CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212479Orig1s000
212479Orig2s000
212479Orig3s000
212479Orig4s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 212479

MEETING MINUTES

Therakind Limited
c/o Poppyridge LLC
22345 Bracketts Road
Shorewood, MN 55331

Attention: Dayton T. Reardan, PhD, RAC
US Agent for Therakind Limited

Dear Dr. Reardan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Oral Solution, 2 mg/ml.

We also refer to the meeting between representatives of your firm and the FDA on October 16, 2018. The purpose of the meeting was to obtain feedback on your regulatory pathway and the development to support a new drug application submission for the oral solution of methotrexate.

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 B
Meeting Category: Pre-NDA

Meeting Date and Time: October 16, 2018, from 3:00-4:00 p.m. EST
Meeting Location: White Oak Building 22, Conference Room: 1315

Application Number: NDA 212479
Product Name: Methotrexate oral solution

Indications: Adult neoplastic diseases, (b) (4) rheumatoid arthritis
Sponsor: Therakind Limited

Meeting Chair: Sally Seymour, M.D.
Meeting Recorder: Sadaf Nabavian, Pharm.D.

FDA ATTENDEES

Sally Seymour, M.D., Acting Director, Division of Pulmonary, Allery, and Rheumatology Products (DPARP)
Nikolay Nikolov, M.D., Associate Director for Rheumatology, DPARP
Mark Borigini, M.D., Clinical Reviewer, DPARP
Tao Liu, Ph.D., Clinical Pharmacology Reviewer, OCP, DCP2
Okpo Eradiri, Ph.D., Biopharmaceutics Branch Chief, ONDP, OPQ
Tien-Mien Chen, Ph.D., Biopharmaceutics Acting Team Leader, ONDP/OPQ
Craig Bertha, Ph.D., CMC Lead, ONDP/OPQ
Carol Galvis, Ph.D., Nonclinical Team Leader, DPARP
Lawrence Leshin, Ph.D., Nonclinical Reviewer, DPARP
Bhawana Saluja, Ph.D., Clinical Pharmacology Team Leader, OCP, DCP2
Saharat Patanavanich, Pharm.D., Safety Regulatory Project Manager, OSE/DMEPA
Idalia E. Rychlik, Pharm.D., Safety Evaluator, OSE/DMEPA
Sadaf Nabavian, Pharm.D., Sr. Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Dayton Reardan, PhD, RAC, US Agent for Therakind
Susan Esther Conroy, PhD, Chief Executive Officer
Jacqueline Windslade, Regulatory Affairs Director

1.0 BACKGROUND

The purpose of the meeting is to discuss Therakind Limited regulatory pathway and the development to support a new drug application submission as a 505(b)(2) pathway for the oral solution of methotrexate. Therakind submitted a request for a meeting on August 14, 2018, to the Division of Pulmonary, Allergy, and Rheumatology Products, and the Division granted the meeting on September 4, 2018. The Division provided the preliminary responses to Therakind on October 11, 2018, and in response Therakind requested to continue with the face-to-face meeting and requested for a discussion on Questions 5, 7, 9, PREA comment under Section 3, prescribing information and a procedural question on submitting their proposed proprietary name. Therakind also submitted their pre-meeting discussion points prior to the face-to-face meeting captured prior to each discussion section of these meeting minutes.

2. DISCUSSION

Question 1:

Does FDA agree that the NDA application can be submitted as a 505(b)(2) application with reference to NDA 008085 (Methotrexate oral tablets, Dava Pharmaceuticals)?

FDA Response:

Yes, we agree that your application can be submitted as a 505(b)(2) regulatory pathway. The choice of a US approved and marketed methotrexate drug product as the listed drug appears reasonable and it is at your discretion. Refer to 505(b)(2) Regulatory Pathway at the end of this document.

Discussion*:*

No further discussion took place.

Question 2:

For Orphan Products: Is there any issue with the recently approved oral liquid formulation of methotrexate (XATMEP NDA 208400) and our planned NDA submission for our oral liquid formulation omitting those two orphan indications approved for XATMEP?

FDA Response:

Xatmep has orphan exclusivity for the following indications:

- *Treatment of acute lymphoblastic leukemia in pediatric patients (0 through 16 years of age)*

- *Management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy*

Your currently proposed indication is: JYLAMVO™ (methotrexate) 2 mg/ml Oral Solution is indicated for the treatment of neoplastic diseases, psoriasis and rheumatoid arthritis.

Orphan drug exclusivity blocks approval of any other application for the same drug for the same indication. Your proposal to carve out the indication(s) granted orphan exclusivity is acceptable.

Discussion*:*

No further discussion took place.

Question 3:

Please confirm for a new formulation such as we propose that should a NDA be approved, it would be eligible for 3 years exclusivity pursuant to Hatch-Waxman.

FDA Response:

Your NDA submission may include a request for exclusivity, however, exclusivity determinations are made at the time of approval of an application.

Discussion*:*

No further discussion took place.

Question 4:

Please confirm that the user fee for a 505(b)(2) NDA would be half that of a full application fee (or $1,294,239.00) and that as a small company filing our first NDA, Therakind would be eligible for a waiver of its first application fee.

FDA Response:

For any user fee questions, contact the User Fee staff at CDERCollections@fda.hhs.gov or 301-796-7900.

Discussion*:*

No further discussion took place.

Clinical Questions

Question 5:

Does FDA agree that the two bioequivalence studies already conducted will be sufficient to support the NDA if supported by in vitro dissolution data demonstrating equivalence of the EU originator reference tablet used in the bioequivalence study (methotrexate "Lederle" 2.5 mg) and the US RLD tablet NDA 008085?

FDA Response:

No, we do not agree. An in vivo relative bioavailability study for your proposed oral solution and the United States(US) listed drug (oral tablet; NDA 008085) under fasting conditions is needed. The reasons are as follows:

a. *Demonstration of comparative bioavailability of your proposed product to the US listed drug will bridge your proposed methotrexate oral solution to FDA's finding of clinical efficacy and safety of the listed drug approved in the US.*

b. *Comparative in vitro dissolution data would not support the bridge between the EU originator reference tablet and the US listed drug tablet (under NDA 008085), as dissolution is drug product-specific. That is, similar dissolution profiles of different drug products, under specific testing conditions, do not confer comparable bioavailability of the drug products.*

Refer to the FDA guidance entitled "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" for recommendations on study design and conduct of a relative bioavailability study.

You do not propose to study the effect of food on the bioavailability of your proposed product. You should also conduct a food-effect study for your proposed drug product. Refer to the "Food-Effect Bioavailability and Fed Bioequivalence Studies" guidance for recommendations on study design and conduct of a food-effect study.

The final to-be-marketed product must be used in the PK studies to support your NDA application.

Therakind's Pre-Meeting Discussion Points:

We request discussion of this item with respect to the following points:

- ***Please refer to Table 7 on page 20 of 145 of the Briefing Book.***
- ***The Applicant has already conducted two fasted BE studies.***

- ***As indicated in Table 7, the formulation of the reference product used in the second BE study (MTX002 – Lederle 2.5mg tablet) is identical to that of the US RLD apart from the fact that the excipient sodium hydroxide is declared. This will be used in only a very small amount to adjust pH and is probably also used in the manufacture of the US RLD but not specified.***
- ***There is evidence that the licence holder of the US RLD was in fact Lederle previously but the correspondence on the FDA website does not go back far enough to fully confirm.***
- ***Thus we consider that the Lederle reference tablet that has already been shown to be bioequivalent to our oral solution is the same as the US RLD***
- ***We do not consider it ethical to conduct a further (third) BE study which will expose additional subjects to a cytotoxic drug.***
- ***Will FDA please reconsider their position or can we have some substantive discussion?***

Discussion:

The Sponsor asked the FDA to reconsider their position on the need for conducting a third bioavailability study as they have already conducted two fasted bioequivalence studies with a non-US approved product. The FDA re-iterated their position and stated that in order for the Sponsor to support filing of the NDA via a 505(b)(2) regulatory pathway, they would need a new relative BA pivotal study to establish a scientific bridge between their proposed product and the US-approved listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. See general comments for the 505(b)(2) regulatory pathway.

Some discussion on granting biowaiver requests took place and FDA stated that the Sponsor would need to demonstrate that the non-US approved product is identical to the FDA-approved reference product. The FDA reiterated that for BCS class 4 category products, an in vitro dissolution type bridge to justify formulation changes may not be acceptable.

The Sponsor asked, if they move forward with conducting a relative bioavailability study of their proposed product to the US approved listed drug, would FDA accept a single-dose study design. The FDA replied that it would be reasonable and recommended that they follow the guidance[1] and link the proposed formulation to the US listed drug.

In regards to the food effect, the Sponsor provided the following points:

Therakind's Pre-Meeting Discussion Points:

- ***The effects of food on the absorption of methotrexate have been studied for the US RLD and are described on the US RLD (NDA 008085) Product Information – which states: 'Food has been shown to delay absorption and reduce peak concentration'***

[1] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf

- ***However, no warning to avoid food when taking methotrexate tablets is included in the US RLD dosing information.***
- ***As the proposed product is an oral solution, it will already be in solution and so any effect on absorption due to food will be no worse than with a tablet***
- ***Thus, as we do not consider that a dosing recommendation will be required regarding administration with food for our oral solution, we consider that a food effect study should not be required.***
- ***We request discussion during the meeting.***

Discussion:

The Sponsor questioned the value of conducting a food effect study for their proposed drug product. The FDA reiterated their position and noted that for any new proposed oral formulations and dosage forms a food effect study is required. FDA referred the Sponsor to the "Food-Effect Bioavailability and Fed Bioequivalence Studies" guidance (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070241.pdf) for further details.

Question 6:

The applicant proposes to reference the Reference Listed Drug (NDA 008085) to support the clinical pharmacodynamics, efficacy and safety sections of the NDA and considers that no new clinical studies are required. Does FDA agree?

FDA Response:

It is premature to agree with your proposal, at this time. Refer to our responses to Question 5. If you cannot demonstrate comparative bioavailability of your proposed product to the US listed drug, additional data and information including additional clinical studies may be needed.

Discussion:

No further discussion took place.

Pharmacology and Toxicology Questions

Question 7:

The applicant proposes to reference the Reference Listed Drug (NDA 008085) together with an evaluation of the toxicity of the excipients to support the non-clinical section of the NDA and considers that no new non-clinical studies are required. Does FDA agree that no new non-clinical studies are necessary for NDA submission?

FDA Response:

We agree that no nonclinical studies are necessary.

Provide structures of any impurities and degradants of the drug substance and drug product in your future NDA submission. Monitor impurities and degradation products of all active ingredients and refer to ICH Guidance Q3A(R) and Q3B(R) for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA as described in the ICH M7 Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (May 2015).

Therakind's Pre-Meeting Discussion Points:

As methotrexate is an established drug, the degradation pathways have been well-characterised. The Jylamvo specification includes limits for the degradation products produced (b) (4) (b) (4). All other degradation products are controlled by the specification for any other impurities.

Related Substances	***Release***	***Shelf Life***
	Impurity (b) (4): NMT (b) (4) %	***Impurity (b) (4): NMT (b) (4) %***
	Impurity (b) (4): NMT (b) (4) %	***Impurity (b) (4): NMT (b) (4) %***
	Any Other Impurities: NMT (b) (4) %	***Any Other Impurities: NMT (b) (4) %***
	Total Other Impurities: NMT (b) (4) %	***Total Other Impurities: NMT (b) (4) %***
	Total Impurities: NMT (b) (4) %	***Total Impurities: NMT (b) (4) %***

- ***As the amount of impurities at release is largely determined by the amount of impurities present in the drug substance, the release specifications are based upon the specifications for the drug substance which has been set in-line with the Ph. Eur. monograph for methotrexate and are identical to those of the USP monograph and pre-approved by FDA for the referenced DMF.***
- ***The shelf life specification for impurity (b) (4) and impurity (b) (4) was set in relation to the British Pharmacopoeia monograph for Methotrexate Tablets. The limit for other degradation products was set in-line with ICH Q3B(R2).***
- ***As methotrexate is an established drug and the specifications for Jylamvo have been based upon established pharmacopoeial monographs and ICH Q3B(R2), Therakind considers the impurities and degradants to be suitably qualified. Further, due to the well-established use of methotrexate and the control of Jylamvo in line with established***

specifications, pharmacopoeial monographs and ICH Q3B(R2) Therakind does not see a requirement for a genotoxicity screen.

- ***Therakind Question: Are any further considerations required for the impurity specifications at release or degradation-product specifications during shelf-life? Does FDA agree that a genotoxicity screen is not necessary?***

Discussion*:*

From the nonclinical perspective, there were no concerns raised. As long as levels of the drug and impurities were within appropriate boundaries set by recommended nonclinical and product quality guidances, we don't foresee any issues with your proposed development plan.

The FDA also requested the Sponsor provide justification for excipients if novel or if they exceed previously approved daily intake levels. The Sponsor may refer to the inactive ingredients database website for further guidance.

Chemistry, Manufacturing, and Controls (M3) Questions

Question 8:

The Applicant proposes that the data package submitted to support the Quality section of the EU MAA (Module 3, Module 2), updated with further stability data and validation data on the commercial manufacturing process, together with updating to reflect US quality requirements, will be adequate for FDA approval. In addition, information on the non-compendial orange flavor excipient will be submitted by the Supplier via a DMF to support this NDA. Additional information is provided within the briefing book. Does FDA agree that the CMC data package is adequate for FDA approval?

FDA Response:

Based on the summary in attachment 2, you appear to be following the approach outlined in ICH guidance M4Q for quality. We recommend that you also refer to other pertinent ICH and Agency guidance for the CMC related information to support your NDA (refer to https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm). Adequacy of the application to support approval will be determined at the time of review after filing.

Discussion*:*

No further discussion took place.

Question 9:

Please confirm that our proposed specifications for the US/FDA are acceptable.

FDA Response:

The current proposed specification for the drug product appears to have all test parameters recommended by ICH Q6A, with the exception of extractables (leachables). Acceptance criteria and associated methods/validation will be evaluated at the time of review.

Therakinds's Pre-Meeting Discussion Points:

- ***Standard components which are used widely in the pharmaceutical industry have been selected to contain, close and dose methotrexate 2mg/ml oral solution. The container to be used for methotrexate 2mg/ml oral solution is a 75ml amber type III glass bottle closed with a tamper-evident child-resistant screw cap. The closed bottle will be placed into a cardboard carton which will also contain a neck insert (adaptor) and a 10ml oral dosing syringe.***
- ***The only materials in contact with the oral solution are the glass bottle, cap liner and neck adaptor.***
- ***The cap liner is made of polyethylene and has a surface area of less than 5cm^2. Upright storage of the bottles for 20 months at ambient conditions has not demonstrated any interaction between the glass bottle and oral solution or the cap liner and oral solution.***
- ***The neck adaptor is made of low density polyethylene. It is only inserted at time of first use by the patient or caregiver, and thus will only have any potential for contact with the solution for the 3 months of open bottle shelf-life. An in-use study has demonstrated no evidence of interaction between the adaptor and oral solution over the 3 month open shelf-life period.***
- ***Thus, we do not consider that additional extractables data are necessary for this container-closure system.***
- ***We have not identified any additional degradants or impurities or extractables to this point in any of our stability programs, hence we do not believe additional studies or data should be required at this time.***
- ***Discussion with FDA requested.***

Discussion:

The Agency recommended that the sponsor refer to the discussion of extractables for oral solutions in the 1999 packaging guidance, which discusses the indirect food additive regulations. The Agency suggested that the sponsor contact the suppliers of the container components and inquire as to the compliance of those components with the indirect food contact regulations.

These regulations may provide sufficient justification for not including routine leachables monitoring as part of the annual stability program.

In terms of the stability studies, the Agency indicated that we generally recommend that oral solution drug products be stored both upright and inverted or horizontal for registration stability studies and that the worst case would then be used for routine storage. This approach is outlined in the 2014 stability guidance for ANDAs, but is equally applicable for NDA drug products. We indicated that not providing the stability data for product stored in both upright and inverted or horizontal position would be a risk they would be taking, particularly if their limited development stability data did show differences in product stability between the alternate storage orientations. The Agency suggested that they add some more samples to their stability program stored inverted/horizontal, even though the program has already started. The Agency suggested that these two issues may be appropriate to discuss further if the sponsor has a pre-NDA meeting later in development.

Question 10:

Is the existing stability program adequate for our proposed NDA or provide comment or feedback?

FDA Response:

In general, the information summarized regarding the stability data appear to be reasonable, with the possible exception of the need for monitoring of leachables. We note that you currently have 6-20 months of long term stability data for the commercial scale batches and 36 months for the pilot scale batches. If there are significant differences in the manufacture of the commercial versus the pilot scale batches, we would recommend that you include at least 12 months of stability data for three of the commercial process stability batches of the to-be-marketed drug product.

Therakind's Pre-Meeting Discussion Points:

We can confirm that we will have in excess of 12 month stability data on at least three commercial process stability batches at the time of an NDA submission. No further discussion is required.

Discussion*:*

No further discussion took place.

Additional Comments:

1. *As a new dosage form, your product triggers PREA. You must have an agreed iPSP before submission of your NDA, otherwise, your submission is considered incomplete, which is grounds for refusal to file. Also, refer to PREA Requirements below.*

2. *The NDA must be complete per 21 CFR 314.50 and contain all sections of the application. Labeling must comply with the requirements of the Physician Labeling Rule (PLR) and Pregnancy Labeling and Lactation Rule (PLLR).*

Discussion*:*

For the PREA requirement, the Sponsor will be seeking their product for adult indications and will exclude from applying for pediatric indications due to the orphan exclusivity approved for Xatmep.

The FDA stated that the proposed oral solution would trigger PREA for any indications that are not currently approved for the Xatmep oral solution and the Sponsor must submit an initial PSP to the Pre-NDA application for review. The FDA reiterated that the Sponsor first needs to address the relative bioavailability study requirement. Then, for each indication, the Sponsor can state that methotrexate is fully assessed for those indications currently approved in pediatrics or plan to request a waiver for those that are not and give the justification for the waiver. The FDA will then issue an official letter with agreement/no agreement with the PSP within 210 days prior to submitting the future NDA for filing.

From the labeling perspective, the FDA stated that the Sponsor must comply with the PLR and PLLR format and requirements, and cautioned the Sponsor on how much data they can rely upon or carve out from the reference label; it is to their benefit to see if there is any useful information to utilize for their product, and to provide adequate justification for using it, if warranted.

The FDA also recommended that the Sponsor review some recently approved labels for methotrexate in PLLR format for reference.

For the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of the labelling, the Sponsor confirmed that the package insert wording will be based on the US reference listed drug.

The Sponsor sought guidance on the procedure for submitting their proposed proprietary name for review and asked if they could submit the documentation to support their proposed proprietary name "Jylamvo" to the Pre-NDA, and the time frame for the submission of the proposal. The FDA recommended the sponsor submit their request for review of their proposed proprietary name to the filed NDA submission. For review of the proposed proprietary name prior to the filed NDA submission, we recommended the Sponsor open an IND to submit their request for FDA review of the proposed proprietary name. The FDA directed the Sponsor to the draft Guidance for Industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names for the requirements of such a submission. If submitted to the IND, it will be under a 6-month review clock, and under the NDA it will be under a 3-month review clock.

3.0 OTHER 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.

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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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.

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's responses to FDA's preliminary comments

8 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SADAF NABAVIAN
12/21/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 212479

MEETING PRELIMINARY COMMENTS

Therakind Limited
c/o Poppyridge LLC
22345 Bracketts Road
Shorewood, MN 55331

Attention: Dayton T. Reardan, PhD, RAC
US Agent for Therakind Limited

Dear Dr. Reardan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Oral Solution, 2 mg/ml.

We also refer to your August 14, 2018, correspondence, received August 14, 2018, requesting a meeting to obtain feedback on your regulatory pathway and the development to support a new drug application submission for the oral solution of methotrexate.

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: October 16, 2018, from 3:00-4:00 p.m. EST
Meeting Location: White Oak Building 22, Conference Room: 1315

Application Number: NDA 212479
Product Name: Methotrexate oral solution

Indications: Adult neoplastic diseases, (b) (4) rheumatoid arthritis
Sponsor: Therakind Limited

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 October 16, 2018, at 3:00 P.M., Conference Room 1315 between Therakind Limited 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. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). 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

The purpose of the meeting is to provide Therakind Limited with guidance on the regulatory pathway and development plan to support a future new drug application submission for the oral solution of methotrexate for the proposed indications of neoplastic diseases, (b) (4) and rheumatoid arthritis. Therakind Limited submitted a meeting request on August 14, 2018, to the Division of Pulmonary, Allergy, and Rheumatology Products. The Division granted the meeting on September 4, 2018. The briefing package was submitted on September 10, 2018.

2.0 DISCUSSION

Question 1:

Does FDA agree that the NDA application can be submitted as a 505(b)(2) application with reference to NDA 008085 (Methotrexate oral tablets, Dava Pharmaceuticals)?

FDA Response:

Yes, we agree that your application can be submitted as a 505(b)(2) regulatory pathway. The choice of a US approved and marketed methotrexate drug product as the listed drug appears reasonable and it is at your discretion. Refer to 505(b)(2) Regulatory Pathway at the end of this document.

Question 2:

For Orphan Products: Is there any issue with the recently approved oral liquid formulation of methotrexate (XATMEP NDA 208400) and our planned NDA submission for our oral liquid formulation omitting those two orphan indications approved for XATMEP?

FDA Response:

Xatmep has orphan exclusivity for the following indications:

- Treatment of acute lymphoblastic leukemia in pediatric patients (0 through 16 years of age)
- Management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy

Your currently proposed indication is: JYLAMVO™ (methotrexate) 2 mg/ml Oral Solution is indicated for the treatment of neoplastic diseases, (b) (4) and rheumatoid arthritis.

Orphan drug exclusivity blocks approval of any other application for the same drug for the same indication. Your proposal to carve out the indication(s) granted orphan exclusivity is acceptable.

Question 3:

Please confirm for a new formulation such as we propose that should a NDA be approved, it would be eligible for 3 years exclusivity pursuant to Hatch-Waxman.

FDA Response:

Your NDA submission may include a request for exclusivity, however, exclusivity determinations are made at the time of approval of an application.

Question 4:

Please confirm that the user fee for a 505(b)(2) NDA would be half that of a full application fee (or $1,294,239.00) and that as a small company filing our first NDA, Therakind would be eligible for a waiver of its first application fee.

FDA Response:

For any user fee questions, contact the User Fee staff at CDERCollections@fda.hhs.gov or 301-796-7900.

Clinical Questions

Question 5:

Does FDA agree that the two bioequivalence studies already conducted will be sufficient to support the NDA if supported by in vitro dissolution data demonstrating equivalence of the EU originator reference tablet used in the bioequivalence study (methotrexate "Lederle" 2.5 mg) and the US RLD tablet NDA 008085?

FDA Response:

No, we do not agree. An in vivo relative bioavailability study for your proposed oral solution and the United States listed drug (oral tablet; NDA 008085) under fasting conditions is needed. The reasons are as follows:

a. Demonstration of comparative bioavailability of your proposed product to the US listed will bridge your proposed methotrexate oral solution to FDA's finding of clinical efficacy and safety on the listed drug approved in the US.

b. Comparative in vitro dissolution data would not support the bridge between the EU originator reference tablet and the US listed drug tablet (under NDA 008085) as dissolution is drug product specific. That is, similar dissolution profiles of different drug products, under specific testing conditions, do not confer comparative bioavailability on the drug products.

Refer to the FDA guidance entitled "*Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" for recommendations on study design and conduct of a relative bioavailability study.*

You do not propose to study the effect of food on the bioavailability of your proposed product. You should also conduct a food-effect study for your proposed drug product. Refer to the "*Food-Effect Bioavailability and Fed Bioequivalence Studies"* guidance for recommendations on study design and conduct of a food-effect study.

The final to-be-marketed product must be used in the PK studies to support your NDA application.

Question 6:

The applicant proposes to reference the Reference Listed Drug (NDA 008085) to support the clinical pharmacodynamics, efficacy and safety sections of the NDA and considers that no new clinical studies are required. Does FDA agree?

FDA Response:

It is premature to agree with your proposal, at this time. Refer to our responses to Question 5. If you cannot demonstrate comparative bioavailability of your proposed product to the US listed drug, additional data and information including additional clinical studies may be needed.

Pharmacology and Toxicology Questions

Question 7:

The applicant proposes to reference the Reference Listed Drug (NDA 008085) together with an evaluation of the toxicity of the excipients to support the non-clinical section of the NDA and considers that no new non-clinical studies are required. Does FDA agree that no new non-clinical studies are necessary for NDA submission?

FDA Response:

We agree that no nonclinical studies are necessary.

Provide structures of any impurities and degradants of the drug substance and drug product in your future NDA submission. Monitor impurities and degradation products of all active ingredients and refer to ICH Guidance Q3A(R) and Q3B(R) for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA as described in the ICH M7 Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (May 2015).

Chemistry, Manufacturing, and Controls (M3) Questions

Question 8:

The Applicant proposes that the data package submitted to support the Quality section of the

EU MAA (Module 3, Module 2), updated with further stability data and validation data on the commercial manufacturing process, together with updating to reflect US quality requirements, will be adequate for FDA approval. In addition, information on the non-compendial orange flavor excipient will be submitted by the Supplier via a DMF to support this NDA. Additional information is provided within the briefing book. Does FDA agree that the CMC data package is adequate for FDA approval?

FDA Response:

Based on the summary in attachment 2, you appear to be following the approach outlined in ICH guidance M4Q for quality. We recommend that you also refer to other pertinent ICH and Agency guidance for the CMC related information to support your NDA (refer to https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm) . Adequacy of the application to support approval will be determined at the time of review after filing.

Question 9:

Please confirm that our proposed specifications for the US/FDA are acceptable.

FDA Response:

The current proposed specification for the drug product appears to have all test parameters recommended by ICH Q6A, with the exception of extractables (leachables). Acceptance criteria and associated methods/validation will be evaluated at the time of review.

Question 10:

Is the existing stability program adequate for our proposed NDA or provide comment or feedback?

FDA Response:

In general, the information summarized regarding the stability data appear to be reasonable, with the possible exception of the need for monitoring of leachables. We note that you currently have 6-20 months of long term stability data for the commercial scale batches and 36 months for the pilot scale batches. If there are significant differences in the manufacture of the commercial versus the pilot scale batches, we would recommend that you include at least 12 months of stability data for three of the commercial process stability batches of the to-be-marketed drug product.

Additional Comments:

1. As a new dosage form, your product triggers PREA. You must have an agreed iPSP before submission of NDA, otherwise, your submission is considered incomplete, which is the grounds for refuse to file. Also refer to PREA Requirements below.

2. The NDA must be complete per 21 CFR 314.50 and contain all sections of the application. Labeling must comply with the requirements of the Physician Labeling Rule (PLR) and Pregnancy Labeling and Lactation Rule (PLLR).

3.0 OTHER 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.

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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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.

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	
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/s/

SADAF NABAVIAN
10/11/2018