to the AMAG protocol.***

The sponsor committed to a continue to evaluate the ongoing clinical trial data from the mirikizumab program to better characterize the timing and nature of hypersensitivity, infusion-related events and anaphylaxis events and their management to inform patients and health care professionals.

FDA stated that they have received the referenced submission and if there are additional comments to be conveyed following a formal review, those comments will be communicated in an advice letter.

Question 5: Does the FDA have any comments on the Program Safety Analysis Plan (Version 1) previously submitted (SN 0044), considering the AMAC Phase 2 UC study interim safety data?

FDA Response:
Based on the phase 2 data you provided in the meeting package, your proposed Program Safety Analysis Plan (Version 1) appears to be reasonable (see also response to Question C4b in the WRO responses dated November 21, 2017).

Question 6: Does FDA agree that the existing pharmacokinetic (PK) bridging studies conducted to support comparability of the 125 mg/mL psoriasis presentation is sufficient to support PK comparability for the 100 mg/mL UC presentation and that no further PK bridging is needed?

FDA Response:
While your proposal appears reasonable, we cannot agree at this time without reviewing the results from the PK comparability studies.

Question 7: Does FDA agree that the bridging plan supports comparability of the Phase 3 presentation to the to-be-marketed presentations for the UC indication?

FDA Response:

Your proposal to establish analytical and PK comparability between the phase 3 presentation (prefilled syringe; 2x 100 mg/mL injection) versus the to-be marketed presentation [redacted] (b) (4) **autoinjector) appears reasonable.** [redacted] (b) (4) **See FDA Additional Comments below.**

Question 8: Does the FDA agree that a drug–drug interaction study conducted in the postmarket setting is acceptable for the UC indication?

FDA Response:

Your proposal to conduct a drug-drug interaction study in the post-market setting appears to be reasonable considering that the drug interaction study should be conducted in the target patient population with the recommended dosing regimen for the treatment of UC. When you submit your BLA, you should provide justification for conducting the drug interaction study in the post-market setting in the clinical pharmacology section of your BLA.

FDA ADDITIONAL COMMENTS

Statistics Comments:
You indicate that details of the specific graphical multiple testing procedure will be prespecified in the statistical analysis plan prior to the first unblinding of efficacy data. We remind you that detailed statistical analysis plan should be submitted prior to the study initiation (as a part of the clinical study protocol or as a standalone document). The statistical analysis plan should include details and assumptions for the sample size estimation, several sensible sensitivity analyses for missing data, and a multiplicity adjustment approach that provides strong control of study-wise type I error rate with respect to multiple endpoints and treatment arms.

Meeting Discussion: The sponsor stated they plan to submit the statistical analysis plans after initiation of the first patient visit but prior to primary efficacy analyses for the induction study (AMAN). FDA reminded the sponsor to submit the key elements of the SAP at the time of the protocol submission. The sponsor committed to submission of the final version of the agreed-upon SAP prior to unblinding.

Device-Related Comments:
The following feedback is related to the device constituent parts of your combination product. As the owner of the combination product it is expected that you maintain the quality control strategy, including design controls, for the device constituent parts of your product.

For more information regarding cGMP requirements for combination products, please refer to the FDA Guidance titled "Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products" issued in January 2017 (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf).

You should identify the subset of design input requirements necessary for your device constituent to safely and effectively achieve the combination product's intended use. For reference, this subset of design input requirements should be referred to as Essential Performance Requirements (EPRs). Other internally established terminology, such as Critical Quality Attributes (CQAs), Key Performance Indicators (KPIs), etc. may be considered equivalent to EPRs if the definition is consistent with that of EPRs and the requirements are applied to the control strategy in the same manner as EPRs. Your EPRs should consider the desired level of reliability of the product and level of risk associated with failure.

For the purposes of initiating clinical trials with your device constituent, you should provide information satisfying #1, #2 for EPRs only (excluding design validation), and #4 for clinical batches being used in the trials, as described below. Alternatively, provide a valid risk-based justification for not providing the information prior to clinical use. All other information is intended to inform your product development and should be provided in any future marketing application(s).

If you intend to refer to documentation (e.g., verification test reports) held within another submission and/or master file, be sure to provide a letter of authorization or right of reference alongside a detailed description of the location of the information within the file (i.e., volume, page number, section header, etc.). It is recommended that you provide a brief overview of how the referenced information is intended to support the review of your submission.
It is recommended that you refer to the eCTD Technical Conformance Guide published in September 2016 (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf) when determining the location of the following information within your submission.

Provide the following information, at a minimum, to support the device constituent parts of the combination product:

1) **Device Description Documentation**
   a) **A complete and detailed description of your device constituent design and delivery system, including any novel features and/or functionalities. This may include**

engineering drawings and detailed descriptions of the individual device constituent components.

b) The principles of operation of your device, from beginning to end of the activation process, in which you explain the drug delivery mechanisms (e.g., mechanical, electrical, etc.) of your device constituent.

c) If the device constituent is being used in an investigational manner, include device labeling stating that the device is for investigational use only.

2) Design Control Documentation

a) Design Inputs/Outputs – A complete and detailed description of the device constituent design inputs and outputs per 21 CFR 820.30, specifically the design requirements/specifications documentation with objective acceptance criteria. Ensure that you clearly describe the acceptability of your design inputs and outputs within the context of the intended use of your combination product. The design inputs and outputs should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, environment of use, etc.

i. EPR Identification

For auto-injectors, we expect the EPRs, at a minimum, the following:

- **Dose Accuracy**
- **Activation Force**
- **Injection Time**
- **Extended Needle Length**

In addition, (b) (4) **provide information to verify that the risk of leakage is sufficiently controlled. Injection time as an essential performance requirement of the device should be included as an important factor in mitigating the risk of device leakage and/or the user failing to complete the injection.**

Please refer to the FDA Guidance titled "Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products" issued in June 2013 (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm147095.pdf) for more details.

(b) (4)

b) Design Verification Documentation – Verification testing documentation should include summary test results of established test methods for the product (e.g.

recognized consensus standards, FDA Guidance, etc.) or complete verification test reports for unique or unrecognized test methods. All verification testing should be directly traced to the design inputs of the device constituent. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should use a statistically significant sample size for verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.

i. As part of design verification, you should verify the EPRs with the to-be-marketed version of the device constituent and the intended biologic/drug product. However, if you plan to rely on verification testing conducted with a surrogate be sure to provide a scientific rationale for the acceptability of the surrogate for the intended biologic/drug product (i.e., fluid characteristics, viscosity, etc.). If available, results of stability / shelf-life testing may be provided if the to-be-marketed version of the device constituent and intended drug/biologic product are used.

c) Risk Analysis Documentation – Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.). Refer to recognized consensus standard ISO 14971 "Medical devices - Application of risk management to medical devices" or device specific Guidance for more details.

d) Design Validation Documentation – Design validation should be performed to ensure the device constituent parts of the combination product meet the intended use of the combination product. Design validation documentation may be in the form of the following:

- **clinical studies with the to-be-marketed presentation of the device,**
- **bridging studies,**
- **literature review regarding the use of the to-be-marketed device constituent presentation in the context of the intended use of the combination product,**
- **summative human factors studies, and/or**
- **simulated actual-use studies.**

It is highly recommended that you conduct clinical studies with the to-be-marketed presentation of the combination product and capture any device constituent failures/malfunctions as part of the clinical study protocol to successfully validate the device constituent parts of the combination product.

e) Stability / shelf-life testing and shipping studies. You should provide documentation that ensures the to-be-marketed version of the combination product maintains the EPRs up to the labeled date of expiry and after actual and/or simulated shipping.

If you plan to use a test subject other than the to-be-marketed version, you should list the differences in the design and provide a risk-based assessment demonstrating how the differences do not significantly impact the product's EPRs. Stability/shelf-life testing and shipping studies may be incorporated into design verification testing.

f) Lot release specifications. In your lot release specifications include the EPRs. If you intend to propose alternative control strategies for the EPRs, we recommend requesting specific feedback regarding your strategy.

3) Traceability Documentation
It is recommended that a traceability matrix is provided to ensure 1) the design outputs are adequately verified to meet the design inputs and 2) the finished combination product is validated to meet the user needs. It is highly recommended that the EPRs are highlighted for ease of review. While a traceability matrix can take many forms, the Agency has provided a high-level example for reference:

Patient / User Needs	Design Input(s)	Design Output(s)	Verification	Validation	Shelf Life / Stability (Y/N)*	Shipping (Y/N)*	Lot Release (Y/N)*

***These columns are applicable only for EPRs**

4) Considerations specific to your device constituent
a) Biocompatibility evaluation – You should provide documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the system components are biocompatible commensurate with the level and duration of patient contact. Refer to the FDA Guidance titled Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" – Guidance for Industry and Food and Drug Administration Staff issued in June 2016 (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf) for more details.

Human Factors Comments:
We find your proposed Human Factors approach, on pages 34-35 of the meeting package, acceptable.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 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 (cder-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

5.0 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 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.

6.0 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.

7.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

8.0 ATTACHMENTS AND HANDOUTS

A copy of the sponsor's agenda and clarification points is attached.

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

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

/s/

KELLY D RICHARDS
05/24/2018