CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214962Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 130544

**MEETING REQUEST-
WRITTEN RESPONSES**

Handa Pharmaceuticals, LLC
Attention: Shelly K. Meachum, RAC
Vice President, Regulatory Affairs
39465 Paseo Padre Parkway, Suite 2600
Fremont, California 94538

Dear Ms. Meachum:

Please refer to your Pre-Investigational New Drug Application (PIND) file for HND-020 (fingolimod orally disintegrating tablets, (b) (4).

We also refer to your submission dated May 18, 2016, containing a pre-IND meeting request. The purpose of the meeting was to discuss the development plan for HND-020 (fingolimod orally disintegrating tablets, (b) (4), which you plan to develop as an alternative dosage form to the currently marketed drug, Gilenya.

Further reference is made to our Meeting Granted letter dated May 31, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 18, 2016, background package.

If you have any questions, call Nahleen Lopez at (240) 402-2659.

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:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-IND

Application Number: 130544
Product Name: HND-020 (fingolimod orally disintegrating tablets, (b) (4))
Indication: Multiple Sclerosis
Sponsor/Applicant Name: Handa Pharmaceuticals

1. BACKGROUND

Handa Pharmaceuticals, LLC ("Handa") requests written responses to questions regarding a plan to develop fingolimod orally disintegrating tablets (ODTs) as an alternative dosage form to GILENYA using the 505(b)(2) pathway.

2. QUESTIONS AND RESPONSES

Question 1: Does the Agency agree that the proposed pharmacokinetic ("PK") clinical study design in healthy volunteers for comparing the bioavailability of the (b) (4) HND-020 (fingolimod orally disintegrating tablets, 0.5mg) to GILENYA® (fingolimod capsules, 0.5 mg) is adequate to evaluate the *in vivo* bioequivalence of HND-020 and GILENYA®? The proposed clinical study protocol is provided in the enclosed background information packet.

FDA Response to Question 1: We recommend two bioequivalence studies, fasting and fed, to compare the bioavailability of (b) (4) (fingolimod orally disintegrating tablets) to GILENYA and one study to compare the bioavailability of the (b) (4) (ODT) with and without water. Bioequivalence based on 90% CI needs to be established for both fingolimod and its active metabolite fingolimod-phosphate. Fingolimod and fingolimod-phosphate need to be quantified using validated sensitive assays. Using truncated AUC is not appropriate to characterize the drug and the active metabolite exposures because the intra-subject variability in AUC for both fingolimod and fingolimod-phosphate is moderate to high; hence, you will need to collect some blood samples at least 144 hours post-dose for both fingolimod and fingolimod-phosphate. See also our responses to Questions 4 and 5.

Question 2: Does the Agency agree that an NDA for the (b) (4) ODT product described in the enclosed Target Product Profile will be acceptable for FDA submission based on favorable data from the proposed PK studies only without requiring clinical safety and efficacy studies (b) (4)

FDA Response to Question 2: In general, yes; however, the determination of acceptability will require review of the results of the pharmacokinetic studies.

Question 3: If the *in vivo* bioavailability data is acceptable, does the Agency agree that comparison of *in vitro* dissolution data between the ODT test product and the RLD (immediate release capsule product) is not necessary for the determination of bioequivalence between the test and reference products?

FDA Response to Question 3: Yes.

Question 4: It is understood from published literature that initiation of fingolimod treatment may result in bradyarrhythmia transient AV conduction delays. Therefore, subjects will be observed for 24 hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement until 6 hours post-dose, and at 8, 10, 12, 14, and 24 hours post-dose. In addition, an electrocardiogram ("ECG") will be performed before dosing and approximately 6 and 24 hours post-dose. Does the Agency agree that the proposed conduct of the clinical studies will adequately ensure subject safety?

FDA Response to Question 4: You should incorporate 144 hours of post-dose cardiac monitoring because the pharmacokinetics of ODT fingolimod and its metabolites are unknown. The cardiac safety monitoring should follow the recommendations for first dose monitoring in the label of Gilenya.

Question 5: Does the Agency agree with the dosing instructions in the clinical protocol for the test and reference products; given that the FDA individual product BE recommendation is for 3x capsule dosing (1.5 mg)? The FDA individual product BE recommendation for fingolimod is provided in the enclosed background information packet for ease of review.

FDA Response to Question 5: There are potential safety concerns regarding the 1.5 mg dose. We do not require you to use the 1.5 mg dose. If you plan to use that dose, you will need to ensure that your IND submission contains an adequate rationale and sufficient plans to ensure safety. See our response to Question 4.

Question 6: In the "Statistical Analysis" section 11.3 of the study protocol, the proposed statistical model reflects the multi-group nature of the study. In the case of a non-statistically significant treatment-by-group interaction term, the analysis will be rerun excluding this term from the ANOVA model in order to obtain ratios and confidence intervals where appropriate. This statistical approach is similar to a bioequivalence study. However, in case the treatment-by-group interaction term is found to be statistically significant (p-values less or equal to 0.05), the AUC and C_{max} ratios and 90% confidence intervals are derived from each group. Does the Agency agree that this statistical approach is acceptable for a 505(b)(2) NDA?

FDA Response to Question 6: See our response to Question 1.

Question 7: In order to avoid a potential clinical hold, does the Agency have any other concerns or suggestions for the conduct of the clinical studies that are not anticipated in our questions?

FDA Response to Question 7: We have no additional comments.

Question 8: The proposed drug product, fingolimod orally disintegrating tablets, (b) (4) is a new dosage form based on the reference product, GILENYA® capsules, 0.5 mg. Based on the FDA/ICH guidance Q1A(R2) and the FDA guidance, *Q1C Stability Testing for New Dosage Forms*, ICH November 1996, a new dosage form may be submitted with 6 months long term and accelerated stability data, with justification. (b) (4)

FDA Response to Question 8: The ICH Q1C guidance that you reference is specific to submission of stability data for new dosage forms by the owner of the original application. We recommend that the initial NDA submission include a minimum of 12 months long-term (25°C/60% R. H.) stability data, plus 6 months accelerated (40°C/75% R. H.) data for three primary batches per strength of the same formulation as the to-be-marketed product in the proposed commercial packaging. Whether we review information submitted to the NDA subsequent to the original submission will be determined based on the timing of the submission and available Agency resources.

Question 9: In accordance with the FDA/ICH guidance, Q1E Evaluation of Stability Data, dated June 2004, would the Agency agree with an approach to assign a 24 month shelf life at the time of approval based on submission of 6-month accelerated data and at least 12-month controlled room temperature stability data that demonstrate little or no change over time and little or no variability for the critical product attributes?

FDA Response to Question 9: This will be a matter for review, based on the extent and quality of the provided data.

Question 10: Handa proposes (b) (4)

FDA Response to Question 10: We prefer that multiple drug substance batches be used for manufacture of the registration batches. If that is not feasible, include your rationale in the NDA submission.

Question 11: (b) (4)

FDA Response to Question 11: Submission of one registration batch manufactured with drug substance from the second supplier is acceptable.

Question 12: Would the Agency consider a disintegration time specification (b) (4) to be appropriate for an orally disintegrating tablet dosage form?

FDA Response to Question 12: No. Although the disintegration time specification will be determined during NDA review, note that FDA generally requires the disintegration time of an ODT to be 30 seconds or less (see Guidance for Industry: Orally Disintegrating Tablets.)[1]

Question 13: If the proposed PK studies demonstrate favorable bioequivalence of fingolimod, does the Agency agree that the information in GILENYA's labeling can be used as the basis for efficacy labeling of the proposed ODT drug product for the same Indication as GILENYA?

FDA Response to Question 13: Yes. A 505(b)(2) applicant that seeks to rely on the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and/or effectiveness as reflected in the FDA-approved labeling for the listed drug. Please note that a 505(b)(2) applicant that seeks to rely on the Agency's finding of safety and/or effectiveness for a listed drug should identify the listed drug in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application include, but are not limited to, an appropriate patent certification or statement. Please also note that, as discussed in the Agency's October 1999 draft guidance for industry *Applications Covered by Section 505(b)(2)*, the approval or filing of a 505(b)(2) application, like a 505(j) application, may be delayed because of patent and exclusivity rights that apply to the listed drug or drugs relied upon. For additional information for sponsors considering the submission of an application through the 505(b)(2) regulatory pathway, please see the information in the 505(b)(2) REGULATORY PATHWAY section in this document.

Question 14: Based on the favorable comparison of the Test product with and without water, does the Agency agree with the following proposed instructions for Dosage and Administration in the proposed product labeling?

(b) (4)

FDA Response to Question 14: This will be a matter of review of the NDA.

3. 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.

[1] http://www.fda.gov/downloads/Drugs /GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf

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/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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.

SECURE EMAIL COMMUNICATIONS

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

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional

information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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/s/

WILLIAM H Dunn
07/14/2016