CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216743Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 216743

MEETING REQUEST-
WRITTEN RESPONSES

Zydus Worldwide DMCC
Attention: Srinivas Gurram (Srini)
US Agent for Zydus Worldwide DMCC
Senior Vice President- Head of RA and CQA Lead- Americas
Zydus Pharmaceuticals (USA) Inc.
73-B Route 31 North
Pennington, NJ 08534

Dear Mr. Gurram:

Please refer to your pre-assigned New Drug Application (NDA) file for Sitagliptin and Metformin Hydrochloride Tablets.

We also refer to your submission dated January 21, 2022, containing a meeting request. The purpose of the requested meeting was to obtain feedback and discuss proposal to ZWD's follow-up questions to FDA's written responses dated November 23, 2021.

Further reference is made to our Meeting Granted letter dated February 1, 2022, 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 January 21, 2022, background package.

If you have any questions, please contact Nowrin Kakon, Regulatory Business Process Manager at Nowrin.Kakon@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mohan Sapru, MS, PhD
Branch Chief
New Drug Products Division III, Branch V
Office of New Drug Products
Member, Emerging Technology Team (ETT)
Office of Pharmaceutical Quality
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: NDA 216743

Product Name: Sitagliptin and Metformin Hydrochloride Tablets
Indication: An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Applicant Name: Zydus Worldwide DMCC
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1. BACKGROUND

Applicant notes that Sitagliptin and Metformin Hydrochloride Tablets is currently marketed in the United States as approved drug, Janumet (sitagliptin and metformin hydrochloride) tablets (NDA # 022044) by Merck Sharp & Dohme. It is available as an immediate release tablet. The approved product, Janumet (sitagliptin and metformin hydrochloride) tablets, contain Sitagliptin phosphate monohydrate and Metformin Hydrochloride in the doses equivalent to 50 mg of Sitagliptin and 500 mg / 1000 mg of Metformin Hydrochloride. ZWD's proposed drug product is an immediate release tablet formulation that contains Sitagliptin (free base) and Metformin Hydrochloride as the active ingredient. Sitagliptin (free base) is different from Sitagliptin phosphate monohydrate salt (Janumet, NDA # 022044). The salt form of metformin i.e., Metformin Hydrochloride is same in the proposed product as well as in the RLD product. ZWD is proposing submission under the 505(b)(2) NDA pathway.

ZWD has following objectives for this Type B meeting:

- To obtain Agency's concurrence on follow-up question by ZWD for requirement of the stability data of the three primary batches
- To obtain Agency's concurrence on requirement of the stability data of one drug product batch manufactured with alternate API source.

2. QUESTIONS AND RESPONSES

The applicant's questions are reproduced below, and FDA's written responses follow each question.

Question 1:

Does the Agency agree that 6 months accelerated & 9 months long-term stability data for three primary batches is acceptable for submission in the initial NDA and

12 months long-term stability data will be submitted within 30 days of original NDA?

FDA Response to Question 1:
Your proposed approach is reasonable provided that the 12-month long-term data are submitted within 30 days of the NDA submission.

Question 2:
Does the Agency agree that 6 months accelerated & 6 months long-term stability data for one exhibit batch manufactured with alternate source API batch is acceptable for submission in the initial NDA along with three exhibit batches manufactured with primary API source as impurity profile and physical properties of primary source and alternate API source are equivalent?

FDA Response to Question 2:

Yes, we agree.

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[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.
- 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

[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

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.

4. 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).[3] 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.[4]

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] 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.
[4] 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/

MOHAN K SAPRU
03/14/2022 02:09:12 PM

NDA 216743

MEETING REQUEST-
WRITTEN RESPONSES

Zydus Worldwide DMCC
c/o Zydus Pharmaceuticals (USA) Inc.
Attention: Srinivas (Srini) Gurram
Vice President & Head of RA & QA, North America
73-B Route 31 North
Pennington, NJ 08534

Dear Srinivas Gurram:

Please refer to your pre-assigned New Drug Application (NDA) file for sitagliptin and metformin hydrochloride tablets.

We also refer to your submission dated September 24, 2021, containing a meeting request. The purpose of the requested meeting was to discuss and obtain the Agency's feedback on establishing the pharmacokinetic (PK) bridge between the proposed drug product and the listed drug (LD) and the requirement for any additional non-clinical pharmacology, safety pharmacology, and toxicology studies to support a future 505(b)(2) NDA submission for sitagliptin and metformin hydrochloride tablets.

Further reference is made to our Meeting Granted letter dated October 12, 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 October 19, 2021, background package.

If you have any questions, contact Michael Oyewole, Regulatory Project Manager, at (301) 796-3897.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Associate Director for Therapeutics
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
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: NDA 216743

Product Name: Sitagliptin and metformin hydrochloride tablets
Indication: An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Sponsor Name: Zydus Worldwide DMCC
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Zydus Worldwide DMCC (ZWD) is proposing to develop sitagliptin and metformin hydrochloride tablets in strengths of 50 mg/500 mg and 50 mg/1000 mg, that consists of sitagliptin (sitagliptin free base), a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride, a biguanide. ZWD intends to rely on the FDA's findings of safety and efficacy for the LD Janumet (sitagliptin and metformin hydrochloride) tablets (NDA 022044), which consists of sitagliptin phosphate monohydrate and metformin hydrochloride.

On September 24, 2021, ZWD submitted a type B Pre-NDA meeting request to discuss and obtain the Agency's feedback on establishing the PK bridge between the proposed drug product and the LD and the requirement for any additional non-clinical pharmacology, safety pharmacology, and toxicology studies to support a future 505(b)(2) NDA submission for sitagliptin and metformin hydrochloride tablets. The briefing package received on October 19, 2021, contained the final questions and background information.

2.0 QUESTIONS AND RESPONSES

Your questions are repeated below with our responses followed in bold.

2.1. Nonclinical

Question 1: Assuming that there are no safety concerns identified for sitagliptin and metformin as drug substance and their drug product, does the Agency agree that no additional non-clinical pharmacology, safety pharmacology or toxicology studies are needed to support the proposed NDA for Sitagliptin and Metformin Hydrochloride Tablets?

FDA Response to Question 1: **We agree that nonclinical studies are not needed for your active pharmaceutical ingredients, sitagliptin and metformin to support NDA filing. However, if other safety issues are identified upon review of your submission, additional nonclinical studies may be required. Note, your product formulation information was not provided in the briefing-package submitted. An adequate justification is required if your drug formulation is different from the listed drug.**

2.2. Clinical

Question 2: Does the Agency agree that the above proposed bioequivalence studies are sufficient for establishing the pharmacokinetic bridge between the proposed drug product and RLD product, JANUMET (sitagliptin and metformin hydrochloride) Tablets, 50 mg/500 mg and 50 mg/1000 mg (NDA # 022044) and to further rely on biopharmaceutical, safety and efficacy data of the Listed drug product for both the strengths?

FDA Response to Question 2: **You are proposing to conduct two open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral (fasting & fed conditions) studies to compare the relative bioavailability (BA) of the proposed drug product to the LD Janumet. sitagliptin and metformin hydrochloride) tablets, 50 mg/1000 mg (NDA # 022044).**

Your plan to conduct the proposed BA studies to establish the PK bridge between the proposed drug product and the LD, Janumet is acceptable. Refer to the FDA guidance for industry, *Bioavailability Studies Submitted in NDAs or INDs – General Considerations* for additional information. [1]

Question 3: Does the Agency agree that bioequivalence waiver will be granted for Sitagliptin and Metformin Hydrochloride Tablets, 50 mg/500 mg based on acceptable bioequivalence study for 50 mg/1000 mg strength under fasting and fed condition, comparable dissolution data and proportional similarity across all strengths?

FDA Response to Question 3: **Your proposal to request a biowaiver for sitagliptin and metformin hydrochloride tablets, 50 mg/500 mg under 21 CFR 320.22(b) appears reasonable. Please note that the adequacy of the biowaiver request is a review issue based on the totality of data submitted at the time of NDA review. The CFR BA/Bioequivalence (BE) requirements for the lower strength of your proposed product may be waived if the following criteria are met:**

[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.

1. **The biowaiver request for the proposed strength (not tested clinically) is included in the NDA.**

2. **BA/BE study (fasting and fed) for the highest strength is acceptable.**

3. **The formulation composition of the lower strength for which biowaiver is requested is proportionally similar to the corresponding highest strength product for which the BA/BE study was conducted.**

4. **The dosage form, release mechanism, and manufacturing process for all strengths are the same.**

5. **Demonstrated similarity factor (f2) of dissolution profile in quality control (QC) dissolution media between the highest strength product for which BA/BE study was conducted and lower strength product for which biowaiver is requested.**

6. **Evidence of linear PK over your proposed dose range.**

Question 4: As per the prescribing information of JANUMET® (sitagliptin and metformin hydrochloride) Tablets (NDA #022044), three pediatric studies were performed for JANUMET®, and it was reported that the efficacy of treatment with sitagliptin was not significantly different from placebo. It was concluded that the safety and effectiveness of sitagliptin and metformin hydrochloride in pediatric patients have not been established.

As mentioned in the purpose of meeting section, ZWD intends to establish pharmacokinetic bridge between the proposed product and listed drug product and rely on safety and efficacy data of RLD product. Accordingly, ZWD will not conduct any pediatric study and labeling information of the proposed product will be same as the listed drug product. Hence, ZWD is requesting waiver for pediatric assessment study for age group from birth up to 17 years.

Does the Agency agree?

FDA Response to Question 4: Yes, we agree. Your proposed fixed combination drug product (FCDP) includes sitagliptin base as one of the active ingredients. This form of sitagliptin differs from that found in the proposed LD, Janumet, which contains sitagliptin as an acid form (sitagliptin phosphate monohydrate). Therefore, your drug product is subject to requirements under the Pediatric Research Equity Act (PREA) as a new active ingredient. Accordingly, you will be required to submit an Agreed initial Pediatric Study Plan (iPSP) with your marketing application (e.g. NDA).

We recommend that your iPSP include the following:

1. **A plan to request a partial waiver of PREA study requirements in patients from birth to less than (b) (4) years of age on the basis that studies would be impossible or highly impracticable.**

2. **A plan to request a partial waiver of PREA study requirements in patients (b) (4) years to 17 years (inclusive) of age on the basis that your drug product would be ineffective in this pediatric age group.**

3. **Provide scientific data to support both waiver requests.**

See the FDA guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans,* for additional details in regard to the timing of your iPSP submission.

2.3 Regulatory

Question 5: Does the Agency agree that 6 months accelerated & 9 months long-term stability data for three primary batches is acceptable for submission in the initial NDA and 12 months long-term stability data could be submitted before mid-cycle of NDA review (within 5 months of original NDA submission)?

FDA Response to Question 5: No. As per the ICH Q1A(R2) guideline, *Stability Testing of New Drug Substances and Products*, we recommend that you provide a minimum of 12 months of long-term (25°C/60% relative humidity (RH)) and 6 months of accelerated (40°C/75% RH) stability data for three primary stability batches in the to-be marketed packaging configuration at the time of NDA submission for the drug product. Information submitted to the NDA subsequent to the original submission may or may not be reviewed as resources allow. The expiry period will be determined based on the quality and extent of data presented in the NDA submission.

3.0 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]

4.0 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.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the

[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

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.

5.0 505(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).[6] 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.[7]

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.

---

[6] 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.
[7] http://www.regulations.gov

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.

6.0 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[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. 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.

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

---

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/

PATRICK ARCHDEACON
11/23/2021 11:20:24 AM