Sophia Lou
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December 20, 2024

Re: Docket No. FDA-2024-P-3479

Dear Ms. Lou:

This letter responds to your citizen petition submitted on behalf of Jingwei Pharmaceutical Company, Ltd. and received on July 24, 2024 (Petition). The Petition requests the Food and Drug Administration (FDA or the Agency) "to require generic[1] drug manufacturers using sitagliptin [active pharmaceutical ingredient (API)[2]] manufactured via a biocatalytic process to clarify the following information:

1. Biocatalyst with a fully complete Certificate of Analysis ('CoA');
2. A detailed process of the biocatalyst preparation;
3. Analytical protocols to test residual enzyme or related decomposition fragments and other biological impurities; and
4. Purging strategies and the fate of the biocatalyst (using appropriate analytical tests)"

(Petition at 1).

We have carefully considered the Petition. For the reasons described below, your Petition is denied insofar as you request that FDA categorically require such information for all ANDAs.

[1] Your petition specifically refers to "generic" sitagliptin drug products. Accordingly, our response reflects the same terminology and is focused on sitagliptin abbreviated new drug applications (ANDAs). However, we note that the same scientific principles, regarding the issues raised in your Petition, would apply to sitagliptin new drug applications (NDAs), including 505(b)(2) NDAs.

[2] For purposes of this response, we use the terms "active pharmaceutical ingredient," "active ingredient," and "drug substance" interchangeably.

I. BACKGROUND

A. Sitagliptin

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The API (sitagliptin phosphate) can be manufactured via a biocatalytic process. This involves using an enzyme (biocatalyst) as a raw material. The biocatalyst can be introduced in different steps in the manufacturing process. Usually, the biocatalyst is used early in the process and introduces a chiral amine group in the synthesis of the starting material or intermediate for the API.

B. Legal Background Summary

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), which established the ANDA approval pathway for generic drugs.[3] To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.[4] The ANDA applicant must identify the listed drug on which it seeks to rely, and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD. FDA will not approve the ANDA if there is insufficient evidence of the foregoing or there is inadequate information to ensure the identity, strength, quality, and purity of the drug.[5] The FD&C Act and implementing regulations do not require that ANDA applicants use the same chemical synthesis or manufacturing process as those used by the RLD, and, relatedly, FDA does not generally require generic drug product impurity profiles to exactly match those of the RLD drug products referenced in their applications.

The premise underlying the Hatch-Waxman Amendments is that drug products that are (1) approved as safe and effective, (2) pharmaceutically equivalent, (3) bioequivalent, (4) adequately labeled, and (5) manufactured in compliance with Current Good Manufacturing Practice regulations, are therapeutically equivalent and can be substituted for each other with the "full expectation that the substituted product can be expected to

[3] For the purpose of this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

[4] An RLD is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" § 314.3(b) (21 CFR 314.3(b)). RLDs are identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the Orange Book, available at http://www.accessdata.fda.gov/scripts/cder/ob/.

[5] See, e.g., sections 505(j)(2)(A) and (j)(4) of the FD&C Act; see also 21 CFR 314.94 and 21 CFR 314.127.

have the same clinical effect and safety profile as the prescribed [RLD] product when administered to patients under the conditions specified in the labeling."[6]

II. DISCUSSION

As previously mentioned, your Petition requests that FDA "require generic drug manufacturers using sitagliptin API manufactured via a biocatalytic process to clarify the following information:

1. Biocatalyst with a fully complete Certificate of Analysis ('CoA');
2. A detailed process of the biocatalyst preparation;
3. Analytical protocols to test residual enzyme or related decomposition fragments and other biological impurities; and
4. Purging strategies and the fate of the biocatalyst (using appropriate analytical tests)"

(Petition at 1).

You state that "[t]he synthesis of API through biocatalysis is very much different from a chemical synthetic process to API, especially when it comes to the study of impurities in the API or the drug product" and that "[i]mpurity control (including the enzymes, degradants of the enzymes, other host cell proteins, DNA, endotoxins, cell wall debris, and antibiotics derived from the fermentation and downstream processing of the biocatalyst) in biocatalytic processes is a very complicated study." (Petition at 2.) Your Petition states, with respect to the synthesis of API through biocatalysis, that "strategies must be implemented to manage the above-mentioned impurities or potential impurities, and robust and reliable test methods of APIs must be established to detect the impurities." (Petition at 2.) You state that "[o]therwise, the patients who are taking these life-saving medicines would be under tremendous risk." (Petition at 2).

While you suggest that if the Agency does not take the Petition's requested actions, "patients who are taking these life-saving medicines would be under tremendous risk" (Petition at 2), your Petition does not define what the nature or magnitude of "tremendous risk" is to the patient. FDA thoroughly evaluates drug products, including impurities or potential impurities of the API. FDA also thoroughly evaluates relevant test methods during its quality review of all drug product applications, including those that have sitagliptin as an API, irrespective of the type of manufacturing process used. In general, FDA disagrees with the premise that sitagliptin API manufactured using a biocatalytic process categorically poses higher risk than sitagliptin API manufactured using a chemical synthetic process. Biocatalysis is a common tool in organic synthesis that uses enzymes, or natural substances, to perform chemical reactions. In the case of sitagliptin, an enzyme is usually used to introduce a chiral amine group in the synthesis of the starting material or intermediate for the API. The information needed to establish that a

[6] Orange Book, 44th Ed., at viii. FDA classifies as therapeutically equivalent, and thus substitutable, those products that are (1) approved as safe and effective, (2) pharmaceutically equivalent, (3) bioequivalent, (4) adequately labeled, and (5) manufactured in compliance with Current Good Manufacturing Practice regulations. See id., at vii.

generic sitagliptin drug product with sitagliptin API manufactured using a biocatalytic process meets the requirements for ANDA approval, including those related to quality, purity and API sameness, may depend on the specific manufacturing process used, including the critical quality attributes (CQA) of the API and at what step in the process the biocatalyst is used.[7] In general, we evaluate the adequacy and sufficiency of information in submissions on a case-by-case basis, and we decline to categorically require for all ANDAs additional impurity control strategies and test methods for sitagliptin API manufactured using a biocatalytic process.

As previously noted, an ANDA must contain, among other things, information to show that the active ingredient of the proposed generic drug product is the "same as" that of the RLD. In carrying out this analysis, the Agency typically takes into account the United States Pharmacopeia (USP) monograph and relevant FDA guidances[8] to evaluate the quality of APIs and the associated drug products.

The API that is the subject of your Petition, sitagliptin phosphate, has a USP monograph, which includes testing for organic impurities using high performance liquid chromatography (HPLC). For sitagliptin drug product applications, applicants are generally expected to include an organic impurity test (either the USP monograph test or the applicant's own in-house validated HPLC test that is comparable to the USP monograph test) in the drug substance specifications.

A. Certificate of Analysis

You state in your Petition that FDA should require generic drug manufacturers seeking approval of drug products containing sitagliptin to provide information to clarify the "[b]iocatalyst with a fully complete CoA (enzyme sequence; [Transmissible Spongiform Encephalopathy / Bovine Spongiform Encephalophathy (TSE/BSE)] free certification; activity; contamination; additives, etc.)" as follows:

[7] See e.g., See Guidance for Industry, *Q11 Development and Manufacture of Drug Substances* (November 2012) at 14 ("The quality of each raw material used in the manufacturing process should be appropriate for its intended use. Raw materials used in operations near the end of the manufacturing process have a greater potential to introduce impurities into the drug substance than raw materials used upstream. Therefore, manufacturers should evaluate whether the quality of such materials should be more tightly controlled than similar materials used upstream.") See also id. at 5 ("when assessing the link between an impurity in a raw material or intermediate and drug substance CQAs, the ability of the drug substance manufacturing process to remove that impurity or its derivatives should be considered in the assessment. The risk related to impurities can usually be controlled by specifications for raw material/intermediates and/or robust purification capability in downstream steps.")

[8] See, e.g., Guidance for Industry, Q7 *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016); Guidance for Industry, *Q11 Development and Manufacture of Drug Substances* (November 2012).

Table 1

Test	Specification
Identity	Enzyme sequence
Prion impurities	TSE/BSE free certification
Activity	A measure of specific activity of the enzyme vs. the substrate
Contamination	Certificate for no contamination during fermentation
Additives	Organic solvents, stabilizers, preservatives
pH	Actual range
Origin	
Batch number	

(Petition at 3).

We disagree with the Petition's suggestion that the Agency should categorically require all ANDAs involving sitagliptin API manufactured using the biocatalytic process to include a certificate of analysis for the biocatalyst that includes all the parameters listed in Table 1. As noted above, FDA evaluates the quality and purity of sitagliptin products and sitagliptin API on a case-by-case basis. Whether a CoA for the biocatalyst is needed, and, if so, what specifications and tests should be included in the CoA, may depend on the specific manufacturing process for the API, including at what step in the process the biocatalyst is used.[9]

We expect applicants to demonstrate their drug substance is made using a well-controlled manufacturing process (e.g., identifying material attributes such as raw materials and starting materials, and process parameters that can have an effect on drug substance CQAs[10,11]). Generally, it is the responsibility of the applicants to identify and justify the specifications of the drug substance based on their specific process. While the Agency evaluates the quality such as specifications of the API (e.g., API of sitagliptin products) in submissions, the Agency generally does not request a complete CoA and specifications for raw materials like biocatalysts (e.g., enzymes) used to manufacture starting materials of APIs like sitagliptin phosphate for the same reasons as discussed below (e.g.,

[9] See footnote 7.

[10] See e.g., Guidance for Industry, *Q11 Development and Manufacture of Drug Substances* (November 2012), at page 8.

[11] See Guidance for Industry, *M4Q: The CTD – Quality* (August 2001), at page 16 ("Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process. Information on the quality and control of these materials should be provided.").

downstream processing).[12] Therefore, we decline to adopt the Petition's suggestion that the Agency should categorically require for all ANDAs a certificate of analysis for the biocatalyst that includes all of the specifications and tests listed in Table 1.

B. Process of the Biocatalyst Preparation

You state in your Petition that FDA should require generic drug manufacturers seeking approval of drug products containing sitagliptin manufactured using a biocatalytic process to submit for review "[a] detailed process of the biocatalyst preparation" (Petition at 3).

We decline to categorically require ANDA applicants to submit a detailed description of the preparation of the biocatalyst. As previously noted, the Agency evaluates the quality information in sitagliptin applications on a case-by-case basis, taking into account the specific manufacturing process, including the CQAs of the API and at what step in the process the biocatalyst is used.

With respect to sitagliptin API manufactured via a biocatalytic process, the biocatalyst (enzyme) is used as a raw material, usually early in the process in a step that introduces a chiral amine group in the synthesis of a starting material for the API. The Agency generally does not require applicants to provide detailed processes of the preparation of such raw materials. The guidance for industry, *Q11 Development and Manufacture of Drug Substances* (November 2012) provides recommendations to identify and control material attributes (e.g., raw materials) and process parameters that can have an effect on drug substance CQAs. It specifically notes: "…when assessing the link between an impurity in a raw material or intermediate and drug substance CQAs, the ability of the drug substance manufacturing process to remove that impurity or its derivatives should be considered in the assessment. The risk related to impurities can usually be controlled by specifications for raw material/intermediates and/or robust purification capability in downstream steps."[13] Further, the process input materials (from starting materials to API) are expected to be well characterized by suitable means, such as available physicochemical characterization tools (including impurity controls). Sitagliptin API is also expected to meet applicable regulatory standards to assure and preserve its identity, strength, quality, and purity.[14] Accordingly, FDA believes that a detailed process for the preparation of the biocatalyst is generally not necessary and declines to categorically require applicants to provide such information. FDA evaluates information submitted by the applicant regarding the identity, strength, quality, and purity of the drug as part of the ordinary course of ANDA review.

[12] See Guidance for Industry, *Q11 Development and Manufacture of Drug Substances* (November 2012).

[13] See Guidance for Industry, *Q11 Development and Manufacture of Drug Substances* (November 2012) at 5.

[14] See section 501(a)(2)(B) of the FD&C Act; 21 CFR parts 210 and 211.

C. Analytical Protocols to Test Residual Enzyme or Related Decomposition Fragments and Other Biological Impurities

You state in your Petition that FDA should require generic drug manufacturers seeking approval of drug products containing sitagliptin API manufactured using a biocatalytic process to have analytical protocols to test "residual enzyme or the related decomposition fragments and other biological impurities it might bring in at necessary low levels." (Petition at 3). You further state that "[i]n some cases, no protein residues should be detected in the API (<2 [parts per million (ppm)]), and the presence of lipopolysaccharides (LPS) should be undetectable." (Petition at 3).

You state in your Petition that strategies must be implemented to manage certain biocatalyst-related impurities or potential impurities (e.g., "the enzymes, degradants of the enzymes, other host cell proteins, DNA, endotoxins, cell wall debris, and antibiotics derived from the fermentation and downstream processing of the biocatalyst"), and test methods of APIs must be established to detect these impurities; and that "[o]therwise, the patients who are taking these life-saving medicines would be under tremendous risk" (Petition at 2). You assert in your Petition that exposure to enzymes either through contact, ingestion, or inoculation can result in allergen-specific immunoglobulin E (IgE) that elicits symptoms of hypersensitivity in certain individuals (Petition at 2).

As noted above, FDA evaluates the quality and purity of sitagliptin products and sitagliptin API on a case-by-case basis, taking into account the specific manufacturing process, including the CQA of the API and at what step in the process the biocatalyst is used. We decline to categorically require generic manufacturers of sitagliptin with API manufactured via a biocatalytic process to provide identification and testing of residual enzyme or related decomposition fragments and other biological impurities (e.g., residual protein). Such information is generally not necessary as discussed below.

The production of sitagliptin API usually comprises multiple steps of operations (e.g., chemical or biocatalytic reaction, pH adjustment, filtration, and extraction in organic solvents). The downstream process of the manufacture of the sitagliptin API is expected to reduce or eliminate any residual enzyme or the related decomposition fragments (e.g., protein) and other biological impurities, and the risk for potential carryover of these impurities is low. Applicants are expected to demonstrate a well-controlled manufacturing process of the drug substance (e.g., identifying material attributes such as raw materials and starting materials, and process parameters that can have an effect on drug substance CQAs), and take into account the ability of the drug substance manufacturing process to remove impurities.[15] Applicants are also expected to include an organic impurity test (either the USP monograph test or the applicant's own in-house validated HPLC test that is comparable to the USP monograph test) in the drug substance specifications.

We further note that, even if the final API contains some amount of residual enzyme, the immunogenicity risk, including for IgE development, from residual enzymes in orally-

[15] See Guidance for Industry, *Q11 Development and Manufacture of Drug Substances* (November 2012), at page 8.

administered drug products is generally considered low. Drug products using sitagliptin as an API have an oral route of administration, and the gut promotes active suppression of orally-ingested antigens, leading to oral tolerance. Due to the low risk of biological impurities during the manufacturing process of sitagliptin API as explained above, FDA generally does not request identification and testing of residual enzyme or related decomposition fragments and other biological impurities (e.g., residual protein). Moreover, we do not agree with the Petition's proposed limits for protein residues (i.e., < 2ppm) and LPS (i.e., undetectable). The Petition does not present scientific evidence or literature to support such limits.

D. Purging Strategies and the Fate of the Biocatalyst

You state in your Petition that FDA should require generic drug manufacturers seeking approval of drug products containing sitagliptin API manufactured using a biocatalytic process to "[c]larify the purging strategies and the fate of biocatalyst, and use of the appropriate analytical tests to support them" (Petition at 3).

In your Petition, you further suggest that generic drug manufacturers must meet the analytical control standards set by the innovator (Petition at 3). You suggest in your Petition that in the case of Januvia, approved under NDA 021995, protein residues can be identified and tested, and that this demonstrates the importance of a holistic analytical control strategy in hosted cell protein (HCP) characterization for biocatalytic route synthesized API. You state in your Petition that a comprehensive analytical control strategy allows process chemists to design a new commercial manufacturing process to remove residual proteins (HCP and enzymes) to insignificant levels (<10 nanograms (ng)/mg) in three representative batches of API (Petition at 3).

With respect to the Petition's suggestion that FDA should require generic manufacturers to clarify the purging strategies and the fate of the biocatalyst, we note that the Agency generally does not request detailed information on purging strategies and a description of the fate of the biocatalyst (i.e., the enzyme) beyond what is recommended in USP <2> for oral dosage products.[16] For sitagliptin API, the Agency generally does not consider information regarding the purging strategies and the fate of the biocatalyst to be necessary because, as previously noted, among other things, the biocatalyst (i.e., enzyme) is used as a raw material; the downstream process of the API is expected to purge biocatalyst-related impurities; the API is expected to meet the applicable regulatory standards, including those regarding specifications related to impurities; and the immunogenicity risk, including for IgE development, from residual enzymes in orally-administered drug products is generally considered low. In addition, we note that, for small molecules like sitagliptin, we do not generally request identification and testing of residual protein such as comparative analytical studies between RLD and ANDA product or HCP characterizations, because the biocatalyst (enzyme) is used as the raw material and the risk is low. Due to the low risk, it is not generally necessary to have a comprehensive analytical control strategy for HCP characterization and we decline to categorically require it. Thus, we decline to categorically require such information and

[16] See *USP general chapter <2> Oral Drug Products—Product Quality Tests.*

will continue to evaluate the information provided in submissions on a case-by-case basis.

Further, as previously noted, an ANDA must contain information to show that the active ingredient of the proposed generic drug product is the "same as" that of the RLD. However, we do not agree that generic drug manufacturers must meet the analytical control standards used by the innovator. Instead, in evaluating both brand and generic drug applications, the Agency takes into account the USP monograph (e.g., acceptance criteria for impurities) and relevant FDA guidances[17] to ensure the quality of APIs and the associated drug products in these applications. Further, the Petition does not present evidence to support that the standards asserted to be those of the innovator (i.e., <10 ng/mg of residual protein) are necessary to ensure the safety of the drug product or otherwise establish that the product meets the requirements for approval.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2024.12.20 10:46:26 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[17] See, e.g., Guidance for Industry, Q7 *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016); Guidance for Industry, *Q11 Development and Manufacture of Drug Substances* (November 2012).