CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215650Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 143919

MEETING MINUTES

Daré Bioscience, Inc.
Attention: Mary Jarosz, RPh, RAC, FTOPRA
Global Head of Regulatory Affairs
3655 Nobel Drive, Suite 260
San Diego, CA 92122

Dear Ms. Jarosz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DARE-BV1 (clindamycin phosphate vaginal gel 2%).

We also refer to the teleconference between representatives of your firm and the FDA on January 22, 2021. The purpose of the Pre-NDA meeting was to discuss your Phase 3 study results in support of an NDA for the treatment of bacterial vaginosis in adult women.

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 Alison Rodgers, Regulatory Project Manager, at 301-796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: January 22, 2021, 2:00 – 3:00 PM EST
Meeting Format: Teleconference

Application Number: IND 143919
Product Name: DARE-BV1 (clindamycin phosphate vaginal gel 2%)
Indication: Treatment of bacterial vaginosis in adult women
Sponsor Name: Daré Bioscience, Inc.
Regulatory Pathway: 505(b)(2)

Meeting Chair: Sumathi Nambiar, MD, MPH
Meeting Recorder: Alison Rodgers

FDA ATTENDEES

Division of Anti-Infectives

Lynette Berkeley, PhD, MT (ASCP)	Clinical Microbiology Reviewer
Kelly Brant, MPH, PhD, DABT	Nonclinical Reviewer
Gregory DiBernardo	Senior Regulatory Project Manager
Maureen Dillon-Parker, MS, RAC	Chief, Regulatory Project Management Staff
Cheryl Dixon, PhD	Statistics Reviewer
Avery Goodwin, PhD	Clinical Microbiology Team Leader
Peter Guerrieri, PhD	Product Quality Reviewer
Dmitri Iarikov, MD, PhD	Deputy Director
Peter Kim, MD, MS	Clinical Team Leader
Dorota Matecka, PhD	Product Quality Team Lead
Cristina Miglis, PharmD, MS	Clinical Pharmacology Reviewer
Terry Miller, PhD	Nonclinical Team Leader
Sumathi Nambiar, MD, MPH	Director
Mukil Natarajan, MD	Medical Officer
Alison Rodgers	Regulatory Project Manager
Kunyi Wu, PharmD	Clinical Pharmacology Team Leader (Acting)

Office of Scientific Investigations

Cheryl Grandinetti, PharmD	Clinical Pharmacologist

Office of Surveillance and Epidemiology

Jason Flint, MBA, PMP	Social Scientist/Human Factors
Nicholas Miles, PharmD	Safety Regulatory Health Project Manager
Millie Shah, PharmD, BCPS	Human Factors Team Leader

SPONSOR ATTENDEES

Daré Biosciences, Inc.

Sabrina Martucci Johnson, MS, MIM	President and Chief Executive Officer
David Friend, PhD	Chief Scientific Officer
Christine Mauck, MD	Medical Director
Nadene Zack, MS	Vice President, Clinical Operations
Mark Walters, BS	Vice President, Operations
Mary Jarosz, RPh, RAC, FTOPRA	Global Head of Regulatory Affairs

Consultants

(b) (4)

BACKGROUND

On November 13, 2020, the Sponsor submitted a Pre-NDA meeting request to discuss their Phase 3 study results in support of an NDA for the treatment of bacterial vaginosis in adult women. The briefing package for the meeting was submitted on December 22, 2020.

The Division sent preliminary comments to the Sponsor on January 19, 2021 [appended]. On January 21, 2021, the Sponsor communicated that they planned to discuss the Division's response to Question 1, the Additional Comments, and also requested clarification regarding the Office of Scientific Investigations' (OSI) request for the clinsite.spt dataset for ORA investigators.

Only the questions and discussion points from the meeting are captured below as the complete question/response preliminary communication document is attached.

DISCUSSION

Question 1: Daré Bioscience has noted FDA's response in the pre-IND meeting for 12 months of stability data at the time of the NDA submission. In consideration that DARE-BV1 has received Fast Track and QIDP designations and the robust results from DARE-BV1-001 in efficacy (Section 20.6.1.4) and safety (Section 20.6.1.5), would the Agency consider an NDA submission with 6 months long-term and 6 months accelerated drug product stability for the registration stability lots? The 12-month stability data on three registration lots would be submitted to the NDA at the end of June 2021 during the review cycle.

FDA Response: *In general, the NDA should include 12-month long-term and 6-month accelerated stability data for three primary stability batches at the time of submission, as*

recommended in ICH Q1A (R2). However, in certain circumstances we can consider accepting less than the ICH recommended stability data at the time of NDA submission provided a stability update will be submitted within 30 days after the initial submission. We are willing to accept submission of 9-month long-term and 6-month accelerated stability data from three registration batches at the time of initial NDA submission with an agreement that the 12-month long-term stability update will be provided within 30 days of NDA submission.

Meeting Discussion:

- The Sponsor stated that they would submit 9-month stability data for the three primary batches in the initial NDA followed by 12-month stability data within 30 days of NDA submission. The Division suggested that in addition to the data for the three primary registration batches, the Sponsor can submit supportive stability information for any other relevant drug product batches they may have. The Sponsor agreed and stated that they plan to submit the NDA in early June 2021.

Additional FDA Comments:

1. **Parenteral benzyl alcohol use in pregnancy is not recommended due to potential toxicity to the fetus. The amount of benzyl alcohol absorbed systemically in pregnant women from DARE-BV1 is unknown. Provide detailed composition of the to-be-marketed formulation of DARE-BV1 used in the Phase 3 trial and any available information regarding the quantity of benzyl alcohol in DARE-BV1 compared to other approved vaginal gels containing benzyl alcohol that are indicated for use in pregnancy.**

Meeting Discussion:

- The Sponsor stated that DARE-BV1 contains (b) (4) benzyl alcohol and that this is the same amount of benzyl alcohol contained in another FDA approved product, Cleocin (clindamycin 2% vaginal cream). The Sponsor noted that they have completed the nonclinical reproductive toxicology studies and there were no adverse findings. The Division stated that DARE-BV1 is a gel and Cleocin is a cream. The Division does not know if absorption of benzyl alcohol is the same in both formulations. The Division requested that the Sponsor provide more information regarding the use of benzyl alcohol in pregnant women. The Sponsor thanked the Division for their feedback and agreed to provide the information.

2. **In your NDA submission, address the following Chemistry, Manufacturing, and Controls (CMC)**
   a) **Include a within-tube content uniformity test per USP <3> recommendations for multi-dose products in the drug product release and stability specifications.**

b) Report degradants in the drug product specification per ICH Q3B (R2) guideline (i.e., specified identified, specified unidentified, unspecified and total degradation product).

c) Details of all analytical methods, specifically those which are non-compendial and the respective methods validation should be submitted to the NDA.

d) The NDA should include results from a one-time test for extractable/leachable testing on three drug product registration batches through the expiry period manufactured using the proposed commercial process and packaged in the to-be-marketed container closure system. Refer to USP <1663>, <1664> for additional recommendations. Any impurities found must be adequately controlled, those found above the applicable thresholds must be adequately qualified.

Meeting Discussion:

- The Sponsor stated that they are conducting multiple tests to ensure within-tube content uniformity (b) (4) and that the final product will have adequate uniformity for patient use. The Division responded that section 19.1 of the meeting background package, states that tubes are filled to 25 grams; however, a single dose is 5 grams. The Division asked if the tubes would be multidose containers as only a portion of the fill would be used for one dose. The Sponsor responded that the instructions for use would state (b) (4) (b) (4). The Division stated that there would still be the potential for physical changes, e.g., separation or changes in gel texture within the tube, and consequently an inadequate dose might be administered. Therefore, the Division recommended the Sponsor include within-tube content uniformity testing per USP <3> in the drug product specification. The Sponsor acknowledged the comments and stated that they are conducting extensive testing and are confident that the correct dose will be administered.
- The Division stated that the Sponsor should include details of their overall control strategy for the drug product in the NDA.
- The Sponsor stated that they would submit extractable and leachable data from 6-month accelerated studies as well as 9-month long-term studies in the NDA submission. The Sponsor has approximately 9-months of real time stability data so they will not have leachable data through expiry at the time of NDA submission. The Sponsor asked if it would be acceptable to submit the complete leachable data when available in an annual report. The Division confirmed that it would be acceptable to submit leachable data for the primary stability batches post-approval when they reach the expiration date; however, available leachable data for these batches should be submitted in the NDA. The Sponsor responded that they will provide any leachable data available at the time of NDA submission.

Post Meeting Comment:

In follow-up to the teleconference the Division would like to clarify that the results of the leachable testing for the three primary stability batches be provided in the NDA. This should include results of leachable testing for the oldest drug product stability samples available at the time of NDA submission (e.g., 9-month old samples). The leachable testing should be continued through the proposed product expiry and reported post-approval (e.g., in the annual report), as appropriate. The extractable/leachable information will be reviewed during the NDA review and additional information, including additional testing, may be requested.

3. **We recommend you request a pre-NDA CMC-dedicated meeting to discuss any outstanding CMC issues in preparation for an NDA submission.**

Meeting Discussion:

- The Sponsor stated that they may request a pre-NDA CMC-dedicated meeting.

Additional Meeting Discussion

Office of Scientific Investigations (OSI)

- The Sponsor inquired if the clinsite.spt dataset for ORA investigators requested by the Office of Scientific Investigations (OSI) is still required. The Division responded that the information for OSI is required to be submitted in the NDA.

Post Meeting Comment:

The process for submitting the BIMO data line listings and clinsite.xpt dataset has not changed. For additional information on the BIMO data line listings and the summary-level dataset (i.e., clinsite.xpt dataset), what information should be submitted, and how these listings and datasets should be formatted, see the following FDA guidance and FDA's Technical Conformance Guide:

- "Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions" available at https://www.fda.gov/media/85056/download
- "Bioresearch Monitoring Technical Conformance Guide" available at https://www.fda.gov/media/85061/download

Pediatrics

- The Sponsor stated that they plan to amend the iPSP with a request for a deferral for the adolescent population. The Division stated that they need to discuss the deferral request with the Pediatric Review Committee (PeRC) and that an agreement on the deferral should be in place before the NDA is submitted. The Sponsor acknowledged the comments and stated that they plan to submit the deferral request shortly.

Agreements/Summary

- The Division asked the Sponsor to summarize the agreements reached during the meeting regarding late submission of application components. The Sponsor responded that they will submit 12 months of stability data 30-days post-NDA submission; they will include any leachable data they have in the NDA submission and the additional expiry data will be submitted in a supplement post-approval.

ACTION ITEMS

- The Division will issue meeting minutes within 30 days.
- The Sponsor may request a pre-NDA CMC dedicated meeting.
- The Sponsor will:
  - Submit a request to amend their iPSP with a deferral for the adolescent population.
  - Submit 12 months of stability data 30 days post-NDA submission.
  - Include available leachable data for the primary stability batches in the NDA.

ATTACHMENTS

Preliminary meeting comments sent to Sponsor on January 19, 2021.

IND 143919

MEETING PRELIMINARY COMMENTS

Daré Bioscience, Inc.
Attention: Mary Jarosz, RPh, RAC, FTOPRA
Global Head of Regulatory Affairs
3655 Nobel Drive, Suite 260
San Diego, CA 92122

Dear Ms. Jarosz:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DARE-BV1 (clindamycin phosphate vaginal gel 2%).

We also refer to your November 13, 2020, correspondence, received November 13, 2020, requesting a meeting to discuss your Phase 3 study results in support of an NDA for the treatment of bacterial vaginosis in adult women.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at 301-796-0797.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker, MS, RAC
Chief, Regulatory Project Management Staff
Anti-Infectives Group 2
Division of Regulatory Operations
for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: January 22, 2021, 2:00 PM – 3:00 PM EST
Meeting Location: Teleconference

Application Number: IND 143919
Product Name: DARE-BV1 (clindamycin phosphate vaginal gel 2%)
Sponsor Name: Daré Bioscience, Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Introduction

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 22, 2021, 2:00 – 3:00 PM between Daré Bioscience, Inc., and the Division of Anti-Infectives. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

IND 143919 for DARE-BV1 was submitted on November 15, 2019. On November 13, 2020, the Sponsor submitted a request for a Pre-NDA meeting to discuss their Phase 3 study results in support of an NDA for the treatment of bacterial vaginosis in adult women. The meeting was granted on November 25, 2020, and the briefing package was received on December 22, 2020. The Division's preliminary responses to the questions listed in the December 22, 2020, briefing package are provided below.

DISCUSSION

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 1: Daré Bioscience has noted FDA's response in the pre-IND meeting for 12 months of stability data at the time of the NDA submission. In consideration that DARE-BV1 has received Fast Track and QIDP designations and the robust results from DARE-BV1-001 in efficacy (Section 20.6.1.4) and safety (Section 20.6.1.5), would the Agency consider an NDA submission with 6 months long-term and 6 months accelerated drug product stability for the registration stability lots? The 12-month stability data on three registration lots would be submitted to the NDA at the end of June 2021 during the review cycle.

FDA Response: *In general, the NDA should include 12-month long-term and 6-month accelerated stability data for three primary stability batches at the time of submission, as recommended in ICH Q1A (R2). However, in certain circumstances we can consider accepting less than the ICH recommended stability data at the time of NDA submission provided a stability update will be submitted within 30 days after the initial submission. We are willing to accept submission of 9-month long-term and 6-month accelerated stability data from three registration batches at the time of initial NDA submission with an agreement that the 12-month long-term stability update will be provided within 30 days of NDA submission.*

NONCLINICAL

Question 2: Based on the communications to date with the FDA, the agreed nonclinical studies to assess the safety of DARE-BV1 and its components are listed in the meeting package (see Section 20.4) and will be included in the NDA. Does the Agency continue to agree that these studies fulfill the nonclinical safety requirements for the NDA?

FDA Response: *The nonclinical studies listed in Section 20.4 are consistent with the recommendations in ICH M3(R2) to support marketing authorization. The adequacy of the studies to demonstrate the nonclinical safety of DARE-BV1 will be determined upon review of the final study reports at the time of NDA submission.*

You indicate in the meeting package that with the exception of the Segment III reproductive toxicity study (rat) and 28-day repeat dose rabbit vaginal irritation study, all of the nonclinical studies have been completed. In addition, all completed nonclinical studies have been submitted to the IND except for the Poloxamer 407 drug metabolism and PK and condom compatibility studies. We are unable to locate the in vivo genotoxicity study reports for Poloxamer 407 and sodium citrate. Please point us to where in your IND submission, the in vivo genotoxicity study reports for Poloxamer 407 and sodium citrate are located. If they have not yet been submitted, provide the final in vivo genotoxicity study reports, along with any remaining final study reports for the nonclinical studies described in Section 20.4, in your NDA submission.

CLINICAL

Question 3: Daré Bioscience has received an Agreed iPSP (dated Aug 19, 2020) with the intent of including adolescents ages 12 to 17 years old in the DARE-BV1-001 Phase 3 study. Although there was significant interest in study participation from an adult population and recruitment for the study was therefore fast and successfully achieved enrollment objectives in the adult population, that was not the case in the adolescent age group. Despite targeted recruitment and enrollment initiatives, the study was able to enroll only one patient under the age of 18 (15-year old). (b) (4) (b) (4). Does the Agency concur with a deferral for the adolescent population?

FDA Response: *A deferral for subjects aged 12 to <18 years may be appropriate. You should submit an amended iPSP prior to the NDA submission outlining your revised plan.*

Question 4: Does Daré Bioscience need to submit an amended Agreed iPSP outlining a deferral for the adolescent population?

FDA Response: *Yes, please see our response to Question 3.*

Question 5 WRO: Daré Bioscience will update the risk assessment and document any HF validation data in a design history file. Does the Agency agree that the proposal aligns with the intent of the Advice Letter dated Nov 5, 2020?

FDA Response: *This approach is reasonable. Please ensure that your documentation records comply with the Quality System regulation, 21 CFR Part 820.*

REGULATORY

Question 6: The NDA will consist of one Phase 3 efficacy and safety study (DARE-BV1-001) and a PK study (DARE-BV1-PK1) in healthy volunteers. There are no other clinical studies with the DARE-BV1 formulation. Does the Agency agree that a waiver of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) is appropriate?

FDA Response: *A waiver of the ISE and ISS is acceptable; however, the Summary of Clinical Efficacy and Summary of Clinical Safety in Module 2 are required.*

Regarding the formatting of the ISE and ISS for the electronic Common Technical Document (eCTD) and Summary of Clinical Efficacy and Summary of Clinical Safety in Module 2, we suggest you review: Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, ;https://www.fda.gov/media/75783/download, to assist in the correct submission of Module 2 for the filing of your NDA submission.

Question 7: Daré Bioscience considers Cleocin® clindamycin phosphate vaginal cream, USP (approved 1992), Clindesse® clindamycin phosphate vaginal cream 2% (approved 2004), (b) (4) (b) (4) as the listed drugs for DARE-BV1. (b) (4)

Does the Agency agree with the listed drugs?

FDA Response: *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 Cleocin (clindamycin phosphate vaginal cream, 2%), and Clindesse (clindamycin phosphate vaginal cream, 2%) appears acceptable. Clarify what information and sections of your NDA (e.g., nonclinical, clinical, clinical pharmacology), including the labeling, you intend to support through such reliance and how you will establish the bridge between your proposed drug product and each listed drug upon which you propose to rely.*

(b) (4)

*Refer to the **505(b)(2) Regulatory Pathway** section below for additional information about submitting a 505(b)(2) NDA.*

Question 8: For the NDA, Daré Bioscience intends to conduct a clinical and nonclinical literature assessment to include clindamycin vaginal creams and ovules indicated for the treatment of bacterial vaginosis. Does the Agency agree with this literature review strategy?

FDA Response: *Please explain the intent of your clinical literature assessment. If your intent is to rely on published literature for which you have no right of reference but that is necessary for approval of your 505(b)(2) NDA, you must establish that reliance on the studies described in the literature is scientifically appropriate. You should include a copy of such published literature in your NDA and identify any listed drug(s) described in the published literature (e.g., by trade name(s)) in accordance with 21 CFR 314.54.*

Additional FDA Comments:

4. Parenteral benzyl alcohol use in pregnancy is not recommended due to potential toxicity to the fetus. The amount of benzyl alcohol absorbed systemically in pregnant women from DARE-BV1 is unknown. Provide detailed composition of the to-be-marketed formulation of DARE-BV1 used in the Phase 3 trial and any available information regarding the quantity of benzyl alcohol in DARE-BV1 compared to other approved vaginal gels containing benzyl alcohol that are indicated for use in pregnancy.

5. In your NDA submission, address the following Chemistry, Manufacturing, and Controls (CMC)
   e) Include a within-tube content uniformity test per USP <3> recommendations for multi-dose products in the drug product release and stability specifications.
   f) Report degradants in the drug product specification per ICH Q3B (R2) guideline (i.e., specified identified, specified unidentified, unspecified and total degradation product).
   g) Details of all analytical methods, specifically those which are non-compendial and the respective methods validation should be submitted to the NDA.
   h) The NDA should include results from a one-time test for extractable/leachable testing on three drug product registration batches through the expiry period manufactured using the proposed commercial process and packaged in the to-be-marketed container closure system. Refer to USP <1663>, <1664> for additional recommendations. Any impurities found must be adequately controlled, those found above the applicable thresholds must be adequately qualified.

6. We recommend you request a pre-NDA CMC-dedicated meeting to discuss any outstanding CMC issues in preparation for an NDA submission.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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.

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."

Corresponding names and titles of onsite contact:

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)				

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[3] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers[4].* 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).[5] 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.[6]

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.

[3] https://www.fda.gov/media/84223/download
[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[5] 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.
[6] http://www.regulations.gov

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*
(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/

SUMATHI NAMBIAR
02/19/2021 01:29:07 PM