CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218637Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 218637

REFUSAL TO FILE

Kamat Pharmatech, LLC.
Attention: Dr. Madhav S. Kamat
Chief Executive Officer
685 US Highway 1
New Jersey Bioscience Center
North Brunswick, New Jersey, 08902

Dear Dr. Kamat:[1]

Please refer to your new drug application (NDA) dated and received July 25, 2023, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for trazodone hydrochloride oral solution.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reason:

Failure to address the requirements under the Pediatric Research Equity Act (PREA)

> You have not provided an agreed initial pediatric study plan (iPSP) with your new drug application for trazadone hydrochloride oral solution for the treatment of major depressive disorder (MDD).
>
> 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable. Under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an iPSP within 60 days of an End-of-Phase-2 (EOP2) meeting, or such other time as may be agreed upon between the Secretary and the applicant [505B(a) and (e) of the FD&C Act]. In the absence of an EOP2 meeting, and in cases where a phase 3 study or a combined phase 2/3 study will not be conducted, sponsors should submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

In our January 2022 written response to your pre-IND meeting request under PIND 143176, and again, in our July 2023 written response to your pre-NDA meeting request, the Division indicated that under PREA, a pediatric assessment is required for your new dosage form, trazodone hydrochloride oral solution; therefore, an agreed iPSP must be submitted with your NDA.

While the following are not issues related to our refusal to file this application, you should also address the following issues if the application is resubmitted:

Regarding your proposal to control (b) (4) at NMT (b) (4) ppm, refer to our response to Question 4 of the Type B WRO meeting (July 10, 2023). (b) (4) is considered a potential mutagen; therefore, provide information on whether it is present in the drug substance. If present, you must follow ICH M7 recommendations in identifying an appropriate acceptable intake level and appropriate corresponding drug product specification for (b) (4)

An alternative option is to use (b) (4) as a surrogate compound to establish an acceptable intake level. The acceptable intake level for (b) (4) is (b) (4) µg/day (b) (4) which corresponds to a drug substance specification of NMT (b) (4) ppm given the maximum daily dose of 600 mg for the drug substance used in a lifetime treatment.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application.

We refer you to the following guidance if you require information on submitting requests for proprietary name review:

- Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names[2]

If you have any questions, please contact Jennifer Shim, Regulatory Project Manager, at Jennifer.Shim@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, M.D.
Director
Division of Psychiatry
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

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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/

TIFFANY R FARCHIONE
09/20/2023 03:50:44 PM

NDA 218637

MEETING REQUEST-
WRITTEN RESPONSES

Kamat Pharmatech LLC
Attention: Dr. Madhav S. Kamat
Chief Executive Officer
685 US Highway 1
NJ Bioscience Center
North Brunswick, New Jersey, 08902

Dear Dr. Kamat:[1]

Please refer to your May 8, 2023, submission containing a Type B, Written Response Only (WRO) meeting request under new drug application (NDA) 218637 for trazodone hydrochloride oral solution. The purpose of the requested meeting was to obtain the Agency's feedback on the proposed content and presentation of the planned NDA submission for trazodone hydrochloride oral solution.

Further reference is made to our Meeting Granted letter dated May 17, 2023, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 11, 2023, background package.

If you have any questions, please contact Jennifer Shim, Regulatory Project Manager at Jennifer.Shim@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, M.D.
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-NDA

Application Number: NDA 218637

Product Name: Trazodone hydrochloride oral solution, 100mg/10mL
Indication: Treatment of major depressive disorder (MDD)
Sponsor Name: Kamat Pharmatech LLC
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

The Sponsor is developing trazodone hydrochloride (HCl) oral solution (100 mg/10 mL) for the treatment of depression. The Sponsor plans to utilize the 505(b)(2) pathway relying upon the proposed listed drug (LD) Desyrel (trazodone HCl, NDA 018207). The antidepressant Desyrel, a selective serotonin reuptake inhibitor and 5HT2 receptor antagonist, was approved in 1981 and is indicated for the treatment of major depressive disorder.

Compared to the LD oral tablet, the Sponsor believes that their oral solution formulation will allow for more flexibility in dose titration and increased convenience for patients with dysphagia or swallowing difficulties, thus increasing adherence. Because Desyrel has been discontinued, the Sponsor proposes to establish a scientific bridge to trazodone HCl oral tablets (ANDA 071196; 100 mg), the designated reference standard (RS) in the FDA Orange Book, in their pivotal comparative bioavailability study.

Under pre-IND 143176, the Division provided informal guidance in 2019 regarding biopharmaceutical and chemistry, manufacturing, and controls (CMC) questions. The Division provided Written Responses in 2022 regarding the Sponsor's proposed CMC, nonclinical, clinical, and regulatory strategies. The Division stated that based on the information provided, the Sponsor's proposed three-arm comparative bioavailability study (including fed and fasting state administration) appeared reasonable. The Division noted that the Sponsor's background materials referred to "rapid dissolution of drug and absorption" which "may also produce rapid onset of action" with the proposed drug product. The Division noted that if the T_{max} is not similar to the LD, additional clinical studies may be required.

The Sponsor has since conducted the planned comparative bioavailability study. The Sponsor's purpose for requesting this meeting is to obtain FDA concurrence on the acceptability of the proposed CMC, nonclinical, clinical, and regulatory strategies.

2.0 QUESTIONS AND RESPONSES

2.1. GENERAL/REGULATORY

Question 1: Does the Agency agree that Module 1 to Module 5 of NDA application organized in accordance with *Guidance for Industry – Good Review Management Principles and Practices (GRMPS) of PDUFA Products* and in-line with eCTD structure with XML backbone of as presented in the Pre-NDA meeting briefing package is acceptable for filing for the proposed NDA product Trazodone Hydrochloride Oral Solution 100mg/10mL?

FDA Response to Question 1: *On face, the proposed NDA submission structure appears acceptable. However, its adequacy for filing will be a matter of review upon receipt of your NDA. Please refer to CFR 314.50 for additional guidance on the content and format of an NDA. Additionally, more information regarding eCTD structure can be found on the Agency's website (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/ectd-resources).*

Question 2: Does the Agency consider the proposed pack of Trazodone Hydrochloride Oral Solution, 100mg/10mL product including a 10 mL dosing syringe with graduations as a drug-device combination product?

FDA Response to Question 2: *Based on the information presented, we agree that your proposed product is a combination product in accordance with 21 CFR 3.2(e)(2) because the proposed co-package consists of a drug (trazodone hydrochloride solution) and device (oral dosing syringe) constituent parts.*

In addition:

1. *Combination products are subject to 21 CFR Part 4 Current Good Manufacturing Practice Requirements for Combination Products, accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products. Refer to additional comments under Question 12b.*

2. *In your future submission, the Form FDA 356h should identify your product as a combination product (see form field 24). Also, identify all facilities involved in the manufacturing of the combination product, including all facilities involved in the manufacturing of each constituent part and all facilities responsible for the disposition (e.g., release) of the combination product.*

3. *For information on the location of device related information, see Section 5 of the Agency eCTD Technical Conformance Guide: Technical Specifications*

Document: Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (November 2022), accessible at https://www.fda.gov/media/93818/download

4. *Part 3 combination products are subject to post-market reporting safety requirements per 21 CFR Part 4.B. For more information on post-market safety reporting requirements for combination products, see: https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.*

Question 3: Does the Agency agree that the drug product Trazodone Hydrochloride Oral Solution, 100mg/10mL is eligible for priority review basis the supporting note submitted in the meeting package for the same?

FDA Response to Question 3: *It is premature to determine priority review status at this time. Review designation will be determined after NDA submission. An NDA will be considered for priority review if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness over existing therapies. For more information, please refer to the guidance for industry,* Expedited Programs for Serious Conditions – Drugs and Biologics *(May 2014).*

2.2. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

Question 4: Does the Agency consider the proposed limit for the organic impurities viz., all specified known impurities, any individual unspecified impurity, and total impurities in the drug substance (Trazodone Hydrochloride, USP) specification as acceptable for filing the proposed NDA?

FDA Response to Question 4: *It is considered reasonable to set a limit of (b) (4)% for each of the ten specified organic impurities and for individual unspecified impurities. The limit of (b) (4)% for total impurities appears reasonable, but you should provide adequate justification in the NDA.*

However, we note that you propose to control (b) (4) at NMT (b) (4) ppm, which may not be sufficient. Provide a risk assessment of genotoxicity potential for this impurity. If (b) (4) is a potential genotoxic impurity, follow ICH M7 to control the impurity at NMT (b) (4) ppm given the maximum daily dose of 600 mg for the drug substance used in a lifetime treatment. Establish an adequate analytical method for (b) (4)

Please be advised that complete evaluation on your impurity controls will be performed at the NDA review stage.

Question 5: Does the Agency consider acceptable the proposed limit for release and shelf-life for [redacted] impurities in the drug product specification?

FDA Response to Question 5: *The proposed limits for the [redacted] impurities in the drug product specification are reasonable from a CMC perspective. However, a final determination on acceptability of the limits for impurities/degradants will be made when all the data are reviewed in their entirety upon submission of the NDA*.

Question 6: Does the Agency consider acceptable the proposed limits for release and shelf life for any individual unspecified impurity and total impurities in the finished product specification?

FDA Response to Question 6: *From the CMC perspective, the proposed limits for individual unspecified impurities are reasonable for drugs with maximum daily doses between 10 mg and 2 g, per the ICH Q3B guideline. However, a final determination on acceptability of the specifications for the individual unidentified and total impurities will be made at the time of review of the NDA when all supporting data are evaluated in their entirety. We further advise that while setting acceptance criteria for potential genotoxic impurities, you should follow the ICH M7 guideline to control their levels in drug product.*

In addition, you should plan to submit a risk assessment for presence of nitrosamine in the drug product in the NDA, as per the FDA guidance for industry: Control of Nitrosamine Impurities in Human Drugs *(February 2021)*.

Question 7: Does the Agency agree that testing as per USP General Chapter <88> of packaging materials is not required considering intended product is for oral dosage form?

FDA Response to Question 7: *A certification that the formulation contacting [redacted] components complies with USP <87> and <88> is required from the manufacturer of the syringe.*

Question 8: Does the Agency find acceptable the data of the in-use study conducted on proposed drug product and thereby the instructions of use recommendations proposed in view of the same?

FDA Response to Question 8: *The proposed testing protocol for in-use stability testing is acceptable. However, apart from in-use stability testing on fresh batches of the drug product, we also recommend performing the in-use stability testing on aged samples of drug product batches towards the end of their shelf-life. A final determination on acceptability of the in-use test data will be made when all the data are reviewed upon submission of the NDA. The instructions for use will be reviewed at the time of NDA submission.*

Question 9: Does the Agency consider acceptable the (b) (4) (b) (4) of the finished product based on the risk assessment submitted in the meeting package?

FDA Response to Question 9: *Your approach for risk assessment of (b) (4) (b) (4) in the drug product is acceptable. However, we cannot comment on the acceptance of the risk assessment reports for (b) (4) including the (b) (4) of the finished product at this time. A determination on acceptability of the risk assessment for the (b) (4) of the finished product, in lieu of testing of drug product batches for their presence, will be made at the time of review after submission of the NDA.*

The Agency recommends that any tests to detect and quantify (b) (4) use a safety limit for (b) (4) of NMT (b) (4) %. Refer to the guidance for industry, (b) (4)

Question 10: Does the Agency consider acceptable the extractable and leachable study reports submitted with the briefing package for proposed product?

FDA Response to Question 10: *We cannot comment on the acceptability of the risk assessment report for the extractables and leachables in your proposed drug product at this time. The extractable/leachable studies must be conducted on the drug product per USP <1663> and <1664>. We expect leachable data to be assessed at each time point during the stability protocol, so that any trends in leachables and secondary leachables may be assessed. A correlation should be established between the extractables identified in the extractable studies and the leachables observed during stability studies.*

Question 11: Proposed product was manufactured using contact parts made with (b) (4) (b) (4) complying as per USP / or compliance with 21 CFR indirect food additive regulations. Does the Agency agree that bulk compatibility

study in addition to hold time of the bulk presented in Pre-NDA meeting package is adequate to demonstrate no risk of contamination from production equipment's during contact with drug product?

FDA Response to Question 11: *The risk of contamination from production equipment during contact with drug product should be addressed through equipment compatibilities studies, including extractables/leachables studies as necessary. The final acceptance of the equipment compatibility study, bulk hold time study, and information to address the risk of extractables/leachables from the manufacturing equipment is a review issue and will be determined at the time of the NDA review with the assessment of the detailed data. However, we have some preliminary comments.*

It appears that you only studied the compatibility of the (b) (4) (b) (4) *We recommend that you also collect data on product compatibility with other* (b) (4) *contacting equipment components, such as* (b) (4) *. In Annexure 14 of your briefing packaging, you provided details of material construction for equipment and risk assessment for extractables/leachables. Please be advised that equipment compatibility is highly process- and product-dependent.*

Your proposed product formulation includes (b) (4) (b) (4) (b) (4) *Therefore, your risk assessment for the equipment compatibility should include the intrinsic risk associated with the materials of construction and the interaction between formulation and equipment under manufacturing conditions. The information listed below, but not limited to this, should be provided in your future NDA to demonstrate the equipment compatibility in addition to your risk assessment and mitigation strategies:*

a. *A statement of compliance for any* (b) (4) *contacting manufacturing components (e.g.,* (b) (4) *) to meet the ASTM* (b) (4) *or equivalent standards.*

b. *A certification (including from vendor) that the formulation contacting* (b) (4) *components comply with requirements for indirect food additives (21 CFR 177).*

c. *A certification that the formulation contacting* (b) (4) *components complies with USP <87> and <88>.*

d. *Provide information to demonstrate that all product-contact* (b) (4) *components used in the manufacturing process are compatible with process materials (i.e., no adsorption, reactivity and other contaminations including leachables to drug product quality under the given process conditions). Perform an extractables and leachables study, if warranted, depending on identified formulation and process related risks.*

Question 12a: Oral syringe and adaptor are proposed to be provided with the proposed product Trazodone Hydrochloride Oral Solution, 100mg/10mL. Details thereof are included in the Meeting Package. Does the Agency consider the same acceptable?

FDA Response to Question 12a: *We cannot comment on the acceptability of the proposed oral syringe and adaptor at this time, given that their adequacy is dependent on the evaluation of all the supporting data which will be evaluated at the time of NDA submission. We refer you to the guidance for industry on* Container Closure Systems for Packaging Human Drugs and Biologics – Chemistry, Manufacturing, and Controls Documentation *(May 1999)*

Question 12b: Further, the proposed product to be supplied with an oral dosing syringe and adaptor, does not result in a new use of the device constituent part i.e., syringe. The syringe is proposed to be co-packaged with the drug product and is not proposed to be separately sold or marketed as a medical device by Kamat Pharmatech LLC. Hence, the device constituent part is considered exempt from the cGMP requirements of the device QS regulation (21 CFR 820), including general requirements concerning records (21 CFR 820.180) and complaint files (21 CFR 820.198). Does the Agency concur with this and agree that the proposed product would be exempt from cGMP and device QS regulations?

FDA Response to Question 12b: *As reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (21 CFR part 820) through a streamlined approach. In some cases, the combination product may be exempt from the device QS regulation (refer to the guidance for industry and FDA staff,* Current Good Manufacturing Practice Requirements for Combination Products *(January 2017).*

Your combination product includes a device constituent part, an oral dosing syringe, that is co-packaged with the drug product. This device constituent part is exempt from the CGMP requirements of the device QS regulation (21 CFR 820), except for certain general requirements concerning records (21 CFR 820.180) and complaint files (21 CFR 820.198) that would be required if it were marketed separately as a medical device.

Assuming that a drug-based CGMP streamlined approach is being used for the combination product and the device constituent part CGMP exemptions cover all of the part 820 provisions included in 21 CFR 4.4(b)(1), the Agency will consider the combination product manufacturer to be CGMP compliant as long as the CGMP operating system is compliant with parts 210 and 211 (no demonstration of compliance with part 820 will be necessary). The guidance for industry and FDA

staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017) indicates that "manufacturers should document their evaluation…if they believe a device constituent part is exempt from any or all provisions under the device QS regulations." Therefore, your documentation demonstrating compliance with 21 CFR part 4 should include your evaluation, or a copy of correspondence from the Agency confirming the exemption, and must be available upon inspection.

2.3. BIOAVAILABILITY

Question 13: Kamat Pharmatech LLC requests the Agency to confirm that prior findings of safety and efficacy for the listed drug can be completely relied upon for our product Trazodone Hydrochloride Oral Solution 100mg/10mL.

FDA Response to Question 13: *The degree to which you can rely on the Agency's findings of safety and efficacy for the listed drug will depend on the results of the scientific bridging between your product and the listed drug (LD). If your product is found to be bioequivalent to the LD, the safety and efficacy determination would be based on findings from the LD.*

2.4. CLINICAL

Question 14: Does the Agency agree that no Integrated Summaries of Effectiveness (ISE) and Integrated Summaries of Safety (ISS) are required to be submitted for proposed NDA Trazodone Hydrochloride Oral Solution, 100mg/10mL as the application is planned to be submitted with relative bioavailability study and no clinical studies were conducted by the sponsor for the proposed NDA product?

FDA Response to Question 14: *Yes, we agree. See our answer to Question 13.*

Question 15: Does the Agency agree that the proposed Trazodone Hydrochloride Oral Solution, 100mg/10mL NDA is not subject of Pediatric Research Equity Act (PREA) as the product is not for the pediatric population and therefore does the Agency agree that Pediatrics Studies are not required for the proposed Trazodone Hydrochloride Oral Solution, 100mg/10mL and no Pediatric Study Plan is required to be submitted with the NDA?

FDA Response to Question 15: *No, we do not agree. Trazodone HCl Oral Solution, 100mg/10mL NDA is subject to PREA, as the oral solution is a new dosage form. Under PREA, pediatric assessments are required for drug products with a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Therefore, an agreed initial Pediatric Study Plan (iPSP) must*

be submitted with your NDA application. The instructions for submitting an iPSP are below in Section 3.0 (PREA Requirements).

As recommended in the draft guidance for industry, Major Depressive Disorder: Developing Drugs for Treatment *(June 2018), your iPSP should include a plan to provide an assessment in two pediatric age groups—7 through 12 years of age and 13 through 17 years of age—to establish safety and efficacy.*

Previously studied antidepressants, with the exceptions of fluoxetine and escitalopram, have not shown efficacy for the treatment of pediatric MDD. Those negative findings have led to a substantial concern about the ability to extrapolate positive antidepressant findings from adult to pediatric patients. The Division's current expectation for establishing substantial evidence of effectiveness for pediatric MDD, even for an antidepressant already approved for adult MDD, includes two independent, adequate and well-controlled clinical trials in pediatric subjects, in addition to pharmacokinetic and safety information in the relevant pediatric age groups (as noted above, 7 through 12 years and 13 through 17 years).

Question 16: Does the Agency agree that the proposed product Trazodone Hydrochloride Oral Solution, 100mg/10mL does not require any studies related to the potential abuse of the drug since Trazodone Hydrochloride, USP is not a controlled substance and the Reference Listed Drug (RLD) Desyrel Tablets pack insert states that drug seeking behavior was not seen in the clinical studies with trazodone hydrochloride?

FDA Response to Question 16: *We agree that no abuse potential studies (nonclinical or clinical) are required for your proposed 505(b)(2) New Drug Application (NDA) for trazodone oral solution.*

2.5. LABELING

Question 17: Does the Agency consider adequate the proposed labeling i.e. draft labels and pack insert proposed for the product and submitted with the meeting package?

FDA Response to Question 17: *Discussion of labeling is premature and will be a matter of review after NDA submission. We remind you that labeling must meet all labeling regulatory requirements, should be consistent with labeling guidance recommendations, and should reflect currently available information for safe and effective use of the drug. Additional labeling resources may be found at https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources.*

Question 18: Does the Agency consider adequate the Instruction of Use in draft pack insert submitted in Pre-NDA meeting package?

FDA Response to Question 18: *See our response to Question 17.*

Question 19: Does the Agency consider acceptable and adequate the submitted threshold analysis report which includes dose accuracy study data demonstrated using proposed syringe and adaptor, User Related Risk Analysis (URRA), comparative analysis with the available similar device of the marketed product proposed to be submitted in the NDA?

FDA Response to Question 19: *Please note that your submission of a threshold analysis (which includes a URRA) as part of a meeting package is not the appropriate mechanism for the Agency's review. Typically, we would request that you submit them to the IND. However, in light of your proposed timeline for submitting your NDA, we request that you submit only the URRA portion of the threshold analysis document to the NDA for our review. Based on a high-level cursory review, the full threshold analysis document does not need to be submitted at this time. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.*

Question 20: Does the Agency agree that based on the complete threshold analysis report submitted, no human factor studies are required to be provided for the proposed NDA application?

FDA Response to Question 20: *See our response to Question 19.*

Question 21: Does the Agency consider acceptable, dosing recommendation for the proposed product and included in the labeling?

FDA Response to Question 21: *See our answer to Question 17.*

Question 22: Does the Agency agree that request for proprietary name review can be submitted after submission of the NDA?

FDA Response to Question 22: *Yes, we agree. Additionally, you may choose to refer to our guidance for industry,* Contents of a Complete Submission for the Evaluation of Proprietary Names *(April 2016).*

3.0 OTHER

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*.[2] 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 FDA.gov.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

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[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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*.

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

SUBMISSION FORMAT REQUIREMENTS

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

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[8]

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).[9] 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 Regulations.gov.[10]

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[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[8] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[9] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

[10] http://www.regulations.gov

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.

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).

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.

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