CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216686Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 140555

MEETING REQUEST-
WRITTEN RESPONSES

Spes Pharmaceuticals Inc.
Attention: Jianwei Yu, Ph.D.
President, CEO & CSO
675 US Highway 1, Suite 118
North Brunswick, NJ 08902

Dear Dr. Yu:[1]

Please refer to your pre-investigational new drug application (PIND) file for fosaprepitant injection.

We also refer to your August 12, 2021 correspondence requesting a meeting to discuss your proposed pre-submission plans for your planned NDA for the prevention of chemotherapy-induced nausea and vomiting indication pursuing the 505(b)(2) regulatory pathway.

Further reference is made to our Meeting Granted letter dated September 1, 2021 wherein we agreed 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 August 26, 2021 background package.

[1] 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.

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, Pharm.D.
Senior Regulatory Health Project Manager
Gastroenterology
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
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: PIND 140555

Product Name: fosaprepitant injection
Indication: prevention of chemotherapy-induced nausea and vomiting

Sponsor Name: Spes Pharmaceuticals Inc.

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

1.0 BACKGROUND

On August 12, 2021, the Sponsor submitted a meeting request regarding their proposed submission plans for their planned NDA pursuing the 505(b)(2) regulatory pathway for the prevention of chemotherapy-induced nausea and vomiting (CINV) indication with the proposed listed drug as NDA 22023 Emend (fosaprepitant) injection, which is currently approved for the prevention of CINV in adults and pediatrics.

The Sponsor's fosaprepitant injection is a pre-mixed ready-to-use or to-be-diluted solution, whereas the listed drug Emend (fosaprepitant) injection is a lyophilized powder for injection that is to be reconstituted and diluted prior to administration. The differences between the Sponsor's proposed product and the listed drug include difference in inactive ingredients (Sponsor's proposed product does not contain polysorbate 80 or lactose anhydrous, but it contains betadex sulfobutyl ether sodium), and certain physiochemical properties such as pH.

Previous correspondences issued for this program include the written responses issued on October 11, 2018 and September 28, 2018.

The Sponsor submitted an initial Pediatric Study Plan (iPSP) in support of their planned NDA on April 22, 2021, and in response, the Agency issued iPSP written response on July 16, 2021.

The August 12, 2021 meeting request was granted, and the background package was received on August 26, 2021.

2.0 QUESTIONS AND RESPONSES

Question 1:
Based on the specifications and justifications provided above, does the Agency agree that the draft specifications limits are appropriate and properly justified? Does the Agency have any further comments for the draft specifications, particularly for bacterial endotoxins?

FDA Response to Question 1:
No, we do not agree. Although the tests in the proposed drug product specification appear to be acceptable, the acceptance criterion for each test is a review issue and will be decided at the time of NDA review based on the manufacturing history and the available drug product batch analysis data (e.g., batches used in the clinical studies, registration, and stability studies [including the in-use stability]) submitted in the NDA. Tests to be omitted during the shelf life (e.g., volume in container) should be justified by the batch stability results.

Additionally, we do not agree that the acceptance criteria of the microbiological tests are appropriate or properly justified. The endotoxins limit of NMT (b) (4) EU/mL calculated using a theoretical body weight of 70 kg appears adequate for adult patients; however, the drug product is proposed for use in patients as young as 6 months old with a body weight of 6 kg. As the proposed dose for pediatric patients is 5 mg/kg, the worst-cas acterial endotoxins exposure level i (b) (4) EU/mL x 5 mg/kg/hr ÷ 3 mg/mL = (b) (4) EU/kg/hr, which exceeds the USP <85> recommended maximum endotoxins dose of 5 EU/kg/hr for pediatric patients. Therefore, the endotoxins specification should be lowered in order to not exceed 5 EU/kg/hr for pediatric patients.

Risk assessment for the elemental impurities (b) (4) should be conducted per USP <232> and (b) (4) Tests may need to be included in the drug product specification based on the results of your risk assessment.

Question 2:
Does the Agency agree that the approach is appropriate and the studies performed meet the Agency's expectation for assessment of extractability and leachability of the primary container closure system, and other product contact materials? Does the Agency have any other suggestions?

FDA Response to Question 2:
The extractable/leachable studies performed for the container/closure system, the plan for the compatibility study with the commercial infusion sets, and the plan for the other product contact materials appear reasonable. However, as part of the NDA submission, provide material certification statements to indicate the material is in compliance to pertinent CFR sections for indirect food additives for

all formulation contacting (b) (4) components used in the manufacturing and holding of the drug product and intermediates. Additionally, confirm that all (b) (4) surfaces and components proposed for manufacturing operations that are in direct contact with your proposed drug product formulation meet the ASTM standards (b) (4) The final decision of the acceptability will be determined at the time of NDA review based on review of the data and the study results submitted in the NDA.

Question 3:
Does the Agency concur that this is a reasonable approach for including alternative API supplier and manufacturing site and will accept the information submitted for review without changing the initial PDUFA date?

FDA Response to Question 3:
We acknowledge your statement that SPES may consider to include an alternative API supplier and an FDA approved alternative finished product manufacturing site in the NDA and that SPES plans to manufacture another three "registration" batches with the API from possibly a new supplier at an FDA audited finished dose manufacturer at appropriate batch sizes. Further, you stated that in order to be considered for approval within the initial NDA submission, at least 3 months of accelerated and long-term storage stability data along with a comparative summary of all pertinent manufacturing information would be provided. We do not object to these statements; however, please be aware that if the facilities are modified at any time during the review cycle (i.e., new firms are added which were not specified as part of the initial submission regardless of when the information is submitted), this modification may trigger the need for the Agency to reset the PDUFA goal date. Alternatively, there are several pathways for submission of drug substance and/or drug product manufacturing facilities that could be considered. For additional information, see the FDA "Guidance for Industry: Changes to an Approved NDA or ANDA" (April 2004- https://www.fda.gov/media/71846/download) or the FDA Draft Guidance (including Appendix C) for "Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information" (April 2016 – Revision 1- https://www.fda.gov/media/97148/download).

- **From the drug substance standpoint, the application should be complete upon submission with all API manufacturers included in the initial submission. Full CMC information should be provided for all API manufacturers, either in the application or in a DMF with the appropriate Letter of Authorization included, and a comparison of drug substance supplied by different companies should also be included in the initial NDA submission.**

- **In general, batch analysis data including three-month stability data stored at long term and accelerated storage conditions for the drug product batches manufactured with the API batches from the alternative supplier and manufacturing site should be submitted at the initial NDA submission. We recommend you obtain the stability data at 0-, 1- and 3-months' time points for both long term and accelerated conditions to aid the evaluation. For this case, you may amend the three-month stability data no later than 30 days of the initial NDA submission.**

From the microbiological perspective, please note that the (b) (4) manufacturing process should be appropriately validated for all proposed drug product manufacturing sites, and the (b) (4) validation information should be reviewed prior to approval. Reference is made to the 1994 Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (https://www.fda.gov/media/71442/download).

Question 4:

Since the proposed finished drug product is intended to be used as a ready-to-use injection (without the need of reconstitution or dilution) and the composition does not contain any antimicrobial preservatives, (b) (4) the following instruction shall be specified in the product label: ' (b) (4) .

Does this satisfactorily address the Agency's concerns for use time limit of diluted solution and the Agency concurs that the draft label appears appropriate?

FDA Response to Question 4:

It is premature to agree. (b) (4) **We remind you that the prescribing information of the drug product is a review issue and will be decided at the time of the NDA review.**

Question 5:

Does the Agency agree this proposed option of "storage at room temperature for up to 90 days" based on the satisfactory stability results up to 9 months at the accelerated

stability conditions? Does the Agency have any other suggestions regarding the draft product label?

FDA Response to Question 5:
It is premature to agree. The expiration of the drug product will be determined at the time of the NDA review based on the stability data. Therefore, it is premature to decide the acceptability of your proposed room temperature storage option for the drug product. To determine the storage length at the room temperature condition after long term storage at the refrigerated condition, we recommend that you conduct additional drug product stability studies at room temperature condition after different durations of the long-term storage in the refrigerator, especially after full proposed expiration dating period at long term storage condition.

In the draft product label, it is stated that the entire volume in the vial may not be used for pediatric patients. From the microbiological perspective, it is recommended that you include a statement that the remaining contents of the vial should be discarded.

Question 6:
Does the Agency concur that the results of the non-clinical in vitro and in vivo studies provided adequate and sufficient evidence for justifying the safety of the proposed Fosaprepitant Injection? Does the Agency agree that the data discussed provide sufficient evidence addressing the Agency's concern of potential adverse effect of the highly alkaline formulation of the proposed drug product on the acid-base balance and electrolyte balance of the bloods, particularly in pediatric patients (b) (4) ?

FDA Response to Question 6:
The results from your in vitro assessment of human blood pH following fosaprepitant injection appear to address our concerns regarding the potential adverse effect of the highly alkaline formulation of the proposed drug product on the pH of blood in adult and pediatric patients ages 6 months and older.

Question 7:
Does the Agency agree that above side-by-side comparison, assessment, supporting data and other nonclinical in vitro and in vivo data presented in this meeting package provide enough evidence to demonstrate that the differences between the two formulations in terms of inactive ingredients and the physicochemical properties will not affect its in vivo PK performance?

FDA Response to Question 7:
Yes, we agree.

Question 8:
Does the Agency concur that a proper "bridge" is established between the proposed drug product and the Listed Drug; and also concur that the Sponsor can submit a request for, and the Agency shall grant, a "bio-waiver" of conducting any in vivo bioavailability or bioequivalence studies between the proposed drug product and the listed drug EMEND for injection per 21 CFR § 320.22(a) & (b)?

FDA Response to Question 8:
No, we do not agree with the "bio-waiver" request. Because the formulation of the proposed drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of the LD, due to the absence of polysorbate 80 and the presence of sulfobutyl ether beta-cyclodextrin sodium, the biowaiver request per 21 CFR § 320.22(b)(1) is not feasible.

However, per 21 CFR 320.24(b)(6), bridging may be possible between the proposed Fosaprepitant Injection drug product, (150 mg/50 mL [3mg/mL], an aqueous solution [150 mg/vial]) and the Listed Drug Emend injection, (lyophilized powder for solution [150 mg/vial]) based on:

1. **The proposed drug has the same active ingredient, same concentration (after dilution), same dosing regimen, and is intended for administration by intravenous infusion with the same rate of administration as the approved LD product.**
2. **The proposed drug product has comparable physiochemical properties as the LD product, (e.g., both are sterile colorless solutions with comparable osmolarity and acceptable pH, etc. [after reconstitution for the LD]).**
3. **Review of the conducted comparative *in vitro* drug metabolism studies in human liver microsomal tissues and an *in vivo* comparative pharmacokinetics/bioavailability studies in beagle dogs to demonstrate that the absence of polysorbate 80 and the presence of sulfobutyl ether beta-cyclodextrin sodium (b) (4) to the formulation of the proposed DP do not alter the PK of fosaprepitant in the relevant models.**

The final decision on the establishment of an adequate bridge to support reliance on the Agency's findings of safety and efficacy for the LD is a review issue and will be determined during NDA review based on the sufficiency of the submitted data.

Question 9:
Does the Agency concur that the ISS is appropriate for supporting the clinical assessment of the proposed drug product assuming that the Agency agrees no

additional clinical studies are required for the proposed drug product? Does the Agency have any comment or suggestion to the risk management approach?

FDA Response to Question 9:
Provided that you are able to establish a bridge to support reliance on the Agency's finding of safety for the stated LD, Emend for injection (NDA 22023), your proposal for the content of the ISS (e.g., literature review of the clinical safety of fosaprepitant from 2008- July 2021 and a summary of AEs reported to FAERS since 2008) appears reasonable.

Although your proposal to not include a risk management plan in the NDA appears reasonable, the determination of the necessary risk management approach for a proposed product is made based on review of the data submitted in the NDA to support its safety and efficacy and the assessment of benefit-risk in the intended use population.

Question 10:
Does the Agency concur that the Agreed iPSP is appropriate (b) (4)

Furthermore, does the Agency agree to rely on the Agency's findings of safety and efficacy of EMEND and no further pediatric assessment will be required for pediatric patients age 6 months to 17 years? Should the Agency deem the submitted data package to be sufficient to support approval in adult patients but not in pediatric patients age 6 months to 17 years, does the Agency concur it is appropriate that the pediatric language in the proposed drug label would be removed pending the submission of additional bridging data in the post-marketing setting for pediatric patients age 6 months to 17 years?

FDA Response to Question 10:
No, we do not agree. We acknowledge your clarification provided confirming that your proposed iPSP in response to our July 16, 2021 iPSP written response is not your "agreed iPSP" and refer you to the FDA comments on your revised "iPSP other" sent September 23, 2021.

(b) (4)

your iPSP should include a plan to assess the safety and efficacy of your drug in this age cohort. We recommend you include a

plan to request deferral of assessment in pediatric patients age 0 to 6 months to post-marketing in your iPSP.

As stated in the July 16, 2021 FDA Pediatric Study Plan Written Response, "If you can establish an adequate bridge between your product and the proposed listed drug (i.e., Emend), then you may rely on FDA's findings of safety and efficacy for Emend for injection for your pediatric assessment for patients ages 6 months and older without the need for additional pediatric studies."

Furthermore, we remind you that the assessment of the acceptability of a request for waiver or deferral of pediatric studies as well as the content of the eventual prescribing information will be determined during review of the proposed NDA.

Question 11:
Are there any questions that the Sponsor should have asked or any other advice or comments from the Agency that the Sponsor needs to consider during the development of this proposed drug product under a 505(b)2 NDA?

FDA Response to Question 11:
For additional information and guidance regarding the content and format of new drug applications (NDAs), we refer you to the following website: https://www.fda.gov/drugs/types-applications/new-drug-application-nda. This site contains links to several available FDA guidance documents to help sponsors as they prepare NDAs. Additionally, please see the section entitled 505(b)(2) Regulatory Pathway below.

3.0 ADDITIONAL COMMENTS

Additional CMC Comments:
We remind you to address the risk of the presence of (b) (4) impurities in active pharmaceutical ingredients (APIs) and drug products in your NDA. Refer to the FDA Guidance for Industry "(b) (4)

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*.[2] 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.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.

[2] 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.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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.

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.[6]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[7] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

[6] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[8]

[8] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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[9] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[10]

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.[11]

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.[12]

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).

[9] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[10] https://www.fda.gov/media/109533/download
[11] http://www.fda.gov/ectd
[12] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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[13] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[14]. Submit all

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

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).[15] 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.[16]

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

[15] 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.
[16] 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.

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/

MARY H CHUNG
10/08/2021 12:00:19 PM