CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216778Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 216778

MEETING REQUEST-
WRITTEN RESPONSES

Zydus Worldwide DMCC (ZWD)
Attention: Srinivas Gurram
US Agent for Zydus Worldwide DMCC
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 extended-release tablets, 50mg/500mg, 50mg/1000mg, and 100mg/1000mg.

We also refer to your submission dated February 2, 2022, containing a meeting request. The purpose of the requested meeting was to discuss follow up questions from the Written Responses issued on December 9, 2021.

Further reference is made to our Meeting Granted letter dated February 22, 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 February 2, 2022, background package.

If you have any questions, call Supendeep Dosanjh, Regulatory Project Manager, at 301-837-7649.

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
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type:	Type C
Meeting Category:	Guidance
Application Number:	NDA 216778
Product Name:	sitagliptin and metformin hydrochloride extended-release tablets
Indication:	As 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

1.0 BACKGROUND

Zydus Worldwide DMCC (ZWD) is proposing to develop sitagliptin and metformin hydrochloride extended-release tablets in strengths of 50 mg/500 mg, 50 mg/1000 mg, and 100mg/1000mg 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 XR (sitagliptin and metformin hydrochloride extended-release) tablets (NDA 202270), which consists of sitagliptin phosphate monohydrate and metformin hydrochloride.

On October 11, 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 extended-release tablets. The briefing package received on November 2, 2021, contained the final questions and background information. Written Responses were issued by the Agency on December 9, 2021.

On February 2, 2022, ZWD submitted an additional meeting request and briefing package to discuss follow up questions from the Written Responses issued on December 9, 2021. The meeting was granted on February 22, 2022, as a type C meeting.

2.0 QUESTIONS AND RESPONSES

Your questions are repeated below with our responses following in bold font.

2.1. Chemistry, Manufacturing, and Controls

ZWD's Follow up Question 1: Based on above facts, our proposed formulation strengths (i.e. 50 mg/1000 mg and 50 mg/500 mg) are proportional similar with 100 mg/1000 mg and would be eligible for biowaiver (50 mg/1000 mg and 50 mg /500 mg) on the basis of (i) Acceptable bio-equivalence studies on 100 mg/1000 mg strength based on above facts (ii) proportional similarity of the formulations across all the strengths and (iii) acceptable in-vitro dissolution testing of all strengths?

Does Agency concur with our proposal?

FDA Response to Question 1: **Yes, the Agency agrees if the proposed strengths (50 mg/500 mg and 50 mg/1000 mg) fulfill the conditions of proportional similarity (see FDA Draft Guidance for Industry, *Bioavailability Studies Submitted in NDAs or INDs – General Considerations*[1]) of formulation across all strengths, there is acceptable bioequivalence studies on the 100 mg/1000 mg strength, and dissolution profile similarity (e.g., f2) is demonstrated, they would be eligible for biowaiver. The evaluation of the submitted data will be completed at the time of the formal biowaiver request during the NDA review. For alternative considerations for approval, you can refer the response issued December 9, 2021.**

ZWD's New Question 2: Does the Agency agree that 6 months accelerated and 6 months long-term stability data for one exhibit batch of all strengths manufactured with alternate source API batch is acceptable for submission in the initial NDA as impurity profile and physicochemical properties of primary source and alternate API source are equivalent?

FDA Response to Question 2: **Yes, we agree with your proposal.**

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

[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.

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]

4.0 505(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). 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.

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

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[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] http://www.regulations.gov

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/

PATRICK ARCHDEACON
04/14/2022 10:35:17 PM

NDA 216778

MEETING REQUEST-
WRITTEN RESPONSES

Zydus Worldwide DMCC
Attention: Srinivas Gurram
US Agent for Zydus Worldwide DMCC
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 extended-release tablets.

We also refer to your submission dated October 11, 2021, received October 12, 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 extended-release tablets.

Further reference is made to our Meeting Granted letter dated October 21, 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 November 2, 2021, background package.

If you have any questions, call Supendeep Dosanjh, Regulatory Project Manager, at 301-837-7649.

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 216778
Product Name:	sitagliptin and metformin hydrochloride extended-release tablets
Indication:	As 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

1.0 BACKGROUND

Zydus Worldwide DMCC (ZWD) is proposing to develop sitagliptin and metformin hydrochloride extended-release tablets in strengths of 50 mg/500 mg, 50 mg/1000 mg, and 100mg/1000mg 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 XR (sitagliptin and metformin hydrochloride extended-release) tablets (NDA 202270), which consists of sitagliptin phosphate monohydrate and metformin hydrochloride.

On October 11, 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 extended-release tablets. The briefing package received on November 2, 2021, contained the final questions and background information.

2.0 QUESTIONS AND RESPONSES

Your questions are repeated below with our responses following in bold font.

2.1. Nonclinical

Question 1: Assuming that there are no safety concerns identified for sitagliptin and metformin hydrochloride 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 Extended-Release Tablets?

FDA Response to Question 1: Given the long history of usage of sitagliptin and metformin hydrochloride containing products, you propose to rely upon labeled information for the listed drug (LD), Janumet XR (NDA 202270), and other published literature of sitagliptin and metformin hydrochloride and that no additional nonclinical studies are needed to support the proposed NDA. We are unable to agree definitively with your proposal prior to reviewing the quality data. Additional nonclinical studies may be needed to bridge potential differences in the quality profile or other attributes between your product and the LD or if unexpected findings are observed in the clinical studies conducted to establish the PK bridge between your product and the LD.

Provide a side by side qualitatively and quantitatively (maximum daily dose) comparison of the excipients contained in your drug product versus the LD. An adequate safety justification should be provided for any excipient present at higher levels than those included in the LD or than those listed in the FDA's Inactive Ingredient Database, considering the route and duration of exposure.

Please note that a 505(b)(2) application may rely for approval upon the Agency's previous finding of safety and/or effectiveness for a listed drug(s) and published literature. Non-US labeling or non-US regulatory authority assessments may not be relied upon as these are neither FDA's findings related to a LD, nor are they published literature. If the studies upon which the non-US conclusions are based have been published, you may be able to rely upon that literature. See section 5.0 below for additional information on the 505(b)(2) regulatory pathway.

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® XR (sitagliptin and metformin hydrochloride extended-release) Tablets, 50 mg/500 mg, 50 mg/1000 mg and 100 mg/1000 mg (NDA # 202270) 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 propose to conduct two relative bioavailability (BA) studies (under fasting and fed conditions) comparing the proposed sitagliptin and metformin hydrochloride extended-release tablets (100 mg/1000 mg) to the listed product Janumet XR (sitagliptin and metformin hydrochloride extended-release) tablets. We agree that the proposed BA studies are sufficient to establish the PK bridge between the proposed drug product and LD, Janumet XR. You should use the to-be-marketed formulations of the proposed product in the pivotal bridging studies.

Question 3: Does the Agency agree that bioequivalence waiver will be granted for Sitagliptin and Metformin Hydrochloride Extended-Release Tablets, 50 mg/500 mg and 50 mg/1000 mg based on acceptable bioequivalence study for 100 mg/1000 mg strength under fasting and fed condition, comparable dissolution data and proportional similarity across all strengths?

FDA Response to Question 3: No, we do not agree. The proposed strengths are not proportionally similar in composition. Therefore, the approval of the strengths not tested clinically needs to be supported based on the following information/data:

a. **Conduct a well-designed dose proportionality study across the different strengths of the proposed drug product.**

OR

b. **In the absence of clinical dose proportionality data, the following path forward (e.g. bracketing approach) is recommended to support the approval of the strengths not tested clinically (e.g. intermediate strength, 50 mg/1000 mg).**

   i. **Demonstration of bioequivalence (BE) based on acceptable BE studies on the strengths representing the extremes in formulation variability (e.g., highest and lowest strengths (50/500 mg and 100/1000 mg).**

   ii. **Inclusion of a biowaiver request at the time of submission for the strengths not tested clinically.**

   iii. **Dissolution profile comparisons with similarity testing (e.g., f2) between the middle strengths vs. highest strength and middle strengths vs. lower strength using the same in vitro dissolution procedures for all strengths.**

The final determination on the acceptance of biowaiver requests will be made during the NDA review.

Question 4: Does the Agency agree on the full PREA waiver request?

Sponsor's Background Information: As per the prescribing information of JANUMET® XR, (sitagliptin and metformin hydrochloride extended-release) Tablets (NDA #202270), three pediatric studies were performed, and it was concluded that the safety and effectiveness of sitagliptin and metformin hydrochloride extended-release have not been established in pediatric patients. ZWD intends to establish pharmacokinetic bridge between the proposed product and listed drug product and rely on safety and efficacy data of the LD 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.

FDA Response to Question 4: Yes, we agree. The proposed fixed dose combination product (FDCP) includes sitagliptin free base as one of the active ingredients. This form of sitagliptin differs from what is found in the listed drug, Janumet XR, which contains sitagliptin phosphate monohydrate. Due to the presence of a new active ingredient your FDCP is subject to requirements under the Pediatric Research Equity Act (PREA) and you will be required to submit an agreed initial Pediatric Study Plan (iPSP) with your marketing application.

We recommend that your iPSP contain the following:

a. **A plan to request a partial waiver of PREA study requirements in patients from birth to less than 11 years of age on the basis that such studies would be impossible or highly impracticable**

b. **A plan to requires a partial waiver of PREA study requirements in patients from 11 years to 17 years (inclusive) on the basis that your drug product would be ineffective in this pediatric age group**

c. **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*[1], for additional details in regard to the timing of your iPSP submission.

2.3. Chemistry, Manufacturing, and Controls

Question 5: The unit composition of Sitagliptin and Metformin Hydrochloride Extended-Release Tablets is provided below in Table 3 for the Agency's evaluation. With the proposed formulation of the drug product, does the Agency concur that the two strengths i.e., 50 mg/500 mg and 50 mg/1000 mg of the proposed drug product are proportional similar to the strength on which we intend to perform the bioequivalence study (i.e., 100 mg/1000 mg), and qualify for the in vivo bioequivalence studies (i.e., bio waiver)?

FDA Response to Question 5: Refer to response for Question 3

Additional Biopharmaceutics Comments:

[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.

The FDA has the following recommendations regarding the dissolution information (method and acceptance criterion/criteria) that should be provided in the NDA submission.

Dissolution Method: Provide in your submission the dissolution method development report supporting the selection of the proposed dissolution test evaluating the proposed drug product. Include the following information in the dissolution method development report:

a. **Solubility data for the drug substance covering the pH range.**

b. **Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.**

c. **Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).**

d. **Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.**

e. **Include the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).**

Dissolution Acceptance Criteria: For the selection of the dissolution acceptance criteria of your product, the following points should be considered and supported by data:

a. **FDA recommends use of the dissolution profile data (i.e., specification-sampling time point and specification value) from the pivotal clinical batches.**

b. **The acceptance criteria should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Level 2 testing (n=12).**

c. **A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be where at least 80% of drug is released. If the maximum amount released is less than 80%, the last time point should be the time when the plateau of the release profile has been reached.**

d. **In general, the selection of the dissolution acceptance criteria ranges is based on mean target value ±10% and >80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an established safe space based on an approved in vitro-in vivo correlation (IVIVC) model, physiologically based biopharmaceutics modeling (PBBM), etc.**

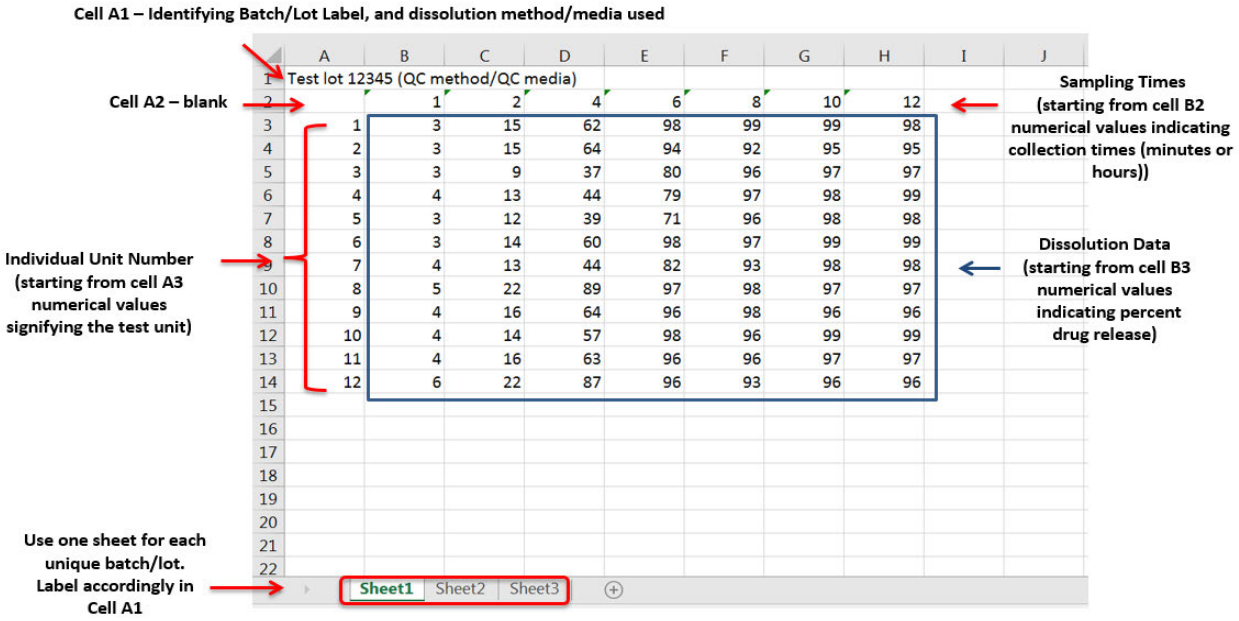
The acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

Dissolution Data Presentation: In the dissolution method development report, and/or batch analysis section, present detailed experimental dissolution data as follow:

a. **In the narrative portion of the dissolution report, include individual vessel data as much as possible, particularly regarding investigation of selection of equipment, media, agitation speed, etc.**

b. **In addition to the mean dissolution data presented in graphical and tabular formats, submit in the "Batch Analysis" section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the pivotal clinical/PK and registration/stability studies in Microsoft Excel ".xls or .xlsx" format shown below. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.**

Example - Reporting of individual vessel dissolution data



	A	B	C	D	E	F	G	H	I	J
1	Test lot 12345 (QC method/QC media)									
2		1	2	4	6	8	10	12		
3	1	3	15	62	98	99	99	98		
4	2	3	15	64	94	92	95	95		
5	3	3	9	37	80	96	97	97		
6	4	4	13	44	79	97	98	99		
7	5	3	12	39	71	96	98	98		
8	6	3	14	60	98	97	99	99		
9	7	4	13	44	82	93	98	98		
10	8	5	22	89	97	98	97	97		
11	9	4	16	64	96	98	96	96		
12	10	4	14	57	98	96	99	99		
13	11	4	16	63	96	96	97	97		
14	12	6	22	87	96	93	96	96		
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Follow the instructions provided in Specifications for File Format Types Using eCTD Specifications[2]

Question 6: Does the Agency agree that by referring the control correspondence in the prospective NDA, no further nonclinical studies would be required to establish the safety at the proposed level of use (i.e., (b) (4) mg/day for oral route of administration)?

FDA Response to Question 6: Yes, we agree

Question 7: Sitagliptin and Metformin Hydrochloride Extended-Release Tablets contains Sitagliptin free base 50 mg/100 mg and Metformin Hydrochloride 500 mg/1000 mg. We wish to propose strength specific specification limit of (b) (4) (b) (4) impurity in the finished product specification derived based on drug product's maximum daily dose recommended in the listed drug's package insert. Does the Agency agree on our evaluation for proposing the different specification limit of (b) (4) impurity in the finished product for different strengths based on daily intake of Metformin Hydrochloride?

FDA Response to Question 7: It is premature to provide any agreement at this time. The Agency has recently published a guidance for the control of nitrosamines in human drugs. The FDA guidance recommends that manufacturers evaluate the risk for nitrosamine contamination or formation in

[2]https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf

their active pharmaceutical ingredients (APIs) and drug products based on factors such as maximum daily dose (MDD), duration of treatment, therapeutic indication, and number of patients treated. The guidance also recommends the acceptable intake (AI) limits for the nitrosamine impurities (b) (4) (b) (4) and (b) (4) . Generally, sensitive methods w quantitation (LOQ) in the parts-per-billion (ppb) range are needed to meet the low AIs recommended for nitrosamines. If a nitrosamine impurity is detected above the LOQ, the manufacturer should develop a strategy to ensure that the nitrosamine level remains within the AI limit in the drug substance and drug product. Such a control strategy may include setting appropriate specification limits to ensure that the nitrosamine level reliably remains well below the AI limit in the API.

The conversion of AI limit into ppm varies by product and is calculated based on a drug's MDD as reflected in the drug label (ppm = AI (ng)/MDD (mg)). Due consideration to potential contributions from excipients should be considered.

Question 8: Does the Agency agree to the above identified in vitro dissolution studies or any additional data/information is expected?

FDA Response to Question 8: Your approach seems reasonable. Refer to response to question 3 and 5 for additional details on dissolution testing.

Question 9: Does the Agency agree on our proposed bracketing approach of generating the alcohol induce dose dumping data?

FDA Response to Question 9: Your proposed bracketing approach of generating alcohol induced dose dumping data seems reasonable.

Additional Biopharmaceutics Comments:
The consumption of alcoholic beverages can affect the release of a drug substance from a modified release (MR) formulation, leading to more rapid release of the drug and altered systemic exposure. FDA recommends that sponsors developing certain MR, solid, oral dosage forms conduct in vitro studies to determine the potential for in vivo dose dumping from alcohol consumption. The sponsor should conduct in vitro assessments of drug release from the drug product using media with various alcohol concentrations on the lowest and highest strengths of the MR drug product. The following points should be considered during evaluation of the in vitro, alcohol-induced, dose dumping of MR drug products:

a. **Dissolution testing should be conducted using the optimal apparatus and agitation speed. Dissolution data should be generated from twelve dosage units (n=12) at multiple time points to obtain a complete dissolution profile.**

b. The following alcohol concentrations are recommended for the in vitro dissolution studies: 0, 5, 20, and 40 percent.

c. The general considerations for selecting the media are as follows:

i. If the optimal dissolution medium is 0.1N HCl: Dissolution profiles in 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations are sufficient.

ii. If the optimal dissolution medium is not 0.1N HCl: Dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal, proposed regulatory dissolution medium are recommended.

d. The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.

e. The f_2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0 percent alcohol as the reference).

f. The report should include complete data (i.e., individual, mean, standard deviation, comparison plots, f_2 values, etc.) collected during the evaluation of the in vitro, alcohol-induced, dose-dumping study.

Based on the results of in vitro assessments, an in vivo BA study of the drug product when administered with alcohol may be needed. Sponsors should consult FDA for need and design of in vivo study or appropriate labeling.

2.4. Regulatory

Question 10: Does the Agency agree that 6 months accelerated & (b) (4) 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 10: No, we do not agree. Per ICH Q1A(R2) guidance, *Stability Testing of New Drug Sustances and Procuts*, it is our expectation 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 drug product batches in the to-be marketed packaging configuration at the time of NDA submission. 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*.[3] 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.[4]

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

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

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

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

- Regulations and related guidance documents.

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

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

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

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

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

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). 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. 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.

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

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

[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

manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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
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