CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217202Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131338

MEETING REQUEST-
WRITTEN RESPONSES

AOP Orphan Pharmaceuticals GmbH
Attention: Scott A. Oglesby, PhD
6518 Green Rise Road
Hillsborough, NC 27278

Dear Dr. Oglesby:

investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Landiolol hydrochloride.

We also refer to your submission dated November 26, 2021, containing a meeting request. The purpose of the requested meeting was to provide the Agency with information on how the content of your planned NDA will be structured to meet regulatory requirements and the Agency's expectations, address prior meeting comments and agreements, and translate into potential label information.

Further reference is made to our Meeting Granted letter dated November 29, 2021 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 December 23, 2021 background package.

If you have any questions, call me at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA

Application Number: 131338

Product Name: landiolol HCl
Indication: For the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.
Sponsor Name: AOP Orphan Pharmaceuticals GmbH

Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Landiolol is a substituted (aryloxy) propanolamine β-blocker. Landiolol is approved in Japan as Onoact® for the control of ventricular rate in patients with supraventricular tachycardia. This indication is similar to that of the β-blocker esmolol approved in the USA. The Sponsor believes that landiolol's properties allow for a fast onset and offset of effect on heart rate (HR), flexible dosing, and rapid dose adaptation combined with a minor effect on blood pressure.

AOP Orphan Pharmaceuticals developed landiolol 300 mg, a sterile lyophilized powder, which is approved in the EU (trade name Rapibloc Lyo). The Sponsor performed additional non-clinical studies addressing receptor binding, including ion channels, for parent and major human metabolites. Studies to qualify the impurities are ongoing. The Sponsor also completed 3 pharmacokinetic (PK)/pharmacodynamic (PD) studies in healthy Caucasian subjects and one PK/PD study in Caucasian subjects with tachycardic atrial fibrillation (AF) or atrial flutter (AFl).

The Sponsor plans to submit an NDA using the 505(b)(2) pathway by relying on published data from the landiolol hydrochloride product approved outside the USA (Onoact). The purpose of the requested meeting was to provide the Agency with information on how the content of the planned NDA will be structured to meet regulatory requirements and the Agency's expectations, and to address prior meeting comments and agreements.

2.0 QUESTIONS AND RESPONSES

2.1. Chemistry, Manufacturing, and Controls

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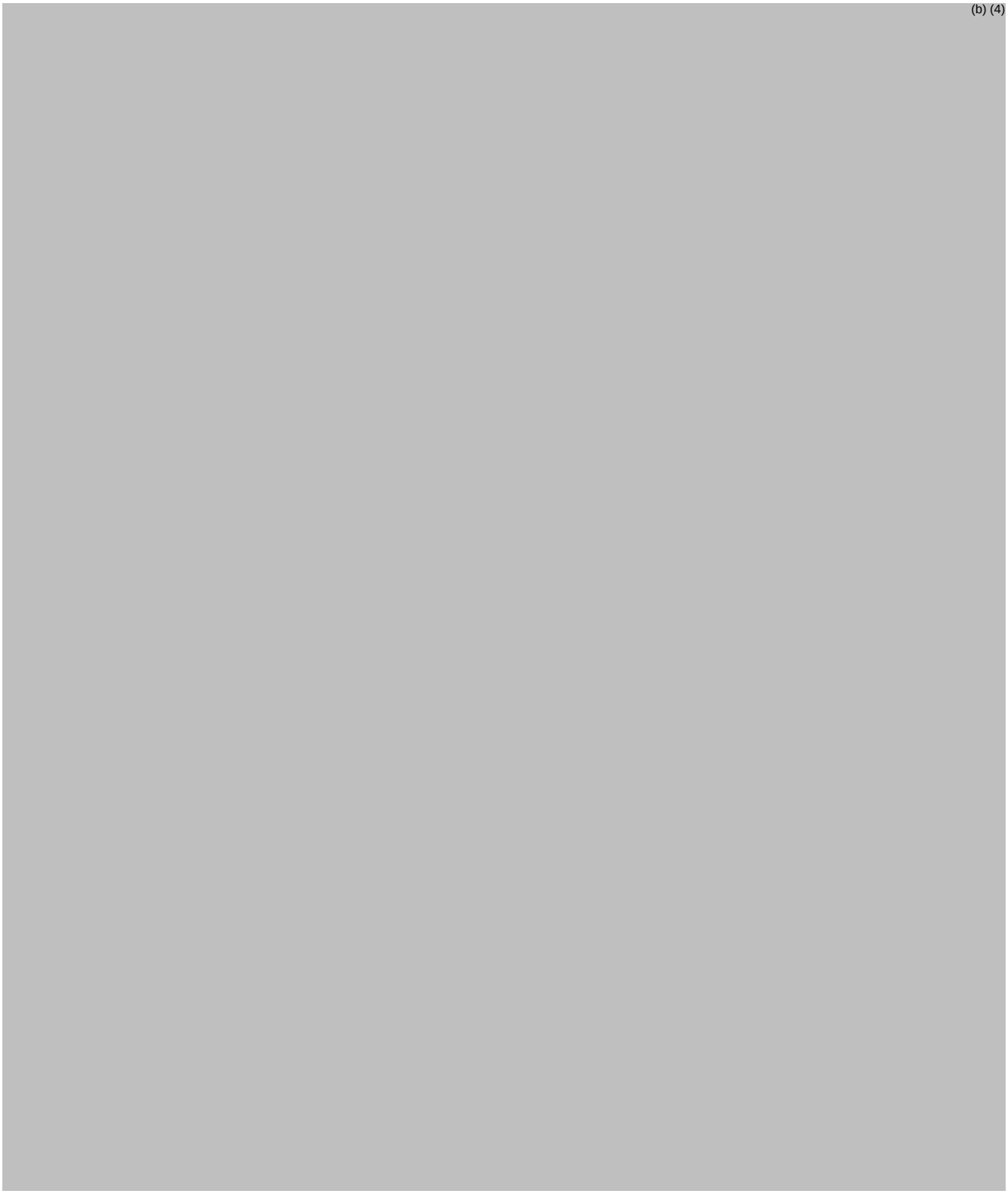

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2.2. Non-Clinical

Question 2: *Does the FDA concur with the sponsor's proposed presentation of nonclinical study and literature data for bridging and that the format and content will be appropriate and sufficient to allow FDA review of the NDA?*

FDA Response:
Yes, we agree with your proposal.

2.3. Clinical

Question 3: *Although the sponsor understands that proposed labeling will be a NDA review issue, does the FDA agree in concept that the above approach is the most appropriate for clear communication to prescribing physicians?*

FDA Response:
While the labelling will be a review issue, we recommend a bulleted description of the dosing similar to the esmolol label, to improve ease of use.

Each specified treatment duration included in the label should be described and supported in greater detail.

Question 4: *Does FDA agree with the proposed threshold reporting approach for adverse reactions in the draft label for landiolol?*

FDA Response:
We agree that a traditional threshold approach may not be feasible considering the nature of the core data you plan to present in support of safety. Your proposed threshold (i.e., adverse reactions with a greater frequency in landiolol treated patients compared to placebo-treated patients, in > 2 landiolol-treated patients and consistent with a beta blocker mechanism of action) appears reasonable. However, the selection of adverse reactions to include in labeling will be a review issue and will be evaluated upon full consideration of the safety database you provide in your application. You should also consider post-marketing adverse reactions for inclusion in your proposed labeling.

Question 5: *The sponsor understands that proposed labeling will be a NDA review issue; however, does the FDA agree that the proposed information to be included provides useful pharmacodynamic information for the prescribing physicians that addresses the FDA suggestion in the prior Type C guidance meeting?*

FDA Response:
Your approach appears to be reasonable. However, the final labeling language and content will be a review issue at the time of your NDA submission.

Question 6: *As communicated to FDA in prior meetings, the sponsor has conducted 3 clinical pharmacology studies in healthy subjects and 1 clinical pharmacology in patients with atrial fibrillation or atrial flutter (Study LDLL600.201). For the latter study, the sponsor will be submitting with the clinical study report the requisite CDISC compliant electronic files.*

For the 3 healthy subject studies, the sponsor plans to submit with the clinical study reports subject level (landiolol and M1 metabolite concentrations per nominal and actual time points) and PK parameter level data in MSExcel files.

Finally, the sponsor developed a physiologically-based PK model and conducted an analysis of landiolol sponsor pharmacokinetic data as well as the published landiolol pharmacokinetic data. The report (to be included in the NDA submission) of this model and the associated analysis is consistent with FDA guidelines on this subject. However, because the analysis was done in 2015 and the company that conducted the analysis is no longer doing business, no accompanying electronic data are available to include in the submission.

Is the above sponsor plan to submit electronic data/files in support of the clinical pharmacology section of the NDA acceptable?

FDA Response:
We have the following comments:

1. Based on the information submitted in the meeting package, it appears that your PBPK model and analysis provide important information supporting your NDA. We recommend you have the electronic data including the modeling files and the report included in your NDA submission to facilitate our review. Refer to the guidance for industry 'Physiologically Based Pharmacokinetic Analyses – Format and Content' (https://www.fda.gov/files/drugs/published/Physiologically-Based-Pharmacokinetic-Analyses-%E2%80%94-Format-and-Content-Guidance-for-Industry.pdf).
2. We note that you propose to conduct an integrated analysis of data from different studies for your dose proportionality assessment. Submit your justification for using cross-study comparison among Studies CPA422-12 and LDLL600.201 in your NDA submission. You should also submit a dose proportionality analysis without using cross-study comparison.
3. Submit a summary of your justification on how the literature data and information (e.g., study design, population, inclusion/exclusion criteria, study endpoints/outcomes, bioanalytical methods/performance) you plan to use in supporting your NDA are reliable and relevant to your drug product.

4. We remind you to evaluate the potential of your drug as a substrate, inhibitor, or inducer of metabolizing enzymes (e.g., cytochrome P450 [CYP]) and transporters during your drug development and submit relevant data/information at the time of your NDA submission. Reference is made to the Agency's *Guidance for Industry: Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (https://www.fda.gov/media/134581/download) and *Guidance for Industry: In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (https://www.fda.gov/media/134582/download).*

2.4. Regulatory

Question 7: *Although the sponsor acknowledges that a potential requirement for a REMS is a review issue, currently the sponsor anticipates that for this intravenously physician-administered product in hospitalized patients a REMS program will not be required.*

Does the FDA agree that this is a reasonable sponsor-expectation?

FDA Response:
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

3.0 OTHER IMPORTANT MEETING LANGUAGE:

PREA REQUIREMENTS
Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with

molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[4]

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[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

[4] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The

meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

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

[7] http://www.fda.gov/ectd

Specifications. For additional information, see FDA.gov.[8]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in*

[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[9] https://www.fda.gov/media/84223/download

Applications Submitted to CBER and CDER Questions and Answers[10]*.* Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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).[11] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[12]

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

[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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

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

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

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

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

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

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

(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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