CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212157Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125585

MEETING MINUTES

Dr. Reddy's Laboratories, Inc.
Attention: Hari Nagaradona, Ph.D.
107 College Road East
Princeton, NJ 08540

Dear Dr. Nagaradona:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DFN-15 (celecoxib oral solution).

We also refer to the meeting between representatives of your firm and the FDA on August 23, 2018. The purpose of the meeting was to discuss the development plan for DFN-15 and the adequacy of data to support the submission of NDA.

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, please contact E. Andrew Papanastasiou via email at emilios.papanastasiou@fda.hhs.gov, or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 4820326

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 23, 2018 from 1:00 PM to 2:00 PM EST
Meeting Location: FDA White Oak

Application Number: 125585
Product Name: DFN-15 (celecoxib oral solution 25 mg/ml)_
Proposed Indication: Acute treatment of migraine with or without aura
Sponsor/Applicant Name: Dr. Reddy's Laboratories Limited

FDA ATTENDEES

Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Associate Director
Heather Fitter, MD, Clinical Team Leader
Emily Freilich, MD, Clinical Reviewer
Laura Jawidzik, MD, Clinical Reviewer
Bilal AbuAsal, PhD, Acting Clinical Pharmacology Team Leader
Mariam Ahmed, PhD, Clinical Pharmacology Reviewer
Andrei Ponta, PhD, Pharmaceutical Quality Reviewer
Kun Jin, PhD, Biostatistics Team Leader
Jinnan Liu, PhD, Statistical Reviewer
Yasmeen Abou-Sayed, PharmD, Division of Risk Management, Analyst

SPONSOR ATTENDEES

Hari Nagaradona, PhD, Vice President & Head of Regulatory Affairs
Anil Namboodiripad, PhD, Sr. Vice President, Product Development
Sagar Munjal, MD, MS, Vice President/Head of Clinical Development
Elimor Brand-Schieber, PhD Director, Clinical Development
Reena Zade, MS, Associate Director, Regulatory Affairs
Hardik Panchal, MS, Manager, Regulatory Affairs
Kevin Carey, Director, Project Management
(b) (4)

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(b) (4)

Sponsor Attendees by phone

D Mallikarjuna Rao, PhD, Sr. Director Regulatory Affairs
Balaji MR, Sr. Director Toxicology
Rajesh Kumar, PhD, Sr. Director, CMC
GVS Sesha Kumar, PhD, Vice President and Head of Intellectual Property
Sumera Hasham, PhD, MBA, Sr. Director and Head Portfolio Strategy, Global Marketing and External R&D
Anirudh Gautam, MPharm, Sr. Director, DMPK
Subba Reddy Inta, Director, Quality Assurance
Ajaya Reka, PhD, Associate Director, CMC

FDA sent Preliminary Comments to Dr. Reddy's Laboratories on August 21, 2018.

1. DISCUSSION

Question 1: Dr. Reddy's has conducted a dose ranging comparative bioavailability study (Study DFN-15- CD-003) for DFN-15 (50 mg/mL) with doses of 120 mg, 180 mg and 240 mg in US population. Dose proportionality was observed in this study. In addition, another open-label single dose comparative bioavailability study (Study DFN-15-CD-008) was conducted with the final to-be- marketed formulation of DFN-15 (25 mg/mL) in healthy subjects in US population to support the 505(b)(2) NDA application. The plasma exposures (Cmax and AUC) data for DFN-15 dose of 120 mg in both fasting and fed states were lower than Celebrex 400 mg in the fed state.

The Agency concurred with the Sponsor during the End-of-Phase 2 meeting that the comparative bioavailability study (Study DFN-15-CD-008) is adequate to provide the necessary clinical bridge for the to-be-marketed formulation of DFN-15 to Celebrex (the listed drug [LD]) for the 505(b)(2) application. Does the Agency continue to concur that no additional clinical studies are needed to establish a clinical bridge to the Listed Drug and support the NDA filing?

FDA Response to Question 1:
On face, your approach to establishing a clinical bridge appears reasonable. See also our response to Question 2.

Discussion
There was no meeting discussion.

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Question 2: Does agency concur that either one or both of the approaches described above would provide support for substantial evidence of clinical efficacy of DFN-15 for the acute treatment of migraine and would be adequate for to support the submission of NDA?

FDA Response to Question 2:
No, we do not agree.

The pivotal trials you have completed and described in this meeting package, on face, would not provide substantial evidence of efficacy. We disagree with your proposal to use DB2 to independently substantiate the findings in DB1 in trial 007. Treatment of the second migraine attack in DB2, despite re-randomization between attacks, cannot be used to provide independent substantiation of efficacy, as the same patients were used for both parts of the study, so that the treatment effects seen in DB1 and DB2 are not independent. In addition, if the primary efficacy analysis for DB2 is a post hoc analysis.

In addition, we have serious concerns about the interpretability of your pivotal studies due to the degree of missing data on the co-primary endpoint of "absence of the most bothersome symptom (MBS)". In an acute migraine trial, our expectation is that there will be very little missing data, yet approximately 15-20% of patients did not provide data for the absence of their MBS. We note that many patients treated an attack that did not include their MBS, even though they were instructed to only treat an attack associated with their pre-randomization selected MBS.

The inability to replicate the positive results from trial 007 in an identically designed second trial (006) is also problematic. At a minimum, you will need to provide independent substantiation of efficacy from a new trial.

Discussion
The sponsor initiated the discussion regarding the most bothersome symptom (MBS), and stated that patients without an MBS measurement at 2 hours should not be considered in the calculation of missing data, nor was it a protocol violation to treat a migraine that was not associated with the patient's pre-specified MBS. Per the sponsor, the protocol instructed patients to identify their MBS at randomization, and then instructed them to treat their first migraine of moderate to severe intensity, regardless of whether the identified MBS was present. The Division referenced the EOP2 meeting minutes, in which FDA recommended two approaches to identification of the MBS, including 1) identification of the MBS immediately prior to treatment and recorded in the e-Diary, or 2) identification of the MBS at randomization, with the expectation that patients would treat the first migraine associated with their previously identified MBS. The sponsor acknowledged that they had received this advice, but were concerned that making patients wait to treat only migraines associated with their MBS would result in higher drop-out rates, and more missing data.

The sponsor also stated that the SAP pre-specified the full analysis set (FAS) as the primary efficacy analysis set, defined as the patients that were randomized, took study medication, had efficacy measurements at 2 hours for both pain free and the MBS, did not take rescue

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medication during the first two hours after dosing, and treated a migraine with only mild pain at onset. Therefore, all patients who did not report their identified MBS at the time of treatment were excluded from the primary analysis. The Division mentioned that the FAS for acute migraine studies is generally defined as patients randomized who had a migraine attack, took study medication, and have at least one post dose efficacy measurement. The Division also mentioned that patients in acute migraine trials who take rescue medication during the first two hours are usually considered treatment failures.

The Division stated that the sponsor should present a sensitivity analysis for all patients according to the usual FAS definition for migraine trials to see if the results are nominally significant. In addition, the Division stated that one of the sensitivity analyses that the sponsor should do is the worse-case scenario where all patients with missing data for either pain-free or the MBS are considered failures for the measurement they are missing at 2 hours

The sponsor stated that the FAS-MBS population (patients who recorded pain intensity and the FAS at 2 hours) included 487 patients, and provided sufficient power to detect a treatment difference between active treatment and placebo, as the sample size estimation was 480 patients for this efficacy trial. The sponsor stated that since their definition for the FAS population required that patients have a 2-hour post dose measurement of pain intensity and assessment of the MBS, patients without MBS measurements at 2-hour would not be considered to have missing data. Therefore, the actual amount of missing data was only 1-2% in the full-analysis set. The sponsor also stated that a sensitivity analysis including all patients (even those without the MBS assessment at 2-hour) yields nominally significant results on the primary endpoint. The sponsor also stated that they conducted a sensitivity analysis using patients that identified a MBS at the time of their migraine attack in the situation when the pre-dose MBS was different from their pre-randomization specified MBS, and this also resulted in nominally significant effects on the primary endpoint. The FDA statistician noted that, for this analysis, there were large amounts of missing data (8% in treatment arm, 9% in placebo arm), and that the treatment effect (12%) could essentially be eliminated in a worse-case scenario situation. The Division indicated that the adequacy of these data would be a review issue.

The sponsor also raised the issue of the requirements for substantial evidence of effectiveness, and acknowledged the Division position on whether DB2 could independently substantiate the findings of DB1 as a stand-alone study. Therefore, they asked whether a single study 007 (DB1) could be sufficient to provide substantial evidence of effectiveness, based on a low p-value. The Division stated that reliance on a single study is typically limited to situations where the drug has a significant effect on mortality or irreversible morbidity, and is generally not considered for symptomatic treatments of a non-life-threatening disease. Therefore, the use of a single study in this situation does not appear appropriate.

Despite the sponsor's initial agreement with the preliminary comments outlining the reasons that DB1 and DB2 did not constitute independent studies, the Division invited a more in-depth discussion about this topic, given that patients were re-randomized in-between the two treatment periods.

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The Division recognized that there were concerns about implicit bias inherent to the study design and conduct that might carry over from DB1 to DB2, but expressed openness to reviewing an argument that DB2 may stand alone as a second independent study. The acceptability of that approach would be a review issue. The sponsor questioned whether the data from Study 006 may be supportive. As part of this discussion, the sponsor stated that they conducted a sensitivity analysis excluding results from one outlier site (in a post hoc analysis), and when this site was excluded, the results for the primary analysis was nominally significant. The Division stated there were significant concerns regarding relying on a post hoc analysis with removal of a study site after completion of the trial and data analysis.

Other Division concerns that were raised regarding the use of DB2 as an independent study were that the patients who completed DB1 did not automatically get re-randomized to DB2, but instead were given a choice to enter DB2. Thus, randomization may not have been adequately preserved in terms of entry into DB2. The sponsor stated that 40% of the patients chose not to continue into DB2. It is unclear whether potential bias may have been introduced into this portion of the trial, as patients self-selected for the second trial. The Division asked the sponsor to provide a detailed discussion on whether randomization was preserved between the first and the second treatments in each study.

The Division asked about whether the analysis of the primary endpoint in DB2 of Study 007 was a pre-specified endpoint in the SAP, and whether it was included as a gated secondary endpoint with shared alpha, or whether the results for DB2 were considered only nominally significant. The sponsor indicated that it was included as a gated secondary endpoint in the pre-specified analysis plan.

In summary, the sponsor proposed that they could provide sufficient data to justify the use of DB2 as a stand-alone independent trial, and the Division agreed that the adequacy of those data would be a review issue. The Division noted the many concerns highlighted during this meeting regarding their planned NDA package, and stated that the sponsor also had an option to conduct another study.

The sponsor also agreed to do the requested food effect analysis. The Division invited the sponsor to resubmit the remainder of their pre-NDA questions in email form or as a Written Response Only (WRO) meeting request if they plan to proceed with the NDA submission and would like formal responses regarding Questions 3-5, 7 and 9 below.

Post meeting comments:
After the meeting, the review team sent the following IR: “We are unable to locate your statistical analysis plans (SAP) for your Studies DFN-CD-006 and DFN-CD-007. Can you please tell us the date you submitted these SAPs (and the submission number) or if you did not submit them to the Agency, please provide a copy of these SAPs by COB Friday, August 24, 2018?”

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The sponsor responded that the SAPs for Studies DFN-CD-006 and DFN-CD-007 had not been submitted to the IND, and on August 24, 2018 the sponsor provided the two requested SAPs. Therefore, a full review of these SAPs will be conducted by the Division, and at that time, verification of the information discussed during this meeting about the SAP will be evaluated. We note that the SAPs for Studies DFN-CD-006 and DFN-CD-007 were not submitted prior to data lock of these studies.

Question 3: For Integrated Summary of Safety (ISS), Dr. Reddy's plans to pool the safety data from one Phase 2 double-blind efficacy and safety study (Study DFN-15-CD-002) and the two Phase 3 double-blind efficacy and safety studies (Study DFN-15-CD-006 and Study DFN-15-CD-007). The safety data generated from all the Phase 1 studies will be presented individually in clinical study reports. Does the Agency concur with this approach of pooling and submission of the safety data for DFN-15 in the ISS?

FDA Response to Question 3:
This question is premature. Please see our response to Question 2.

Discussion
There was no meeting discussion.

Question 4: For Integrated Summary of Efficacy (ISE), Dr. Reddy's plans to pool the efficacy data from one Phase 2 double-blind efficacy and safety study (Study DFN-15-CD-002) and the two Phase 3 double-blind efficacy and safety studies (Study DFN-15-CD-006 and Study DFN-15-CD-007). Does the Agency concur with this approach of pooling, analysis and submission of the efficacy data for DFN-15 in the ISE?

FDA Response to Question 4:
This question is premature. Please see our response to Question 2.

Discussion
There was no meeting discussion.

Question 5: The draft statistical analysis plans (SAPs) and mock tables, listings and figures (TLFs) for developing the ISS and the ISE are presented in Appendix 1 and Appendix 2 respectively. Does the Agency concur that the SAPs for the analyses and mock TLFs of the pooled datasets from the two Phase 3 double-blind studies (Study DFN-15-CD-006 and Study DFN-15-CD-007) and one Phase 2 double-blind efficacy and safety study (Study DFN-15-CD-002) of DFN-15 are appropriate for the ISS and the ISE?

FDA Response to Question 5:
This question is premature. Please see our response to Question 2.

Discussion
There was no meeting discussion.

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Question 6: As previously communicated with the Agency in the Agreed iPSP, a pediatric clinical study was to be initiated after the effectiveness of DFN-15 was established in adult patients with acute migraine. The pediatric study was expected to be initiated after the availability of topline data from the first DFN-15 clinical study in adults from the Phase 3 studies (study DFN-15-CD-006 and DFN-15-CD-007). However, the Sponsor now proposes to amend the agreed iPSP with revised timelines described below once the agency comments on the approaches described in Question 2 regarding the effectiveness of DFN-15 to treat migraine in adult.

- Estimated pediatric protocol submission date: within 4 months of obtaining formal approval of DFN-15's effectiveness in adults
- Estimated study initiation date: within 6 months of submission of the pediatric protocol
- Estimated final report submission date: within 4 years of initiation of the pediatric study

Does the agency concur with the proposal to amend the iPSP with revised timelines to conduct the pediatric study?

FDA Response to Question 6:
On face, it is reasonable to delay the pediatric studies until effectiveness is determined in adults. The exact timeline to be agreed upon will be a matter of review.

Discussion
There was no meeting discussion.

Question 7: Dr. Reddy's plans to submit CDISC compliant SDTM and ADaM datasets for the pivotal Phase 1 comparative BA study (DFN-15-CD-008), Phase 2 study (DFN-15-CD-002), and the two Phase 3 studies (DFN-15-CD-007 and DFN-15-CD-006). The datasets for the pilot PK studies conducted with earlier formulations of DFN-15 (prototype formulations of Celecoxib Oral Solution will not be included in the NDA. Does the Agency concur with this approach of not submitting the datasets for pilot studies using the 50 mg/mL prototype formulations of DFN-15 in the NDA?

FDA Response to Question 7:
This question is premature. Please see our response to Question 2.

Discussion
There was no meeting discussion.

Question 8: Dr. Reddy's does not plan to include copies of the published literature articles for clinical references in the NDA submission but will provide them upon request. Does the Agency concur with this approach?

Reference ID: 4600316

FDA Response to Question 8:
Although not required, we prefer that you include a copy of all the published literature articles referenced for ease of review at the time of NDA submission.

Discussion
There was no meeting discussion.

Question 9: Dr. Reddy's plans to include Case Report Forms (CRFs) of the subjects who experienced serious adverse events (SAEs) and subjects who discontinued the study due to AEs. Other CRFs will be available upon request. Does the Agency concur with this strategy of submission of CRFs?

FDA Response to Question 9:
This question is premature. Please see our response to Question 2.

Discussion
There was no meeting discussion.

Question 10: Dr. Reddy's relies on Celebrex as the Reference Listed Drug (RLD) for safety data. Celecoxib is not known to have human abuse potential, and in long term clinical use has not been associated with human abuse. Dr. Reddy's believes that the DFN-15 formulation does not enhance the likelihood of abuse potential as it does not lead to exposures differing from the RLD, and thinks that abuse potential assessment or consideration for scheduling is not warranted. Does the Agency concur that DFN-15 does not require additional abuse potential evaluation?

FDA Response to Question 10:
On face, we agree that additional abuse potential evaluations may not be necessary, but this will be a matter of review.

Discussion
There was no meeting discussion.

Additional Comments:

1. We note that a high fat meal resulted in reduction of DFN-15's C_{max} and AUC_{0-2h} by ~ half, as compared to the fasting state, after administration of the to-be-marketed DFN-15 formulation. Therefore, we remind you of our previous comment at the EOP2 meeting and recommend that you conduct a post hoc subgroup analysis for subjects who received DFN-15 in your pivotal studies under fed condition. You should stratify the analysis with regard to type of meal (e.g., high-fat or low fat, heavy vs. light meal) of food intake relative to dosing of your drug.

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2. We acknowledge that the finished product is tested for microbial content according to USP Chapters <61> and <62>. However, we note that the microbial limits for TAMC ([redacted] (b) (4) CFU/mL) and TYMC ([redacted] (b) (4) CFU/mL) are above the Agency's expectations for an aqueous oral solution. Therefore, the Agency recommends the TAMC and TYMC limits be revised to align with the suggested acceptance criteria of USP <1111> for nonsterile aqueous preparations for oral use.

3. Note that non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43. In order to control for the presence of BCC in your product you should consider the following:

   a. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

   b. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

      As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment. For more information, we refer you to Envir Microbiol 2011; 13(1):1-12 and J. Appl Microbiol 1997; 83(3):322-6

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2.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 19, 2018, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at
https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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.

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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.

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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.

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)).

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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.

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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*

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.

3.0 ATTACHMENTS AND HANDOUTS

The slides displayed by Dr. Reddy's Laboratories at the August 23, 2018, face to face meeting are appended to this letter.

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Attachment 1.

DNP Pre-NDA Meetings
General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.
8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder

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for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.

9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.

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5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units.
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
    - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
    - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
    - Pulse Rate: <60 bpm, >100 bpm

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- Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
- Temperature: >38.0 °C, <36.0 °C
- Respiratory rate: <12 breaths/min, > 20 breaths/min

6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   a) Age
   b) Sex
   c) Dates of screening, randomization and starting therapy
   d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   f) Prior medications and concomitant medications with dates of start and end
   g) Vital signs and laboratories, sorted by date, with reference ranges *
   h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
   i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
   j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
   k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

   Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

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CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address. A special Section of the Clinical Pharmacology Summary should identify and discuss the critical findings and issues and indicate how the unresolved issues are addressed.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies*)* and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

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2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

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2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

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Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and

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in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as

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metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for ≥ 90% of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m^2) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality

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of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?

Indicate whether Cmax and Cmin of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how

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much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both)) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, Cmax and t1/2 of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, Cmax and CL/F on

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Clcr for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, Cmax, tmax and t1/2 of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of Cmax, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

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2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to Km, controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the in vitro findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration

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range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for Ki, IC_{50} and Vmax for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/Ki ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default

Reference ID: 4600316

interval. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the

Reference ID: 4600326

clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on Cmax, AUC and Cmin of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in Cmax, AUC and Cmin than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?

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Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug

Reference ID: 4600326

of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at ≤ –20° C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

Applicable to therapeutic proteins only

2.9.5.6 What bioanalytical methods are used to assess therapeutic protein

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concentrations?
Briefly describe the methods and summarize the assay performance.

2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.8 What is the performance of the neutralizing assay(s)?

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Reference ID: 4202326

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/

ERIC P BASTINGS
09/13/2018

Reference ID: 4202326

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125585

MEETING MINUTES

Dr. Reddy's Laboratories, Inc.
Attention: Hari Nagaradona, Ph.D.
107 College Road East
Princeton, NJ 08540

Dear Dr. Nagaradona:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DFN-15 (celecoxib) oral solution.

We also refer to the meeting between representatives of your firm and the FDA on August 30, 2016. The purpose of the meeting was to discuss development of celecoxib oral solution for the treatment of migraine headaches for submission as a 505(b)(2) NDA.

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 Harold Sano, PharmD, Regulatory Project Manager at (301) 796-2429.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
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: B
Meeting Category: End of Phase 2

Meeting Date and Time: August 30, 2016
Meeting Location: 10903 New Hampshire Avenue
White Oak Building #22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: IND 125585
Product Name: DFN-15 (celecoxib) oral solution
Indication: Acute treatment of migraine with or without aura
Sponsor/Applicant Name: Dr. Reddy's Laboratories, Inc.

Meeting Chair: Billy Dunn, MD
Meeting Recorder: Harold Sano, PharmD

FDA ATTENDEES
Billy Dunn, MD, Director, Division of Neurology Products (DNP)
Heather Fitter, MD, Clinical Team Lead, DNP
Suhail Kasim, MD, Clinical Reviewer, DNP
Susan Daugherty, RN, Regulatory Project Manager, DNP
Harold Sano, PharmD, Regulatory Project Manager, DNP
Martha Heimann, PhD, Chemistry Team Lead, Office of Pharmaceutical Quality (OPQ)
Andrei Ponta, PhD, Chemistry Reviewer, OPQ
Xinning Yang, PhD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Kun Jin, PhD, Statistical Team Lead, Office of Biostatistics (OB)
Junshan Qiu, PhD, Statistical Reviewer, OB

SPONSOR ATTENDEES
Hari Nagaradona, PhD, Vice President and Global Head of Regulatory Affairs
Raghav Chari, PhD, Executive Vice President
Anil Namboodiripad, PhD, Senior Vice President, Drug Development
Sagar Munjal, MD, Senior Director/Head of Neurology Clinical Development and Medical Affairs
Elimor Brand-Schieber, PhD, Associate Director, Clinical Development-Neurology
D. Mallikarjuna Rao, PhD, Senior Director, Regulatory Affairs
Robert Hanes, MS, Director, CMC
Tarun Deshmukh, Manager, Regulatory Affairs

SPONSOR ATTENDEES BY TELEPHONE:
Balaji MR, MVSc, Director, Toxicology
Bijay Kumar Padhi, PhD, Associate Director, Formulations
Anirudh Gautam, MPharm, Senior Director, DMPK
Rajeev Raghuvanshi, PhD, Vice President, Global Head, CMC
(b) (4)

1.0 BACKGROUND

The requested meeting is an End of Phase 2 meeting to discuss further development of DNF-15 (celecoxib) oral solution, a nonsteroidal anti-inflammatory drug, for the treatment of migraine headache for submission as a 505(b)(2) NDA. DFN-15 as an oral solution is anticipated to provide faster onset of action in migraine patients. To support the 505(b)(2) NDA submission, the sponsor plans to conduct a single dose bioavailability study comparing DFN-15 with the reference product Celebrex and to conduct two Phase 3 double-blind, randomized, efficacy, and safety studies in patients with acute migraine (with or without aura).

FDA sent preliminary comments to Dr. Reddy's Laboratories Limited on August 24, 2016.

2. DISCUSSION

2.1. Regulatory Questions

Question 1: DRL plans to submit an NDA for DFN-15 (25 mg/ml) as a 505(b)(2) NDA that will include clinical data comparing the pharmacokinetics (PK) of DFN-15 to Celebrex 400 mg and two phase 3 pivotal efficacy and safety studies in acute migraneurs. DRL plans to rely on the Agency's findings of the safety for Celebrex 400 mg to establish the safety of DFN-15. Does the Agency agree that Celebrex 400 mg is an appropriate listed drug for DFN-15?

FDA Response to Regulatory Question 1:
The Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on Celebrex appears acceptable. For information for sponsors considering the submission of an application through the 505(b)(2) pathway, see the 505(b)(2) REGULATORY PATHWAY section in this document.

Meeting Discussion: There was no meeting discussion.

2.2. Chemistry Manufacturing and Controls (CMC) Questions

Question 2: (b) (4) genotoxic impurity arising from the manufacturing process of celecoxib. A study has been carried out by the drug substance manufacturer (b) (4) to verify and estimate (b) (4) levels by LC-MS/MS. The results of the study indicated that the level of (b) (4) is below the Limit of Quantitation (LOQ) (LOQ: (b) (4) ppm) in all the batches of drug substance tested. Hence, the

drug substance manufacturer has included (b) (4) levels in the final drug substance release specifications and will report the results for first batch of every year and multiple of 10th batch based on skip test methodology. DRL plans to request the vendor to perform analysis of (b) (4) content in a drug substance batch(s) for clinical/registration batches of DFN-15 and report the results in the Certificate of Analysis (COA). Subsequently, DRL will accept vendor's COA from the batches for commercial supplies based on their skip test methodology. Does the Agency concur with this approach?

FDA Response to CMC Question 2:
The overall approach is acceptable.

Meeting Discussion: There was no meeting discussion.

Question 3: (b) (4) (b) (4)

Meeting Discussion: There was no meeting discussion.

Question 4: In the "*Study May Proceed*" letter dated July 20, 2015, the Agency has recommended performing (b) (4) DRL is planning to perform these studies in one of the three registration batches of the drug product. Does the Agency agree with the proposed approach for (b) (4) studies on one registration batch for NDA submission?

FDA Response to CMC Question 4:
The overall approach is reasonable. As you prepare for the NDA submission, ensure that all stability studies are in line with ICH guidelines.

Meeting Discussion: There was no meeting discussion.

Question 5: In the "Study May Proceed" letter dated July 20, 2015, the Agency recommended including the droplet size as part of release and stability testing of the drug product, considering it a critical quality attributes and that could impact product performance. However, DRL would like to clarify that DFN-15 is a clear solution (b) (4) and monitor its droplet size during the stability studies for phase 3 clinical and registration batches. Does the Agency concur with the proposed method and determination procedure for the droplet size distribution of DFN-15?

FDA Response to CMC Question 5:
Drug product attributes should be linked to the clinically relevant counterparts (e.g., bioavailability). The proposed particle size method consists of (b) (4) . It is unclear whether the proposed method can be discriminatory after sample preparation. Provide data demonstrating that the laser diffraction method is discriminatory.

Meeting Discussion: There was no meeting discussion.

Question 6: DRL is proposing to use (b) (4) caps as a closure system for DFN-15. (b) (4) DRL proposes to use the (b) (4) caps for Phase 3 clinical supplies and for the to-be-marketed product of DFN-15. Does the Agency agree with this approach?

FDA Response to CMC Question 6:
The adequacy of the container closure system is a review issue. Ensure that the application contains enough information to show that the container closure system and its components are suitable for the intended use. This includes information demonstrating that the container closure system protects the dosage form adequately; is compatible with the dosage form; and is composed of materials that are considered safe for use with the dosage form and the route of administration. Since the drug product is a non-aqueous oral solution, perform an extractable/leachable study to confirm that the container closure system does not adversely impact the drug product. Additionally, ensure that the drug product cannot be contaminated by the migration of an ink or adhesive component. As you prepare for your submission, refer to the guidance for industry, "Container Closure Systems for Packaging Human Drugs and Biologics."

Meeting Discussion:
The sponsor asked about the type of information required for the submission of the NDA regarding the cap portion of the container/closure system. The Division indicated that an extractables study should be performed on the cap as the drug product formulation is a non-aqueous solution. Depending on the results of the extractables study, the leachable study may be omitted with adequate justification.

2.3. Nonclinical Questions

Question 7: The route of administration for DFN-15 is oral and DRL plans to rely on the Agency's findings of nonclinical safety for DFN-15 from the listed drug, Celebrex 400 mg for oral use. DFN-15 consists of generally used excipients for oral administration and no novel excipients are used in the formulation. However, DFN-15 formulation contains (b) (4)

Considering the extensive safety data for celecoxib and the availability of both human and nonclinical data for various excipients, including (b) (4), used in DFN-15, DRL believes that there are no systemic toxicity concerns with oral administration of the DFN-15 formulation and feels that no additional nonclinical studies are necessary to characterize the systemic toxicity of DFN-15 to support the 505(b)(2) NDA submission. Does the Agency concur with this approach?

FDA Response to NonClinical Question 7:
Based on the information provided, the amount of (b) (4) in the clinical formation may be acceptable; however, we ask that you provide the following information:

- If available, the intake (mg/day) of (b) (4) or its components (b) (4) at the maximum daily dose of approved products containing the excipient or its components.
- Copies of the references cited in support of the proposed amount of (b) (4) or its components in DFN-15.

A final determination as to the adequacy of the data will be a matter of review.

Meeting Discussion: There was no meeting discussion.

2.4. Clinical Pharmacology/Clinical Questions

In support of 505(b)(2) NDA submission, DRL plans to conduct:
(1) A Phase 1 bioavailability study comparing DFN-15 120 mg (celecoxib oral liquid 25 mg/mL) with the listed drug Celebrex 400 mg, and

(2) Two pivotal Phase 3, two-migraine episodes, double blind placebo-controlled randomized efficacy and safety study in patients with acute migraine with or without aura.

The clinical data from these studies will establish the pharmacokinetic profile of celecoxib delivered from DFN-15 relative to the listed drug and provide additional data to support the clinical efficacy, safety and tolerability profile of DFN-15. Details of study design and endpoints of these proposed studies are provided in Appendix 1 and Appendix 2, respectively.

Dose proportionality was observed in the first comparative bioavailability study in healthy volunteers conducted in the United States (US) for DFN-15 120 mg, 180 mg, and 240 mg (Study DFN-15-CD-003). However, no significant difference in dose-response was seen in a trial (Study DFN-15-CD-002) in patients with migraine headaches for the primary endpoint, pain freedom rate at 2 hours post-dose, between DFN-15 120 mg and 240 mg, indicating a ceiling effect (28.6% and 26.1% respectively) in acute migraineurs with or without aura. A similar ceiling effect was also reported in prior migraine studies that were conducted with rofecoxib, which found no significant differences between rofecoxib 25 mg and 50 mg for pain freedom rates at 2 hours. In two migraine studies, Trial 161 and Trial 162, the pain freedom rates at two hours were 19.9% and 26.2% for rofecoxib 25 mg; 23% and 26.6 % for rofecoxib 50 mg, respectively (Silberstein, 2004; Saper, 2006).

Therefore, DRL plans to conduct both the single-dose comparative bioavailability study and two pivotal phase 3 studies only with the 120 mg dose of DFN-15 (25 mg/mL).

Question 8: DRL proposes to conduct an open-label single dose comparative bioavailability study with the final to-be-marketed formulation of DFN-15, Celecoxib Oral Solution 120 mg (25 mg/mL) and Celebrex 400 mg in healthy subjects in a US population to support the 505(b)(2) NDA application. The total absorption (AUC) is reported to go up by 10% - 20% for Celebrex in fed state (Celebrex Package Insert). The plasma exposures (C_{max} and AUC) data for DFN-15 120 mg in both fasting and fed states will be determined in this study and are expected to be lower or in a similar range as compared to that of Celebrex 400 mg in the fed state. The protocol synopsis of this proposed study is presented in Appendix 1.

Does the Agency agree that the proposed study design is adequate to provide the necessary clinical bridge to the listed drug, Celebrex 400 mg (NDA 020998) to support the 505(b)(2) application and that no additional pharmacokinetic studies are needed for approval?

FDA Response to Clinical Pharmacology/Clinical Question 8:
On face, yes. We recommend you complete this study before initiation of the pivotal trials to ensure that the PK of celecoxib from your new formulation is consistent with your expectations. Include blood pressure measurements in your PK trial at baseline, T_{max}, and end of study.

Meeting Discussion: There was no meeting discussion.

Question 9: DRL plans to conduct two Phase 3 studies to generate substantial evidence for DFN-15 efficacy and safety in adult migraineurs. These studies will be randomized, double- blind studies and will be conducted in the US. Each study will randomize approximately 600 male and female migraine patients, aged 18-65 years, who experience 2 to 6 migraine attacks (with or without visual aura) per month. Patients will be randomized 1:1 to receive either DFN-15 or placebo, to treat one migraine attack (Attack 1), dosing the drug when the headache is at a moderate to severe pain level. Patients will then be re-randomized into a second double-blind period to treat another migraine attack (Attack 2), dosing at any pain level. Safety and tolerability will be determined throughout each study. The primary endpoint for both studies will be the proportion of subjects who are pain free at 2 hours post-dose with DFN-15 compared to placebo in the first treated attack (Attack 1). The protocol synopsis for these proposed Phase 3 studies is presented in Appendix 2.

Does the Agency concur if a statistically significant ($p < 0.05$) difference is observed between DFN-15 and placebo arm for the primary end point in both Phase 3 studies for the first period (Attack 1) that these studies will be considered adequate to support the NDA?

FDA Response to Clinical Pharmacology/Clinical Question 9:
We do not agree with your proposed primary endpoint for your Phase 3 trials. A primary endpoint that measures an effect on headache pain alone is not sufficient to obtain a claim for the acute treatment of migraine. You must demonstrate either an effect on 4 co-primary endpoints (pain, nausea, photophobia, and phonophobia) or on the co-primary endpoints of pain and the most bothersome migraine associated symptom (MBS) at 2 hours. Please refer to the guidance for industry, "Migraine: Developing Drugs for Acute Treatment (October, 2014)".

We have the following comments about your proposed Phase 3 protocols:

1. You stated that previous work with your product demonstrated no significant dose response on pain freedom at 2 hours when the 120 mg, 180 mg and 240 mg doses were studied. You provide this as your rationale for selecting the 120 mg dose for the Phase 3 trials. We understand this rationale but also recommend that you consider studying a lower dose in your efficacy trials due to the risk profile associated with NSAIDs.
2. You should include blood pressure measurements in a subset of patients treated with DFN-15 compared to placebo at baseline and all planned study visits.

Meeting Discussion: There was no meeting discussion.

Question 10: For the migraine Attack 1, subjects would be instructed to dose with study medication at the onset of moderate to severe pain and for migraine Attack 2 re-randomized subjects (1:1, DFN-15:placebo) will be instructed to dose with study medication at any pain level. Does the Agency concur that the data from Attack 2 can also be reported in the DFN-15 label if statistical significance ($p < 0.05$) is observed between DFN-15 and the placebo arm?

FDA Response to Clinical Pharmacology/Clinical Question 10:
On face, this may be acceptable. It is premature to determine which endpoints will be described in the label as this will be a matter of review based on the totality of evidence provided in the study reports.

Meeting Discussion: There was no meeting discussion.

Question 11: DRL intends to evaluate the effect of DFN-15 on the Most Bothersome Symptom (MBS) among nausea, photophobia, and phonophobia as one of the key secondary endpoints. The rationale and justification for sponsor proposal is described in Appendix 4.

11a. Does the Agency concur that the MBS can be used as a key secondary endpoint?

FDA Response to Question 11a:
No. Please see the response to Question 9.

Meeting Discussion: There was no meeting discussion.

11b: Does Agency concur with the approach to identifying the MBS just prior to dosing rather than identifying it at randomization?

FDA Response to Question 11b:
While we have no objection to your proposed approach, we are concerned that if patients are not required to record their MBS prior to randomization, they may have an opportunity to take the study medication for a migraine attack and then retrospectively select their MBS. The eDiary should include restrictions whereby a patient may not retrospectively enter their MBS after they enter study efficacy data. A copy of the proposed eDiary with eDiary guide should be submitted for review, as well as information about the training that study participants will receive regarding eDiary entries.

Meeting Discussion:
The Division discussed the following two possible approaches for capturing information on the most bothersome symptom (MBS):

1. Patients could select their MBS during the run in baseline period (prior to randomization) and treat the first migraine attack associated with their prospectively selected MBS at onset.
2. Alternatively, as proposed by the sponsor, patients could enter their MBS in the eDiary at the time of the index migraine attack, prior to dosing.

The Division emphasized that if the sponsor selected the second option above to record the MBS, it was critical that clear documentation be provided to demonstrate that the MBS was selected and recorded prior to investigational product administration. The sponsor asked if it could provide information about the eDiary and get feedback from the Division; this plan was acceptable to the Division.

Question 12: The recommended dose for Celebrex for acute pain is 400 mg initially followed by 200 mg more if needed for the first day. In clinical trials, acute dosing of Celebrex up to 800 mg once daily has been well tolerated. No change in platelet count was observed in healthy volunteers who received up to 800 mg Celebrex once daily and up to 600 mg Celebrex twice daily for 7 days (Celebrex Package Insert). Multiple doses of Celebrex 800 mg twice daily and 1200 mg twice daily, in healthy adults (non-fasting) yielded mean C_{max} values of 2694 ng/mL and 3668 ng/mL, respectively, on Day 1 and 3573 ng/mL and 5205 ng/mL, respectively, on Day 12. In addition, the safety of Celebrex 800 mg has been demonstrated with daily dosing in patients in a Familial Adenomatosis Polyposis study.

The C_{max} and AUC_{0-t} of celecoxib from Study DFN-15-CD-003 for a 120 mg dose of DFN-15 was reported to be 1061.91 ng/mL and 3059.68 ng*hr/mL, respectively.
The C_{max} and AUC for 120 mg of DFN-15 in both fasting and fed states are expected to be similar or less than Celebrex 400 mg in the fed state.

The proposed two Phase 3 studies will collect safety data in approximately 1200 patients with 2 migraine attacks. Does the Agency concur that no additional long term safety data is required for 120 mg dose of DFN-15 if the C_{max} of celecoxib from DFN-15 in both fasting and fed states is below or similar to Celebrex 400 mg in fed state?

FDA Response to Clinical Pharmacology/Clinical Question 12:
If the data from your proposed PK study demonstrate that the systemic exposure with your DFN-15 final oral solution is no greater than that with the RLD, it may be acceptable to rely on long-term safety data from the RLD to support the safety of your product.

Meeting Discussion: There was no meeting discussion.

Question 13: Does the Agency agree that the 3 planned clinical studies (comparative bioavailability study and 2 double-blind Phase 3 efficacy and safety studies) are adequate to support a 505(b)(2) application for DFN-15 for adult migraineurs and that no additional clinical studies are required for NDA filing?

FDA Response to Clinical Pharmacology/Clinical Question 13:
On face, your proposal appears reasonable. Whether additional clinical studies will be required is a matter of review.

Meeting Discussion: There was no meeting discussion.

Additional Comments

Statistics

- Without a detailed statistical analysis plan, the following comments are preliminary.
- Per the FDA migraine draft guidance, the proposed key secondary endpoint should be the co-primary endpoint. Please specify how you plan to test the co-primary endpoints with the control of overall type I error at the pre-specified level.
- Please clearly define the full analysis set population.
- Please provide your rationale for the proposed sample size.
- In general, we would expect that missing data in this migraine trial is minimal. Even though the last observation carried forward (LOCF) for handling missing data is not recommended, our expectation is that your plan for using LOCF will not impact the results dramatically if the amount of missing data is minimal.
- Please propose sensitivity analyses to evaluate potential deviations such as model assumptions, etc.
- Please plan to perform subgroup analyses on age, gender, and ethnicity.

Meeting Discussion:
The following statistical points were discussed during the meeting:

- The sponsor asked if it would be acceptable to test both co-primary endpoints at the 0.05 (two sided) level simultaneously and the Division agreed that this would be acceptable.
- The sponsor provided clarification that the full analysis population was defined as all randomized subjects who during the treatment period took at least one dose of study medication and have at least one post baseline efficacy time point assessment. The Division said this was acceptable.
- The sponsor agreed to provide the rationale for sample size calculation in the protocol.
- There was no specific discussion on missing data, but the Division commented that in migraine trials the expectation is that there would be very little missing data.
- Sensitivity analyses should focus on areas where variation may effect the primary analysis, e.g., differences in baseline MBS or handling of missing data.
- In subgroup analyses, age groups should be pre-classified based on the distribution of age among the target population.

Clinical Pharmacology

- We recommend that you ask patients to record the timing and type (e.g., high-fat or low-fat, heavy vs. light meal) of food intake relative to dosing of your drug and that you consider incorporating the collection of this information into the eDiary. This information will help evaluate the potential effect of food intake on the efficacy of your drug product.

Your study DFN-15-CD-005 demonstrated that a high fat meal reduced the Cmax and early exposure (AUC0-2hr) of celecoxib by 60% and 65%, respectively. Since efficacy is assessed in your proposed Phase 3 studies at the 2 hour time point, based on your previous study results from study DFN-15-CD-005, the intake of food may influence the efficacy results in the Phase 3 trials.

- We recommend that you record the concomitant use of drugs that increase gastric pH (e.g., proton pump inhibitors, H2 blockers, and antacids) because these drugs may have the potential to reduce celecoxib exposure. Per the approved label of Celebrex, co-administration of Celebrex with aluminum- and magnesium-containing antacids resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC.
- You should prohibit concomitant use of CYP2C9 inducers with celecoxib in the pivotal trials. Celecoxib is mainly metabolized by CYP2C9 and its exposure was significantly reduced by CYP2C9 inducers (Drug Metabol Drug Interact. 2003;19(4):287-95).
- We recommend that you exclude the CYP2D6 substrates with a narrow therapeutic index from the proposed Phase 3 studies. Celecoxib is an inhibitor of CYP2D6 and was reported to increase the exposure of CYP2D6 substrates in humans (Clin Pharmacol Ther. 2003 Aug;74(2):130-7) .

Meeting Discussion: There was no meeting discussion.

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

Meeting Discussion:
The sponsor enquired if the suicidality assessment could be waived in the two Phase 3 trials. The Division stated that prospective assessment for suicidality would be required and explained that the assessment does not have to be complex or burdensome. The Division invited the sponsor to include in the protocol a brief clinical screening assessment consistent with routine clinical practice.

3.0 OTHER IMPORTANT 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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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 PSP, including a PSP 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/U CM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting

mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

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

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors 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), sponsors 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).

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 draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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, in part, 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, in part, 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., trade name(s)).

If you intend to rely, in part, 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 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also

include that information in the cover letter for your marketing 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 efficacy 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 X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
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.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

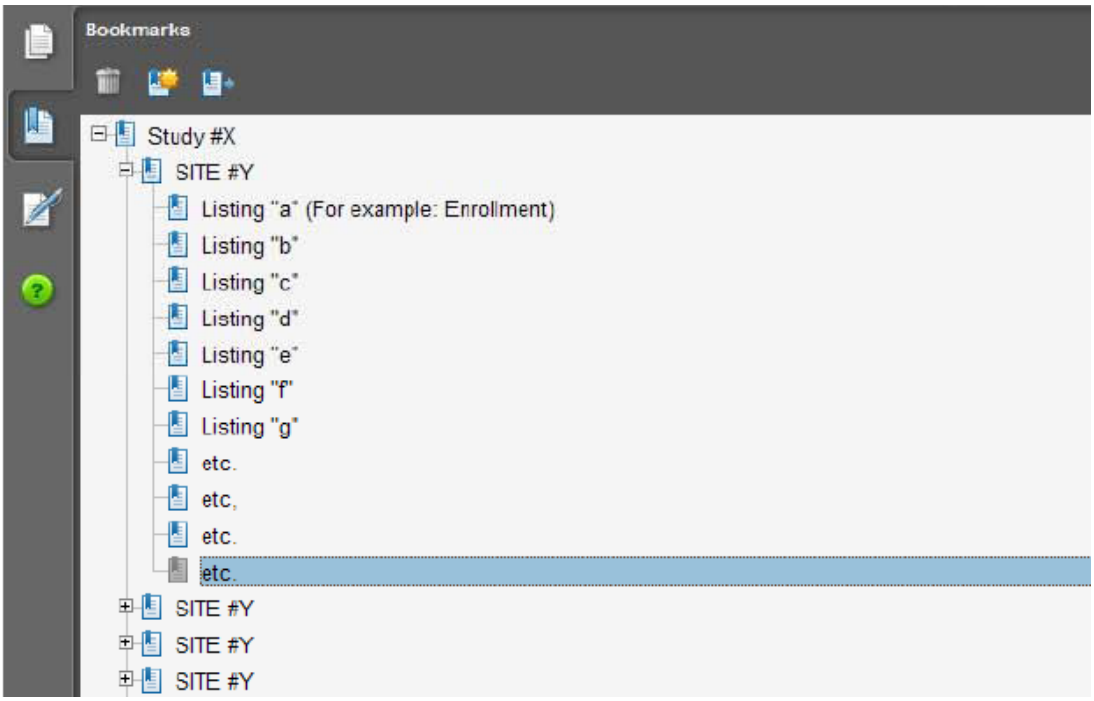
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

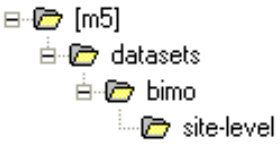
A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-	STF File Tag	Used For	Allowable

NDA Request Item[1]			File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Handout provided by the sponsor attached.

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

WILLIAM H Dunn
09/22/2016