CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210884Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108,088

REVISED MEETING MINUTES

Dr. Reddy's Laboratories, Inc.
Attention: Hari Nagaradona, PhD
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-02 (sumatriptan) nasal spray.

We also refer to the teleconference between representatives of your firm and the FDA on December 13, 2017. The purpose of the meeting was to discuss your planned application.

A copy of the revised official minutes of the meeting has been revised as per your January 16, 2018 request, and is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

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:
Revised Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**B**
Meeting Category:	**Pre-NDA**
Meeting Date:	**December 13, 2017**
Meeting Location:	**FDA White Oak**
Application Number:	**IND 108,088**
Product Name:	**DFN-02 (sumatriptan nasal spray)**
Indication:	**migraine**
Sponsor/Applicant Name:	**Dr. Reddy's Laboratories**
Meeting Chair:	**Eric Bastings, MD**
Meeting Recorder:	**Lana Chen, RPh**

FDA ATTENDEES

Division of Neurology Products
Eric Bastings, MD, Deputy Director
Heather Fitter, MD, Clinical Team Leader
Laura Jawidzik, MD, Clinical Reviewer
Mariam Ahmed, PhD, Clinical Pharmacology Reviewer
Martha Heimann, PhD, CMC Lead
Thomas Wong, PhD, Chemistry Reviewer
John McMichael, ICC Team Lead, CDRH/ODE/DAGRID/GHDB
Marc Neubauer, Reviewer, CDRH/ODE/DAGRID/GHDB
Lana Chen, RPh, Project Manager

SPONSOR ATTENDEES

Dr. Reddy's Laboratories
Hari Nagaradona, PhD, Vice President & Global Head of Regulatory Affairs
Anil Namboodiripad, PhD, Senior Vice President & Head of Development & Commercialization, External R&D
Rajeev Raghuvanshi, PhD, Senior Vice President and Global Head – CMC, Differentiated Formulations R & D
Sagar Munjal, MD, MS, Vice President/Head of Clinical Development, Operations & Medical Affairs
(b) (4)
D. Mallikarjuna Rao, PhD, Senior Director, Regulatory Affairs
Balaji, MR, MVSc, Senior Director - Nonclinical Development & Toxicology
Anirudh Gautam, MPharm, Senior Director, DMPK

Sumera Hasham, PhD, MBA, Senior Director and Head Portfolio Strategy, Global Marketing and External R&D
Elimor Brand-Schieber, PhD, Director, Clinical Development – Neurology
Javier Gonzalez, Director, Packaging Development & Design
Rajesh Kumar, PhD, Senior Director, Product Development & CMC
Rajesh Ramesh Patil, PhD, Associate Director, Research & Development
Joyce Zhao, Associate Director, Device Engineering
Reena Zade, MS, Associate Director, Regulatory Affairs
Tarun Deshmukh, MPharm, Associate Director, Regulatory Affairs
Kevin Carey, Director, Project Management
Girish Karanth, Director, Research & Development
Ravi Prasad Rao,Director, Analytical Research & Development
Subbareddy Inta, Director, Quality Assurance, Proprietary Products

DISCUSSION

Regulatory Questions

DRL intends to submit a NDA for DFN-02 according to 505(b)(2) regulatory pathway. Based on the Agency's feedback provided in End of Phase 2 (EOP-2) meeting minutes dated December 04, 2013, DRL has used Imitrex (sumatriptan succinate) SC injection as the Listed Drug and relying on Agency's previous findings of safety and effectiveness for Imitrex subcutaneous (SC) injection, to support this NDA.

Question 1
In a pivotal comparative bioavailability study, the plasma concentration of sumatriptan from DFN-02 was shown to be bracketed between Imitrex 4 mg and 6 mg subcutaneous injections. DRL plans to rely on the approved product labeling of Imitrex injection and the Agency's previous findings of the efficacy and safety of Imitrex Injection for the establishment of efficacy and safety for DFN-02. Based on EOP 2 meeting discussion, the proposed indications for DFN-02 are for 1) the acute treatment of migraine with or without aura in adults and (b) (4) (b) (4) which are similar to the Listed Drug. Does the Agency agree that these indications will be applicable to DFN-02?

FDA Response: The determination of your final indication will be made during the review of your NDA. On face, your proposed indication for migraine appears acceptable. (b) (4) (b) (4)

Meeting Discussion: None.

Chemistry Manufacturing and Control Questions

Question 2
DDM is a novel excipient used in the manufacturing of DFN-02. DRL will reference the Type IV DMF # (b) (4) through a letter of authorization for chemistry, manufacturing and control information. The specifications and certificate of analysis for batches of DDM used in the nonclinical and registration/clinical batches of DFN-02 will be provided in Section 3.2.P.4.6 of the NDA. The proposed specifications of DDM for commercial batches of DFN-02 will remain same as that used for the clinical and registration batches. Does the Agency concur with the specifications for the novel excipient, DDM used in the DFN-02 formulation?

FDA Response:
On face, the proposed specifications appear reasonable. However, a final determination will be made during the NDA review.

Meeting Discussion: None.

Question 3
DFN-02 is a single-dose disposable drug-device combination product. The DFN-02 nasal spray device components were designed and manufactured by (b) (4) and all relevant device information will be included in (b) (4) DMF # (b) (4) (b) (4) is currently in the process of including a specific DFN-02 subsection to their established DMF with all their device constituent design control documents. The corresponding letter of authorization will be submitted in the DFN-02 NDA. In addition to information on container closure system, DRL is proposing to include following information in Section 3.2.P.7 of DFN-02 NDA:

- Sequence of Operation of the final assembled product (combination product)
- List of standards used during the device development
- Design Verification report
- Biocompatibility report
- Shipping test report
- Human Factors Validation Study report
- Updated user-risk analysis and mitigation (application FMEA)
- Compliance statements as per 21 CFR 820.20

Does the agency agree with the proposed contents of Section 3.2.P.7 in DFN-02 NDA are adequate for this drug-device combination product?

FDA Response:
We recommend you refer to the eCTD Technical Conformance Guide published in September 2016 when determining the location of the information within your submission. (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf)

HF Validation Reports should be placed in m5.3.5.4. (other study reports) and not in m3.

Meeting Discussion: None.

Question 4

DRL has initially described the device used for DFN-02 as a container closure system in the IND. However, based on learnings from other products, DRL changed its approach during product development process and considered DFN-02 as a drug-device combination product. The available device functional data obtained from the three registration batches (initial release and stability at accelerated and long term conditions) was used to satisfy the functional requirements for Design Verification (DV) for this drug-device combination product. In addition, (b) (4) the manufacturer of the device, performed the design verification (b) (4). All test parameters evaluated were in alignment with the FDA Guidance ("Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation", 2002). Does the Agency agree with this Design Verification strategy for DFN-02?

FDA Response:

In addition to the information you proposed to submit, provide the following to support your nasal spray device:

1. A complete and detailed description of your device constituent design and delivery system, including any features and functionalities unique to your device. This should also include engineering drawings and detailed descriptions of the individual device constituent components.

2. A complete and detailed device constituent design requirements and specifications document, including design inputs and outputs in accordance with 21 CFR 820.30 design controls. Ensure that you clearly describe the acceptability of your design control inputs within the context of the intended use of your combination product. Be sure to identify the essential performance requirements of your device. The essential performance requirements of any device constituent parts are the design outputs necessary for your device constituent to safely and effectively achieve the product's intended use. The essential performance requirements should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, and design of the constituent parts of the combination product. Your design requirements and essential performance requirements should consider the desired level of reliability of the product and level of risk associated with failure to meet the essential performance requirements.

For nasal sprays, we expect the essential performance requirements to include, at a minimum, the following:

- Pump Delivery (Spray Weight)
- Spray Pattern and Plume Geometry Shape
- Spray Content Uniformity (SCU)
- Droplet / Particle Size Distribution
- Actuation Force

Please refer to the FDA Guidance titled Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation issued in July 2002 (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf) for more details.

3. Stability and shelf-life testing. You should provide documentation that ensures the final finished combination product maintains its essential performance requirements up to the labeled date of expiry.

4. Lot release specifications. Provide the lot release specifications associated with the device constituents of the combination product, including all essential performance requirements.

5. It is recommended that a traceability matrix is provided to ensure each design requirement has been adequately verified and validated. The following is an example traceability matrix for the essential performance requirements of the device constituent as a summary of the testing completed to support the device constituents of the combination product:

Essential Performance Requirement	**Specification**	**Verification**	**Validation**	**Shelf Life / Stability (Y/N)**	**Shipping / Transportation (Y/N)**	**Lot Release Testing (Y/N)**

Meeting Discussion: The sponsor asked if it was necessary to define and verify all the essential performance requirements noted by CDRH; in particular, the spray content uniformity, plume geometry shape, and actuation force. For spray content uniformity, the sponsor stated they have tested this parameter only during the release of registration batches and not during the stability testing, as per prior request for guidance discussion with the Agency. The sponsor proposed to follow the same approach for commercial batches. FDA responded that this proposal is acceptable. Regarding plume geometry, FDA stated that historically this has not been required for the drug product specifications; this test attribute is normally evaluated in the product/device developmental stage. The sponsor confirmed that plume geometry was conducted during development and release of registration batches. The sponsor confirmed that plume geometry data will be included in the Design Verification report as part of NDA submission.

The sponsor stated that for actuation force, they have stability samples that are 36 months aged (real time testing), and they wanted to know whether it is acceptable for Design Verification to perform actuation force testing on these samples, and not on samples that have been aged for earlier time periods (i.e. 12 months, 24 months, etc.). FDA responded that the proposal is acceptable. The sponsor confirmed that actuation force data will be included in the Design Verification report as part of NDA submission. In addition, the sponsor wanted to know if it is acceptable to perform actuation force testing only at incoming inspection for the release of the device components and not as part of commercial product release and stability testing. FDA responded that the proposal is acceptable.

(b) (4)

Question 5
The proposed specifications for "to-be-marketed product" are based on USP monograph of Sumatriptan Nasal Spray, FDA Guidance for Industry "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation," data generated by DRL on DFN-02 to date and the Agency's recommendations provided in the Advice letter dated April 23, 2014. Does the Agency concur with the proposed drug product specifications for DFN-02?

FDA Response:

In addition to the information you propose to provide, you should include complete design verification documentation. Verification testing documentation may include summary test results of established test methods for the product (e.g., recognized consensus standards, FDA Guidance, etc.) or complete verification test reports for unique or unrecognized test methods. All verification testing should be directly traced to the design requirements of the device. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should conduct testing to verify the essential performance requirements of the combination product with the to-be-marketed version of the device constituent and the intended biologic/drug product; however, if you plan to rely on verification testing conducted with a different test fluid be sure to provide a scientific rationale for the acceptability of the test fluid as a surrogate for the intended biologic/drug product (i.e., fluid characteristics, viscosity, etc.). Valid justifications for any test results not being able to pass its acceptance criteria should be provided, if applicable. Furthermore, you should utilize a sufficient number of device constituent test samples that will be statistically relevant for your performance testing.

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

Meeting Discussion: None.

Question 6
DRL has performed extractable and leachable study on DFN-02 device components in accordance to the USFDA guidance for industry "Nasal Spray and Inhalation Solution, Suspension, and Spray

Drug Products — Chemistry, Manufacturing, and Controls Documentation" July 2002. Extractables study was performed using primary packaging components (b) (4) and also parts of device (b) (4) that come in contact with drug formulation during actuation. Leachable analysis for DFN-02 was initially performed using stability samples stored at 40°C and 75% RH for 6 months to identify the possible leachable compounds. Further, the stability samples of three registration batches at accelerated (40°C and 75% RH) and long term storage conditions (25°C and 60% RH) were monitored for three leachables as described in Section 10.2.6 of this information package. Does agency agree with this approach?

FDA Response:
Yes, pending review of the data provided in the NDA.

Meeting Discussion: None.

Nonclinical Questions

Question 7
The nonclinical safety of DFN-02 is supported by a battery of studies conducted by DRL to support clinical trials and the NDA. In addition, DRL will also reference the safety data provided in the Type V DMF # (b) (4) in support of DDM safety. All the nonclinical safety studies were aimed to evaluate the local tolerance, systemic toxicity and systemic exposure of sumatriptan, and DDM used in the DFN-02 formulation. DRL has completed the in-life phase of a 2-year intranasal carcinogenicity study of DDM alone at 4 dose levels in rats. The final study report will be submitted along with the NDA. Apart from these studies, DRL is also relying on the Agency's previous findings of the safety and efficacy of the Imitrex SC injection to support the NDA.
The Agency had advised during the End-of-Phase 2 meeting (Meeting Minutes dated December 04, 2013) that as long as the systemic exposure of DDM in humans has been demonstrated to be low (b) (4) ng•hr/mL), the reproductive and developmental toxicity testing for DDM are not necessary. DRL confirms that the plasma levels of DDM are low (b) (4) ng•hr/mL) in both pilot (DFN-02-CD-008) and pivotal (DFN-02-CD-009) pharmacokinetic studies. Hence, DRL is not planning to perform reproductive and developmental toxicity studies.
All the required nonclinical studies as per relevant guidelines have been completed to support nonclinical safety of DFN-02. Does the Agency agree that the nonclinical program completed for DFN-02 is adequate to support the NDA submission and no additional studies are required?

FDA Response: As described in the briefing document, the nonclinical studies conducted for DFN-02 appear sufficient to support submission of an NDA.

Meeting Discussion: None.

Clinical Questions

Question 8
DRL does not plan to provide copies of the published literature articles for clinical references as part of the NDA submission but will provide them upon request. Does the Agency concur with this approach?

FDA Response: 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 should include copies 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)). You also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. If you provide literature references in accordance with the 505(b)(2) requirements, we recommend that you provide hyperlinks to those references cited in your application.

If the published studies are not necessary to support approval, providing copies in the NDA submission is not required, but recommended.

Meeting Discussion: None.

Question 9
DRL plans to pool safety data from the double-blind Phase 2 efficacy and safety study (DFN-02-CD-012) and the open-label Phase 3 safety study (DFP-02-CD-010) for the Integrated Summary of Safety (ISS) section in the NDA. The safety data generated in all Phase 1 studies will be presented individually in clinical study reports. Does the Agency concur with this approach of pooling, analysis and submission of safety data for DFN-02 in ISS?

FDA Response:
You may pool the safety data from the Phase 2 and Phase 3 study. However, you should still provide safety analyses of the controlled portion of the study as proposed in the ISS. For ease of review, please provide integrated datasets for studies DFN-02-CD-010 and DFN-02-CD-012.

Meeting Discussion:
FDA suggested that the following safety pools be evaluated in the ISS: 1) the double-blind placebo-controlled trial, including patients that treated a migraine with a single dose of IP, 2) the-double blind placebo-controlled trial, including patients that treated a single migraine with two doses of IP, 3) the double-blind placebo controlled trial, including all patients that received any number of IP, 4) the open-label long-term safety study without a comparator group. The long term extension trial will be used to evaluate general safety, but more importantly to evaluate local nasal toxicity or any adverse events (AEs) of special interest, and 5) the all treated group that will include the double-blind placebo-controlled trial and the open-label safety study. This will only include one group (active treatment), and will report on rates of AEs seen in this trial. The ISS should describe how the rate of AEs seen in the open-label trial compares to that seen in the controlled trial. This all treated grouping can provide information about the relationship of an AE to time in study or number of doses received.

Question 10
The draft statistical analysis plans (SAPs) and mock up tables, listings and figures (TLFs) for developing the Integrated Summary of Safety (ISS) are included in Appendix 1 of the information package. Does the Agency concur that the SAP for the analysis and mock up TLFs of the pooled datasets from the double-blind Phase 2 efficacy and safety study (DFN-02-CD-012) and the open-label Phase 3 safety study (DFP-02-CD-010) of DFN-02 are appropriate for ISS?

FDA Response: Your proposal for the ISS appears adequate.

Meeting Discussion: None.

Question 11
DRL plans to include Case Report Forms (CRFs) of the subjects who experienced serious adverse events (SAE), severe adverse events and subjects who discontinued the study due to AE's. Other CRFs will be available upon request. Does the Agency concur with this strategy of submission of CRFs?

FDA Response: CRFs should also be provided for AEs of special interest. You should also provide narratives for all deaths, SAEs, discontinuations due to AEs, and AEs of special interest. Please see below for the recommended content of the narratives.

Meeting Discussion: The sponsor clarified that there were no pre-specified AEs of special interest. The sponsor also clarified that there were very few discontinuations (10 total). Five were due to serious adverse events, and five were due to other AEs.

NDA Format and Content

Question 12
Based on earlier communication from the agency (End-of-Phase 2 meeting minutes dated December 04, 2013), DFN-02 does not trigger PREA. DRL will submit a formal pediatric waiver request (Module 1.9) in the NDA. Does the Agency concur with proposed plan?

FDA Response: We agree that your product does not trigger PREA. For that reason, a waiver is not required.

Meeting Discussion: None.

Question 13
DRL plans to submit CDISC compliant SDTM and ADaM datasets for the pivotal Phase 1 comparative BA study (DFP-02-CD-009), Phase 2 efficacy and safety study (DFN-02-CD-012) and Phase 3 safety study (DFP-02-CD-010). The datasets for pilot PK studies (studies 1756/09, 1932/09, 1931/09, 2010/10, 2419/11 and DFN-02-CD-008) conducted with prototype formulations of DFN-02

will not be provided as part of NDA. Does the Agency concur with this approach of not submitting the datasets for pilot studies with prototype formulation of DFN-02 in the NDA?

FDA Response: On face, your proposal appears adequate.

Meeting Discussion: None.

Question 14
All the nonclinical studies conducted with DFN-02 were initiated before December 17, 2016. Therefore, DRL plans to submit trial summary (TS) dataset (ts.xpt) for nonclinical repeated dose toxicology and carcinogenicity studies, which includes the study start date in the form of TSPARMCD = STSTDTC and TSVAL= "yyyy-mm-dd. In addition, an electronic dataset of tumor findings (tumor.xpt) will be submitted for the carcinogenicity study along with the TS dataset. Does the Agency agree with the proposed plan for submission of nonclinical datasets for NDA?

FDA Response: Your plan for submission of nonclinical datasets appears acceptable.

Meeting Discussion: None.

Contents of Labeling

Question 15
As per the End-of-Phase 2 meeting minutes dated December 04, 2013, the bioavailability of sumatriptan from DFN-02 is demonstrated to be bracketed between Imitrex 4 mg and 6 mg SC injections in pivotal comparative bioavailability study (Study DFN-02-CD-009) and the long-term safety in migraine patients has been established in the Phase 3 study (DFP-02-CD-010). Efficacy of DFN-02 in migraine patients has also been demonstrated in the Phase 2 study DFN-02-CD-012. DRL plans to submit draft labeling for DFN-02 in 505(b)(2) NDA by relying on the currently approved Imitrex SC injection labeling and based on clinical pharmacokinetic results obtained in pivotal comparative bioavailability study. In addition, DRL proposes to (b) (4) (b) (4) (b) (4) e

FDA Response: It is premature to discuss the contents of labeling.

Additional comments:

1. The patient narrative requested in the response to Question 11 should include the following information:

- Patient age and gender
- Adverse event onset and stop dates (presented as relative Study Day number)
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Any abnormal vital sign measurements
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by available clinical data

- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

2. 2. From a technical standpoint, the tentative table of contents format for the planned NDA is acceptable. However, please see additional comments below.

- Include the sequence number and/or date of submission on the leaf title of the cover letter and form so that reviewers can quickly identify each submission form

- The leaf title of the cross-reference document (1.4.4.) should include the application number (e.g. cross reference from NDA123456)

3. The sponsor's options for cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

- To use the first option (i.e. placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (paper and/or non- eCTD format) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document along with a hypertext link to the location of the information, when possible.
- To use the second option (cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. xlink:href="../../**ind900000**/0009/m2/24-nonclin-over/nonclinical-overview.pdf">). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to bla-103796-QOS or something similar). The cross-reference information in the leaf title allows the reviewer to know that the document resides in another application.

4. Prior to using cross application linking in an application, it is recommended that you submit an "eCTD cross application links" sample, to ensure successful use of cross application links.
   To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at:-
   http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

- If possible, include "SPL" in the leaf title of the SPL document
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6., should be provided in tabular format and linked to the referenced studies in m5.
- Make sure "BIMO" is included in the study tagging file (STF) of the BIMO study in m5.3.5.4 and all leaf title of the BIMO document(s), should also include "BIMO" (e.g. BIMO-study-report or "BIMO-protocol").

Meeting Discussion: None.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 5, 2017, 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.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

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

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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.

SECURE EMAIL COMMUNICATIONS

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

505(b)(2) REGULATORY PATHWAY

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

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

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

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and

effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

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

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

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

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

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

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.

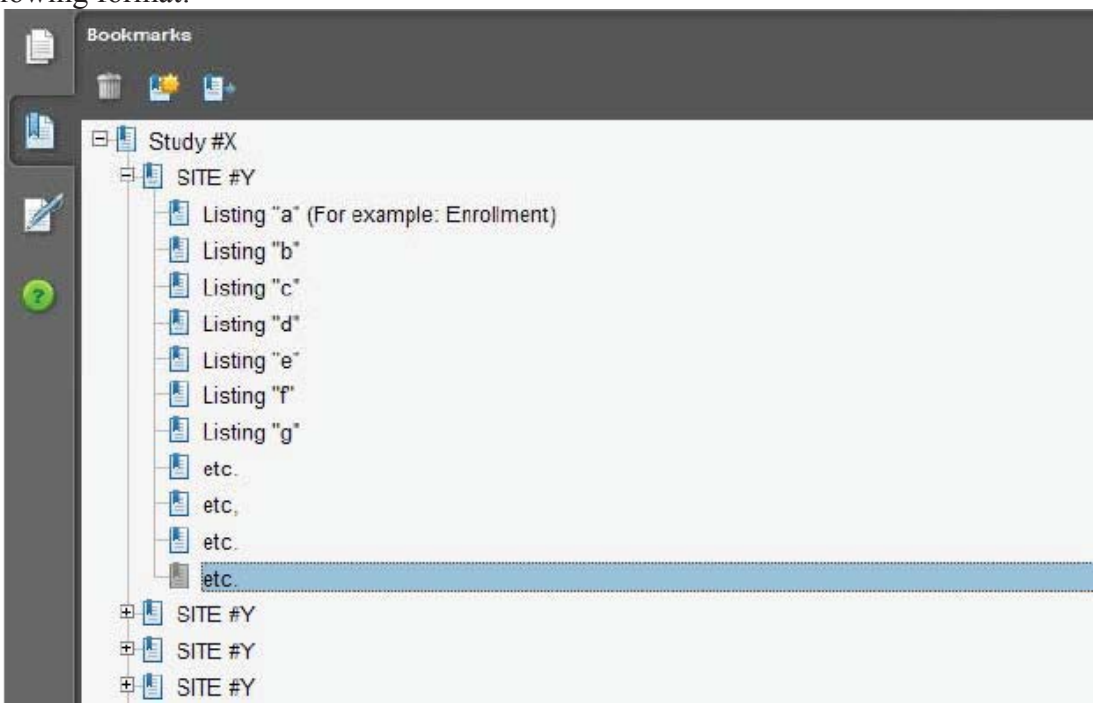
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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-NDA Request Item[1]	STF File Tag	Used For	Allowable 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

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.

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

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

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

/s/

ERIC P BASTINGS
03/16/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108,088

MEETING MINUTES

Leslie Harris, PhD, RAC
Dr. Reddy's Laboratories, Inc.
200 Somerset Corporate Blvd
7th Floor
Bridgewater, NJ 08807

Dear Dr. Harris:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DFP-02 (sumatriptan) nasal spray.

We also refer to the meeting between representatives of your firm and the FDA on November 5, 2013. The purpose of the meeting was to discuss your End of Phase 2 meeting package.

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 Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM OF MEETING MINUTES

Meeting Type: **B**
Meeting Category: **End of Phase 2**

Meeting Date: **November 5, 2013**
Meeting Location: **FDA White Oak**

Application Number: **IND 108,088**
Product Name: **DFP-02 (sumatriptan nasal spray)**
Indication: **Migraine**
Sponsor/Applicant Name: **Dr. Reddy's Laboratories**

Meeting Chair: **Eric Bastings, MD, Acting Director**
Meeting Recorder: **Lana Chen, RPh, Project Manager**

Division of Neurology Products
Eric Bastings, MD, Deputy Director
Nushin Todd, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Donald Charles Thompson, PhD, Toxicologist
Martha Heimann, PhD, Pharmaceutical Assessment Lead
Akm Khairuzzaman, PhD, Chemistry Reviewer
Andre Jackson, PhD, Clinical Pharmacology Reviewer
Hao Zhu, PhD, Clinical Pharmacology Team Leader
Lana Chen, RPh, Project Manager

Quynh Nhu Nguyen, Combination Products Human Factors Specialists, CDRH,
Human Factors Premarket Evaluation Team
Julie Villanueva Neshiewat, PharmD, Safety Evaluator,
Division of Medication Error Prevention and Analysis (DMEPA)
Irene Chan, PharmD, Safety Team Leader, DMEPA
Ermias Zerislassie, OSE Project Manager

SPONSOR ATTENDEES

Attendance: in person

Dr. Reddy's Laboratories (DRL)
Leslie Harris, PhD, RAC Director, Regulatory Affairs, Proprietary Products
Kent Allenby, MD, FACP Vice President, Drug Development, Proprietary Products
Sagar Munjal, MD, MS Director, Clinical Development, Proprietary Products

Raghav Chari, PhD Executive Vice President, Proprietary Products
Anil Namboodiripad, PhD Vice President, Corporate Development, Proprietary Products
Balaji MR Director, Safety and Toxicology, Proprietary Products
Rajeev Raghuvanshi, PhD Vice President, Oral/Nasal Formulations, Proprietary Products
Vishwavijay Singh Associate Director, Project Management, External R&D and Global Marketing
(b) (4)

Attendance; via teleconference
Mary Hilgart, MS, PMP Director Project Management, Proprietary Products DRL
D. Mallikarjuna Rao, PhD Director Regulatory Affairs, Proprietary Products DRL
(b) (4)

DISCUSSION

Regulatory/Clinical Questions

Question 1: DFP-02 is being developed for submission as a 505(b)(2) NDA that will include data comparing the pharmacokinetics (PK) of DFP-02 nasal spray to Imitrex (sumatriptan succinate) Injection 4 mg and 6 mg (NDA 020080) in healthy adult subjects. DRL plans to rely on the Imitrex approved product labeling and the Agency's previous findings of the efficacy and safety of Imitrex Injection 4 mg and 6 mg for the establishment of safety and efficacy for this product. Does the Agency agree that these are appropriate listed drugs for DFP-02?

FDA Preliminary Comments:
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 Imitrex Injection appears acceptable.

Meeting Discussion:
None.

Question 2: The proposed indications for DFP-02 are for 1) the acute treatment of migraine with or without aura in adults and 2) (b) (4) Does the Agency agree that these are appropriate indications?

FDA Preliminary Comments:
We agree.

Meeting Discussion:
None.

Clinical Pharmacology Questions

Question 3: DRL proposes to conduct a single pivotal comparative bioavailability (BA) study in healthy subjects to support the 505(b)(2) NDA application for DFP-02 nasal spray, entitled " A Randomized, Three-Way Cross-Over Study to Compare DFP-02 10 mg and Subcutaneous Sumatriptan Pharmacokinetics (4 mg and 6 mg), Safety and Tolerability in Healthy Adult Subjects Under the Fasted Condition (DFP-02-CD-009)". Does the Agency agree that the proposed study design is adequate to provide the necessary bridge to Imitrex Injection 4 mg and 6 mg for the 505(b)(2) application using Imitrex (NDA 020080) and that no further pharmacokinetic studies will be needed for approval?

FDA Preliminary Comments:
The proposed study appears to be reasonable.

Meeting Discussion:
None.

Question 4: In the comparative BA study, bioavailability of DFP-02 (A) will be concluded to be bracketed between that of Imitrex 6 mg (B) and Imitrex 4 mg (C) if the upper bound of the 90% confidence interval (CI) of the geometric mean ratio of A/B for Cmax, AUC 0-t and AUC 0-inf is less than 125% and the lower bound of 90% CI of the geometric mean ratio of A/C for Cmax, AUC 0-t and AUC 0-inf is higher than 80%. Does the Agency agree that if the bioavailability of DFP-02 is shown to be bracketed between Imitrex 6 mg and Imitrex 4 mg, then DFP-02 can rely on Imitrex 6 mg and 4 mg for the establishment of the safety and efficacy of DFP-02?

FDA Preliminary Comments:
We agree that if the bioavailability of DFP-02 is shown to be bracketed between Imitrex 6 mg and Imitrex 4 mg, then DFP-02 can rely on Imitrex 6 mg and 4 mg for the establishment of the safety and efficacy of DFP-02. However, the results will not support the claim of (b) (4)

Meeting Discussion:
None.

Clinical Questions

Question 5: In addition to the comparative BA study, DRL proposes to conduct a single open-label safety study in at least 100 adult patients with a diagnosis of acute migraine headache with or without aura who, on average, experience 2-6 migraines per month, who will be treated over a period of 6 months. Does the Agency agree to the proposed open-label safety study design?

FDA Preliminary Comments:
We agree. At a minimum, we require that you provide safety data on 100 patients who treated an average of at least 2 migraines per month, for a minimum of 6 months.

Meeting Discussion:
None.

Question 6: Does the Agency agree that the 2 planned clinical studies (comparative BA study and open-label safety study) are adequate to support the 505(b)(2) application for DFP-02 and that no additional clinical studies are necessary?

FDA Preliminary Comments:
Please refer to our comments under Human Factors and the 505(b)(2) Regulatory Pathway at the end of this document. Please also note that the Division will not allow language in labeling that suggests a second dose of medication at 1 hour is safe and effective unless there is data to support it. If you would like to pursue repeat dosing claim in labeling, your trial would also need to evaluate the safety and efficacy of a second dose in subjects with an inadequate response to the first dose (for example, by re-randomizing patients who had an inadequate response to drug or placebo).

Meeting Discussion:
The sponsor clarified that labeling information for their product will be consistent with the language used for the Imitrex labels.

Question 7: Based on the proposed indication of treatment of acute migraine in adults and the results of pediatric studies presented in the Imitrex labeling, DRL intends to request a waiver for the assessment of DFP-02 in a pediatric population. Does the Agency agree with the proposal of a waiver for pediatric studies?

FDA Preliminary Comments:
Your product does not appear to trigger PREA, therefore, you would not be required to request a waiver for pediatric studies. Please also refer to our comments under PREA Requirements.

Meeting Discussion:
None.

Nonclinical Questions

Question 8: DRL believes the nonclinical studies performed to date with DFP-02, along with the DDM studies included in the Type II DMF, support the nonclinical safety of DFP-02 for NDA filing, and pending FDA review, for NDA approval of DFP-02 (Sumatriptan Nasal Spray). Does the Agency concur that the nonclinical toxicology program described in this briefing document is sufficient to characterize the local and systemic safety of both the excipient DDM in DFP-02 and DFP-02 for the 505(b)(2) NDA, and that no additional nonclinical studies are needed to support NDA filing?

FDA Preliminary Comments:
On face, the proposed nonclinical program appears acceptable, provided:

- The low systemic exposure in humans to the DDM excipient ((b) (4)ng*hr/mL) is confirmed.
- The data from the subchronic and chronic toxicity studies indicate no local toxicity (e.g., preneoplastic changes) that would warrant an assessment of the carcinogenic potential of DFP-02 in locally-exposed tissues.

The adequacy of the nonclinical studies will be a matter of review.

Meeting Discussion:
The Sponsor asked when feedback could be expected from the division on whether or not a carcinogenicity study of DFP-02 would be needed, based on review of the planned subchronic and chronic toxicity studies. The Division stated once the chronic studies have been received, the Sponsor could anticipate receiving feedback within a few months, depending on the workload at the time.

Question 9: DRL plans to submit a waiver for carcinogenicity testing of DFP-02 with the chronic study reports. DRL would appreciate the Agency's feedback on our plan, outlined below in the questions.

a) Sumatriptan has already been evaluated for carcinogenicity and is approved for intranasal administration. DRL believes that the carcinogenic potential of sumatriptan has been adequately evaluated. Does the Agency concur that systemic sumatriptan carcinogenicity studies are not needed to support NDA filing?

FDA Preliminary Comments:
We agree that carcinogenicity studies to assess the systemic carcinogenic potential of sumatriptan are not needed to support NDA filing.

b) DDM is a novel excipient with minimal systemic exposure in humans. It is negative in the genotoxicity battery, is metabolized to endogenous substances, and has no systemic toxicity. In a human PK study, very low plasma levels (near the limit of quantification) of DDM were seen. DRL has ongoing intranasal 6-month rat and 9-month dog studies that will be completed prior to

NDA filing. Based on these considerations, DRL believes that DDM has no carcinogenic potential and that the intranasal studies will support safe chronic intranasal use of DFP-02. Does the Agency concur that systemic DDM carcinogenicity studies are not required to support NDA filing (pending review of the chronic study reports)?

FDA Preliminary Comments:
See Preliminary Comments under Question 8.

c) Does the Agency concur that intranasal DDM carcinogenicity studies are not required to support NDA filing (pending review of the chronic study reports)?

FDA Preliminary Comments:
See Preliminary Comments under Question 8.

Meeting Discussion:
The sponsor asked whether the carcinogenic potential of DFP-02 could be assessed in a 6-month transgenic mouse model, if an intranasal carcinogenicity study was needed. The Division stated that it is unlikely that a transgenic mouse model would be acceptable for an intranasal product but would confirm following further internal discussion.

Post-Meeting Note:
Carcinogenicity studies in transgenic animals have been accepted only for drugs administered by the oral route because of the absence of data via other routes.

Question 10: DDM is a novel excipient with minimal systemic exposure in humans. It is negative in the genotoxicity battery, is metabolized to endogenous substances, and has no systemic toxicity. Based on these considerations, DRL believes that DDM does not have any potential for adverse reproductive effects. Does the Agency concur that no additional reproductive or developmental studies are needed to support the DFP-02 NDA filing?

FDA Preliminary Comments:
See Preliminary Comments under Question 8.

Meeting Discussion:
The Sponsor asked if a non-GLP intravenous range-finding embryo-fetal development study in pregnant rats submitted under DMF (b) (4) would be considered as developmental/ reproductive toxicity data for DDM. The Division stated an assessment of embryo-fetal development would not be necessary if the circulating levels of DDM in patients were documented to be as low (i.e., plasma AUC (b) (4) ng•hr/mL) as anticipated.

Post-Meeting Note:
If reproductive and developmental toxicity studies are needed for DDM, it is very unlikely that a non-GLP dose-range finding study would be adequate to meeting the requirement for an embryo-fetal development study in rodent.

The Division has confirmed that nonclinical safety data to support use of DDM should be submitted in a Type V DMF. Agency clearance is required prior to submission of a Type V DMF. The clearance process may be initiated by sending a request to dmfquestion@cder.fda.gov that explains the necessity for filing the information in a Type V DMF. Supporting CMC information should be submitted in a separate, Type IV, DMF. Additional information on DMFs is provided on the Agency website: http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/drugmasterfilesdmfs/default.htm

Question 11: In the 4-week rat study, cross-contamination was noted in several toxicokinetic (TK) samples. DRL has performed a thorough and complete appraisal to better understand the TK findings in the completed 4-week and 13-week studies. As a conclude that the errant TK sample results are due to cross-contamination after the samples were taken from the animals, and are not due to misdosing. (See full evaluation provided in Appendix 5.) Extensive corrective measures were adopted in the subsequent DFP-02 nonclinical studies to reduce the risk for cross-contamination. The TK data generated in the 4-week rat study and all subsequent toxicity studies conducted are deemed to be acceptable good laboratory practices (GLP) studies and supportive of the safety of DFP-02.

a) Does the Agency agree that the 4-week intranasal toxicity study in rats is acceptable for NDA filing (at this initial review)?

FDA Preliminary Comments:
We agree.

Meeting Discussion:
None.

b) Does the Agency agree that DRL has properly addressed the crosscontamination issue, and that the DFP-02 nonclinical toxicity studies appear acceptable for NDA filing?

FDA Preliminary Comments:
Based on the information provided in the briefing package, it appears that the cross-contamination issue has been addressed; however, the impact (if any) on the adequacy of the pivotal nonclinical studies will be a matter of review.

Meeting Discussion:
None.

Chemistry, Manufacturing, and Controls Questions

Question 12: For drug product and delivery system, DRL has developed the release and stability specifications which are presented in Table 44. These specifications will be implemented for the proposed clinical batches, NDA registration batches, and commercial batches. Does the Agency concur with the proposed specifications?

FDA Preliminary Comments:
In general, the proposed test parameters appear to be reasonable, pending review of the analytical methods and acceptance criteria. However, as per the *"Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation."* consider the following comments when finalizing the specification:

a) We recommend that you establish limits for *in vitro* spray performance characteristics such as deliverable volume, spray droplet size distribution, spray content uniformity, spray pattern and plume geometry for each formulation before initiating critical clinical or bioequivalence studies.

b) As per the guidance mentioned above, include tests for viscosity and weight loss on stability.

Meeting Discussion:
None.

Question 13: The (b) (4) nasal delivery system will be used as the device for dispensing the DFP-02 nasal formulation, which is a (b) (4) Does the Agency agree that the proposed filling process and container/closure system are acceptable for the proposed clinical trial batches?

FDA Preliminary Comments:
In principle, the agency concurs with your strategy. However, if the proposed clinical trial batch filling process is different than that of the future commercial operation (b) (4) you should demonstrate appropriate equivalency of the products obtained using the different filling mechanisms.

Meeting Discussion:
FDA emphasized that the applicant should provide a side by side manufacturing comparison between the two facilities and quality data to establish equivalence. The applicant has agreed to provide all comparative data between the sites.

Question 14: The proposed stability protocol for 3 registration batches of drug product manufactured at a scale of (b) (4) or (b) (4) of the proposed commercial lot size is presented in

Table 45. Does the Agency agree that this protocol and batch size will be adequate to support expiration dating assignment for the commercial product?

FDA Preliminary Comments:
In general, the agency agrees on stability batch size strategy and stability protocol. However, note that the primary stability batches manufacturing process should be representative of the commercial process.

Meeting Discussion:
None.

(b) (4)

(b) (4)

(b) (4)

Meeting Discussion:
None

Additional Comments:

HUMAN FACTORS

Additional human factors studies will be required to support the usability of your product. You should perform a comprehensive risk analysis. This analysis will allow you to identify the use-related risks associated with your product. This analysis should include a comprehensive evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies. We need this information to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the device). Your use-related risk analysis will guide you in the design of a human factors validation study protocol for your product.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm2 59748.htm.

PREA REQUIREMENTS

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

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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. trade name(s)).

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

If 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*

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

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

/s/

ERIC P BASTINGS
12/04/2013