CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210737Orig1s000
210737Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210737

MEETING PRELIMINARY COMMENTS

Cumberland Pharmaceuticals, Inc.
2525 West End Avenue
Suite 950
Nashville, TN 37203

Attention: Beth A. Zaborny
Senior Manager, Regulatory Affairs

Dear Ms. Zaborny:

Please refer to your meeting request submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Injection.

We also refer to your February 26, 2018, correspondence, received February 26, 2018, requesting a meeting to seek guidance on the format, content, presentation and organization of data, dataset structure, and acceptability of data for your future New Drug Application (NDA) submission for methotrexate pre-filled syringe injection.

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 (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 27, 2018, from 11:30-12:30 P.M. EST
Meeting Location: Teleconference (number to be provided by the Sponsor)

Application Number: NDA 210737
Product Name: Methotrexate Pre-Filled Syringe
Indication: Rheumatoid Arthritis and Polyarticular Juvenile Idiopathic Arthritis
Sponsor: Cumberland Pharmaceuticals, Inc.

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 April 27, 2018, at 11:30 a.m., as a teleconference between the Sponsor and the Division of Pulmonary, Allergy, and Rheumatology Products. 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the teleconference (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the 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

The purpose of the meeting is to discuss Sponsor's proposed format, content, presentation and organization of data, dataset structure, and acceptability of data for a future NDA submission for methotrexate pre-filled syringe injection. Cumberland Pharmaceuticals, Inc. submitted a meeting request on February 26, 2018, to the Division of Pulmonary, Allergy, and Rheumatology Products. The Division granted the meeting on March 21, 2018. The briefing package was submitted on March 27, 2018.

2.0 DISCUSSION

Question 1:
Does the Agency agree that FDA's previous findings of safety and effectiveness of SC MTX in adults with RA and psoriasis, and in children with PJIA in combination with a summary of the pertinent published literature is sufficient for review of a 505(b)(2) New Drug Application and the NDA may be accepted for filing?

FDA Response:
From a clinical perspective, we agree. We also have the following comments:

1. The choice of which approved product(s) to reference in your 505(b)(2) application is at your discretion.

2. Your question did not ask about other aspects of the application that will be required to support your application, such as clinical pharmacology, chemistry, manufacturing and controls, and pharmacology-toxicology data. However, we recommend the following:

    a. Your NDA must include an Integrated Summaries of Efficacy (ISE) and Safety (ISS) in Module 5. The ISE and ISS can be relatively short and refer to Summaries of Clinical Efficacy and Safety in Module 2.

    b. Include a 'Summary of Biopharmaceutic Studies and Associated Analytical Methods' (2.7.1) and a 'Summary of Clinical Pharmacology Studies' (2.7.2) in Module 2.7 of your proposed NDA describing the pertinent data from published literature or other sources to support all clinical pharmacology related labeling for your proposed product.

    c. We note that you have not proposed conducting a relative bioavailability study, nor have you addressed the need to submit an alternative plan on demonstrating acceptable bioavailability of the proposed drug product compared to the listed drug. Per 21 CFR 320.24(b)(6), you may submit justification and supporting data demonstrating that the differences in the active and inactive ingredients between the proposed and listed drug products do not contribute to differences in their *in vivo* performance. Provide a side-by-side comparison table with the physicochemical characteristics of your proposed product and the listed drug, including the description, quantitative composition, pH, osmolality, drug concentration, injected volume, and other relevant physicochemical properties. If, upon review of the above information, we conclude that the proposed differences in formulation would not affect the safety and/or efficacy of the API, based on 21 CFR 320.24(b)(6), we would consider the bridge (bioavailability/bioequivalence) between your proposed drug product and the listed drug product to have been established. However, be aware that if we decide that the above information is not adequate, data from an *in vivo* relative bioavailability study would be needed to support the approval of your proposed drug product.

Question 2:
Does the Agency agree that no Risk Management Plan is necessary in section 1.16 of the eCTD application and the NDA may be accepted for filing?

FDA Response:
While we agree that a specific Risk Management Plan is not needed, submit support for your argument in your NDA submission.

We do not anticipate that a human factors (HF) validation study is needed. However, you will need to submit a comprehensive use-related risk analysis (URRA) along with your full justification for not submitting an HF validation study before we can provide our final determination.

Note that the comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, and the potential negative clinical consequences of use errors and task failures.

It may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Submit your use-related risk analysis, comparative analyses and justification to not conducting a HF validation study for our review. We will notify you if we concur with your determination.

The requested information should be submitted to your application prior to filing. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information. Guidance on human factors procedures to follow can be found in:

Applying Human Factors and Usability Engineering to Medical Devices, available online at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Question 3:
Cumberland intends to seek approval of the same indications that OTREXUP is approved for in the United States - treatment of severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (PJIA), who are intolerant of or had an inadequate response to first-line therapy, and symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy. Cumberland does not intend to pursue the use of SC MTX in neoplastic diseases as the proposed doses and route of administration are not appropriate for use in many of the oncology indications for which methotrexate is used (which require intravenous dosing in grams rather than milligrams).

Therefore, the planned package insert will be similar to that of the approved OTREXUP labeling.

Does the Agency agree with this approach for filing a 505(b)(2) Application?

FDA Response:
For a pre-filled syringe methotrexate product that is intended for subcutaneous administration at the dosage strengths that you have proposed, the indications that you have proposed appear appropriate. With the exception of proprietary information about your proposed product, the prescribing information for your product would be the same as that for the listed product. As per the Pregnancy and Lactation Labeling (PLLR) Final Rule (79 FR 72064) and associated Draft Guidance: *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2014), the prescribing information for your product will also be required to be in compliance with the PLLR format requirements.

Question 4:
Does the Agency agree that Cumberland does not have to submit an Initial Pediatric Study Plan (iPSP) and the NDA may be accepted for filing?

FDA Response:
We agree that your proposed application is unlikely to trigger PREA. Provide the justification for why your product does not trigger PREA in your NDA submission. We also refer you to our comments under Section 3, PREA REQUIREMENTS, towards the end of this document.

Question 5:
Does the Agency agree that non-clinical summary information is not required in Modules 2 and 4 of the eCTD submission and that the related information in the package insert will be from the reference listed drug?

FDA Response:
We agree that the nonclinical information is not required in Modules 2 and 4 of the eCTD submission and the related information in the package insert will be from the reference listed drug.

Question 6:
Cumberland will submit the results of an extractable and leachable study in the NDA demonstrating leachates are below levels of toxicological concern. Assuming the Agency agrees with the conclusions of the study, does the Agency agree that routine testing will not be required for leachables?

FDA Response:
It is premature to agree that no leachables testing will be required. We expect that the extractable study is vigorous enough to establish a good correlation between extractables and leachables per USP <1663> and <1664>. We further recommend you follow the recommendations outlined in ICH Q6A regarding the control of extractables for parenteral drug products.

Question 7:
Many of the adverse events and reports in the literature are associated with MTX used in oncology with the intravenous form. To avoid unnecessary duplication and irrelevant reports generated from the literature Cumberland proposes to (b) (4) ***Does the Agency concur that the program should be focused in this area?***

FDA Response:
We do not have regulations regarding the methodology of literature surveillance. In accordance with 21CFR 314.80, an applicant is required to have procedures for surveillance, receipt, evaluation, and reporting of adverse drug experiences for their product. Sponsors must report adverse drug experiences they receive or otherwise obtain from any source including the scientific literature for their product.

3.0 ADDITIONAL INFORMATION

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 none of the criteria apply at this time to your application, 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* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's

finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**

1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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

/s/

SADAF NABAVIAN
04/24/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210737

MEETING MINUTES

Cumberland Pharmaceuticals, Inc.
2525 West End Avenue
Suite 950
Nashville, TN 37203

Attention: Beth A. Zaborny
Senior Manager, Regulatory Affairs

Dear Ms. Zaborny:

Please refer to your meeting request submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Injection.

We also refer to the meeting between representatives of your firm and the FDA on July 25, 2017. The purpose of the meeting was to discuss your overall development plan for methotrexate pre-filled syringe injection.
.
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 (301) 796-2777.

Sincerely,
{See appended electronic signature page}
Sadaf Nabavian, Pharm.D.
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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 C
Meeting Category:	Guidance
Meeting Date and Time:	July 25, 2017; 4:00-5:00 p.m. EST
Meeting Location:	Teleconference
Application Number:	NDA 210737
Product Name:	Methotrexate Injection
Indication:	Rheumatoid Arthritis and Polyarticular Juvenile Idiopathic Arthritis
Sponsor:	Cumberland Pharmaceuticals, Inc.
Meeting Chair:	Badrul A. Chowdhury, MD, PhD
Meeting Recorder:	Sadaf Nabavian, PharmD

FDA ATTENDEES
Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Peter Starke, M.D., Associate Director for Labeling, DPARP
Janet Maynard, M.D., M.H.S, Clinical Team Leader, DPARP
Anup Srivastava, Ph.D., Pharmacology/Toxicology Reviewer, DPARP
Carol Galvis, Ph.D., Pharmacology/Toxicology Acting Team Leader, DPARP
Anshu Marathe Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II, Office of Clinical Pharmacology (OCP)
Manuela Grimstein, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, OCP
Craig Bertha, Ph.D., Product Quality Reviewer, OPQ/ONDP/DNDPII
Sadaf Nabavian, Pharm.D., Sr. Regulatory Project Manager, DPARP

SPONSOR ATTENDEES
Leo Pavliv, R.Ph., Executive Vice-President, Operations & Chief Development Officer
Beth A. Zaborny, Senior Manager, Regulatory Affairs
Matthew Hight, Regulatory Affairs Associate

1.0 BACKGROUND

Cumberland Pharmaceuticals submitted a type C meeting request to discuss the overall development plan for methotrexate pre-filled syringe injection.

The FDA's preliminary comments were sent to Cumberland Pharmaceuticals on July 24, 2017. After review of these comments Cumberland stated their intent to continue with the meeting as scheduled. They provided the discussion points via email to Ms. Sadaf Nabavian to further discuss FDA's comments to Questions 1(a) and 6 and sought further guidance on the published data for the recently approved methotrexate PFS supplement under another NDA.

Any discussion that took place at the meeting is captured in the discussion sections. Cumberland Pharmaceuticals questions are in ***bold italics*;** FDA's response is in *Italics*; Cumberland Pharmaceuticals response to FDA's preliminary responses prior to the meeting is in ***bold italics*** and any discussion points captured during the meeting is in normal font under the Discussion Sections. The slides, attachments and handouts are included in Section 6.

DISCUSSION

Question 1a:

Based on the above information, is a 505(b)(2) NDA or an abbreviated NDA (ANDA) the appropriate submission pathway and does the Agency have a preference whether (b) (4) ***OTREXUP, or the 25 mg/mL vial product is used as the RLD?***

FDA Response:
You propose an application for the following dosages of the methotrexate prefilled syringes: 7.5 mg/0.3 mL, 10 mg/0.4 mL, 12.5 mg/0.5 mL, 15 mg/0.6 mL, 17.5 mg/0.7 mL, 20 mg/0.8 mL, 22.5 mg/0.9 mL, and 25 mg/1 mL. Note that a prefilled syringe with a concentration of 25 mg/1 mL was approved under NDA 204824 on May 31, 2017, in the following dosages: 10, 15, 17.5, 20, 22.5, and 25 mg. Currently, the 7.5 and 12.5 mg dosages are not approved in a 25 mg/mL concentration. If your application proposes dosages that are not approved, you could submit a 505(b)(2) application that would include all the dosages you propose. Alternatively, you can submit an application for dosages that match the approved dosages as an abbreviated NDA (ANDA). The choice of the product you plan to reference is at your discretion. Refer to the 505(b)(2) information in Section 3 of this document for further details.

Discussion:

The Sponsor sought guidance from the Division in which approved products, Otrexup (b) (4) would be the best choice to rely upon from the regulatory standpoint as the drug referenced by their application. The Division responded that it is at Sponsor's discretion to choose the product that they wish their application to reference. However, whichever product they choose, they will need to provide support and justification for any differences between their product and the reference product.

Further discussion took place on the differences in the concentration between Cumberland's proposed product and other currently marketed products. The Sponsor stated that information regarding the prefilled syringe with a concentration of 25 mg/ml to which the Division referred as having been recently approved under NDA 204824 could not be found. The Division

responded that we will follow up with the corresponding office to ensure that the most updated information for NDA 204824 is published on the FDA website. The Division reiterated that even if the concentration does not match, the choice of which product to reference is at Sponsor's discretion.

Post-Meeting Comment:

The recently approved supplement for NDA 204824 has been uploaded and is now publicly available at Drugs@FDA.

Question 1b:
To support the new product and indication, Cumberland is relying on
The Agency's previous findings of safety and effectiveness of MTX in adults with RA (oral route) and psoriasis (oral, IM, and IV routes), and in children with JRA(1) (oral, SC, and IM routes) Information in the published literature supporting the safety and efficacy of subcutaneously administered MTX for RA, PJIA, and psoriasis
Does the Agency agree with this approach?

FDA Response:
For a 505(b)(2) application, your approach is reasonable. For an ANDA, consult with the Office of Generic Drugs.

Discussion:

No discussion took place.

Question 2:
From a risk assessment perspective, it has been determined that a Human Factor study for the proposed product is not necessary based on the following:

- ***In the absence of an auto-injector, the prefilled syringe is unexceptional, has been used for multiple approved products, and requires no special instruction for patient use other than routine label/protocol instruction;***
- ***The prefilled syringe does not present any potential obstacles towards correct patient use since the entire dose is delivered in a single administration, the patient manually controls the rate of injection, and the needle is automatically covered when the injection is completed, reducing the chance for any accidental exposure.***

Does the Agency concur that a Human Factor study is not required?

FDA Response:
For a 505(b)(2) application, your approach is reasonable. For an ANDA, consult with the Office of Generic Drugs.

Discussion:

No discussion took place.

Question 3:
Methotrexate is approved in different formulations for a number of indications including: (Neoplastic Diseases, Psoriasis, Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis)
Cumberland intends to seek approval of the same indications that OTREXUP (b) (4) are approved for in the United States - treatment of severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (PJIA), who are intolerant of or had an inadequate response to first-line therapy, and symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy. Does the Agency agree that these are appropriate indications?

FDA Response:
For a 505(b)(2) application, your approach is reasonable. For an ANDA, consult with the Office of Generic Drugs.

Discussion:

No discussion took place.

Question 4:
Cumberland proposes to submit the application with (b) (4) months of data at 25°C/60% RH and (b) (4) months at 40°C/75% RH from 3 batches each at 0.3 and 3 batches at 1.0 mL fills at (b) (4) L pilot scales, respectively, and one batch each at 0.3, 0.6, and 1.0 mL at the (b) (4) L (commercial batch size) scale. These batches are in the inverted position. The (b) (4) L processes and equipment are essentially the same. The proposed expiration date is (b) (4) months. Is this proposal acceptable to the Agency?

FDA Response:
Yes, the approach is reasonable. The acceptability of the expiration dating period will be determined at the time of review, based on the data.

Discussion:

No discussion took place.

Question 5:
Cumberland proposes to submit one (1) executed batch record each for the lowest and highest concentration or fill weight presentation. Is this proposal acceptable to the Agency?

FDA Response:
Yes, this is acceptable. However, we may later request other executed batch records as per 21 CFR 314.50(d)(1)(i)(b), if warranted by our evaluation.

Discussion:

No discussion took place.

Question 6:
Are the proposed drug product specifications proposed in the Meeting Package acceptable to the Agency?

FDA Response:
The acceptability of the specification will be determined at the time of review. However, in terms of the parameters tested, we recommend that there be a chiral assay and determination of enantiomeric impurity of the drug substance [i.e., for (b) (4) *]. Also, we recommend inclusion of tests with acceptance criteria to assure the uniformity of dosage units, leachables, and osmolarity. Alternatively, you may provide scientific justification and supporting data for why the inclusion of these additional tests and acceptance criteria are not necessary.*

Discussion:

With regard to the question about routine extractables/leachables testing, the Division stated that based on the composition of the formulation, and assuming the Sponsor uses typical pre-filled syringe components, routine testing of extractables may not be necessary, but that this will depend on supporting data provided. The Division referred the Sponsor to the ICH Q6A guideline for specific recommendations for parenteral drug products with respect to extractables/leachables and the question about enantiomeric purity testing. The Division stated that testing of enantiomeric purity of the drug substance using the USP monograph methodology would be acceptable, but again referred the sponsor to Q6A as there are specific recommendations for when testing of the enantiomeric purity of the drug substance in the formulation is also appropriate. The Division indicated that testing of the drug product for enantiomeric purity may not be necessary if it is found that racemization of the chiral center of methotrexate does not occur in the formulation.

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct

(including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please

note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

SADAF NABAVIAN
08/23/2017