CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214070Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 141151

MEETING REQUEST-
WRITTEN RESPONSES

Bond Avillion 2 Development LP
(b) (4)

Attention: (b) (4)

Dear (b) (4):

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for budesonide/albuterol sulfate pressurized inhalation suspension (BDA MDI).

We also refer to your submission dated September 15, 2021, containing a meeting request. The purpose of the requested meeting was to gain Agency feedback and agreement on specific nonclinical, clinical, regulatory, and submission-related topics for the NDA.

Further reference is made to our Meeting Granted letter dated September 20, 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 October 25, 2021, background package.

If you have any questions, please call me at (240) 402-4483.

Sincerely,

{See appended electronic signature page}

Linda Ebonine, PA-C
Senior Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Application Number:	141151
Product Name:	budesonide/albuterol sulfate pressurized inhalation suspension (BDA MDI)
Indication:	As-needed treatment of bronchoconstriction and prevention of exacerbations in patients with asthma aged 4 years and older
Sponsor Name:	Bond Avillion 2 Development LP
Regulatory Pathway:	505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Bond Avillion 2 Development LP (Avillion) submitted a meeting request dated September 15, 2021, to request a Type B meeting with the Agency. Avillion would like to gain Agency feedback and agreement on specific nonclinical, clinical, regulatory, and submission-related topics for the NDA. BDA MDI is a pressurized metered dose inhaler administered via oral inhalation containing budesonide and albuterol sulfate.

The Division granted the meeting as written responses only on September 20, 2021, and the Sponsor provided a meeting briefing package on October 26, 2021. The Sponsor's questions from the package are provided in *italics* followed by FDA responses in normal font.

2.0 QUESTIONS AND RESPONSES

Introductory Comment:

BDA MDI is a novel combination of an inhaled corticosteroid (ICS) and short-acting beta-agonist (SABA) proposed for a novel indication (as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older). As the proposed BDA MDI intent of use may substantially impact patient management, an Advisory Committee meeting may be warranted.

We also note support for effectiveness in subjects 4 to 11 years of age will rely upon 62 (75%) of the 83 subjects enrolled in the MANDALA trial. Top-line efficacy results for the primary endpoint of time to first severe exacerbation of the MANDALA trial with the dose used in subjects 4 to 11 years of age (BDA MDI 80/180) was marginal (hazard ratio 0.835; 95% CI: 0.702, 0.992). As noted in the comment dated June 8, 2020, consider additional analyses, such as a Bayesian approach, to support efficacy in pediatric subjects by borrowing efficacy information from the adult population. Whether effectiveness is supported in subjects 4 to 11 years of age will be a review issue.

Question 1:
Does the Agency agree that results from the nonclinical qualification of impurities and degradants, the right of reference for toxicology data for HFA-134a, and results from the nonclinical safety assessment of extractables and leachables constitute a complete nonclinical package such that no additional nonclinical studies are required for filing and review of a 505(b)(2) NDA for BDA MDI?

FDA Response:
Pending review of the complete nonclinical submission, as well as addressing the following comment, the nonclinical support appears reasonable for filing and review of a 505(b)(2) NDA for BDA MDI. We acknowledge submission of right of reference (b) (4) for HFA-134a. However, the toxicology data for HFA-134a reside with (b) (4). The proprietary status of the toxicology data for HFA-134a should be confirmed at the time of NDA submission. If necessary, right of reference for the HFA-134a data should be obtained from the (b) (4) at the time of an NDA submission.

Question 2:
Does the Agency agree with a nonclinical literature search cut-off date of approximately 3 months prior to NDA submission?

FDA Response:
Yes, we agree.

Question 3:
Based on the totality of information now available for BDA MDI, which includes robust data demonstrating the contribution of budesonide in 2 clinical studies, does the Agency agree that (b) (4) ?

FDA Response:
(b) (4)

Question 4:
Does the Agency agree that the list of AE preferred terms associated with local and systemic ICS effects is comprehensive and adequately defines the drug class AE associated with ICS?

FDA Response:
The list of AE preferred terms associated with local and systemic ICS effects is appropriate; however, we expect that you also include AE preferred terms to assess safety events known to occur with SABA, including CNS, cardiovascular, and metabolic effects.

Question 5:
Does the Agency agree with a clinical literature search cut-off date of approximately 3 months prior to NDA submission?

FDA Response:
While we consider 3 months to be reasonable, the choice of appropriate cut-off date for the clinical literature search is at your discretion.

Question 6:
Does the Agency agree that reference to these NDAs will meet the requirements of a 505(b)(2) marketing application for BDA MDI?

FDA Response:
You intend to support your NDA, in part, by relying upon FDA's previous findings for NDA 020503 Proventil HFA and cross-referencing information from other approved applications for which you have obtained right of reference (NDA 021949 Pulmicort Flexhaler, NDA 020929 Pulmicort Respules, NDA 208294 Bevespi Aerosphere, and NDA 212122 Breztri Aerosphere). We agree that your application should be submitted pursuant to the 505(b)(2) regulatory pathway as you plan to rely upon FDA's previous findings for a listed drug, NDA 020503 Proventil HFA. You must establish that reliance upon FDA's previous findings for Proventil HFA is scientifically justified and provide an appropriate patent certification or statement with respect to each patent for the listed drug. See section 3.0 below for additional information on the 505(b)(2) regulatory pathway. Note that cross-referencing information from NDAs for which you have obtained right of reference does not constitute 505(b)(2) reliance. However, you should describe how the cross-referenced information is applicable to your proposed product.

Question 7:
Does the Agency agree with the proposed pediatric safety data analysis plan or the 120-day Safety Update Report?

FDA Response:
We agree with your proposed pediatric safety data analysis plan and the 120-day Safety Update report.

Question 8:
Does the Agency agree with the approach for each of the contents proposed and outlined for Module 5 of the NDA?

FDA Response:
Yes, we agree with the outlined approach.

Question 9:
Does the Agency agree that the basis of submission and approval information can be provided in Introduction to Summary Section 2.2 of the 505(b)(2) NDA?

FDA Response:
Yes, we agree.

Additional Statistical Comments:

You propose a while-on-treatment estimand (Efficacy Estimand) as primary in both the DENALI and MANDALA trials. This estimand appears to be aligned with the primary trial objective. However, for the MANDALA trial, we also recommend including a supplementary treatment policy estimand by including all observed data regardless of changes in maintenance therapy or premature discontinuation of randomized treatment, as the treatment policy estimand is also of regulatory interest.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

Pediatric Study Plans.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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.

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

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

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

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).

MANUFACTURING FACILITIES

[5] http://www.fda.gov/ectd
[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for

[7] https://www.fda.gov/media/84223/download
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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).[9] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[10]

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

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

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

[11] https://www.fda.gov/media/85061/download

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/

LINDA EBONINE
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