July 23, 2024

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition Requesting FDA to Take Certain Actions With Respect to the Manufacturing of Sitagliptin Active Pharmaceutical Ingredient

Dear Sir or Madam:

On behalf of Jingwei Pharmaceutical Company, Ltd. ("Jingwei"), the undersigned hereby submits this Citizen Petition pursuant to 21 U.S.C. § 355 and 21 C.F.R. §§ 10.25 and 10.30 to request the Commissioner of Food and Drugs to take certain actions to ensure the safety and effectiveness of sitagliptin active pharmaceutical ingredient ("API") when manufactured using a biocatalytic process. These actions are necessary to ensure drug quality and protect patient safety.

I. Actions Requested

For the reasons set forth below, the undersigned respectfully requests the Commissioner of Food and Drugs to 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).

The grounds for these requests are set forth in detail below.

II. Statement of Grounds

The enzyme process of Merck & Codexis for the preparation of sitagliptin is an excellent example of green chemistry. It won the "Greener Reaction Conditions" Presidential Green Chemistry Challenge award in 2010 [1]. This biocatalytic process eliminated the hazardous high-pressure hydrogenation, all metals (rhodium and iron), and wasteful metals removal, and operations for chiral purity upgrade. The benefits of the process include a 56% improvement in

productivity with existing equipment, a 10–13% overall increase in yield, and a 19% reduction in overall waste generation [2].

The 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. Impurity 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. The source, quality, and specification of enzyme/biocatalyst should be clarified, and thorough process research has to be performed to understand the whereabouts of the impurities brought in by enzyme/biocatalyst. Moreover, 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. Otherwise, the patients who are taking these life-saving medicines would be under tremendous risk [3].

It is difficult for generic manufacturers to prepare API with a consistent impurity profile through a biocatalytic process. Unlike a chemical catalyst, which is typically a simple complex of ligand and metal, a biocatalyst is usually a very complex enzyme or whole cell. The purging of the residue or decomposition fragments of a biocatalyst from the product is not easy. More importantly, the technology of detecting residue or decomposition fragments of biocatalysts in an API is still very challenging. Therefore, systematic and thorough studies must be carried out to understand the impurity profile of an API prepared by biocatalysis. Unfortunately, many generic manufacturers lacking the necessary technology entered this field and produce APIs using biocatalysis. So, the Food and Drug Administration ("FDA") has to be very careful when reviewing and approviong the drugs produced by such generic manufacturers for the sake of protecting the health and safety of patients.

Sitagliptin (JANUVIA) 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 [4]. An estimated 30 million people in the United States are living with diabetes, 90% to 95% of whom have type 2 diabetes mellitus [5]. Exposure to enzymes either through contact, ingestion, or inoculation can result in allergen-specific IgE that elicits symptoms of hypersensitivity in certain individuals [6]. People with diabetes are usually frail and have multiple complication diseases. In recent years, the FDA has gradually strengthened the approval requirements for new diabetes drugs [7]. For APIs prepared from different processes, their impurity profiles are different, especially those preparations involving a biocatalytic process. The API might contain the enzymes themselves, other host cell proteins, DNA, endotoxins, cell wall debris, and antibiotics derived from the fermentation and downstream processing of the biocatalyst. More importantly, the biocatalytic process involved in the production of sitagliptin API is at the very last step a chemical reaction, which poses more risk of residue from the biocatalyst or biological system of the biocatalyst preparation. Because generic drugs do not undergo clinical trials to demonstrate safety or effectiveness, special attention should be paid to approve and monitor the production of such API to minimize the risk raised by the biocatalyst.

Generic manufacturers of sitagliptin have the incentive to use biocatalytic processes as its advantages have been showcased by the originator. Under certain circumstances, it would be

possible that generic manufacturers source enzyme or API from unauthorized sources and might forge documents to circumvent the Biosecure Act (S.3558).

It is thus recommended that FDA require generic drug manufacturers seeking approval of drug products containing sitagliptin to clarify the following [3,8]:

(1) Biocatalyst with a fully complete CoA (enzyme sequence; TSE/BSE free certification; activity; contamination; additives, etc.) as follows:

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, stabilisers, preservatives
pH	actual range
origin	
batch number	

(2) A detailed process of the biocatalyst preparation should be submitted and reviewed.

(3) Analytical protocols should be in place to test residual enzyme or the related decomposition fragments and other biological impurities it might bring in at necessary low levels. In some cases, no protein residues should be detected in the API (<2 ppm) and the presence of lipopolysaccharides (LPS) should be undetectable [8].

(4) Clarify the purging strategies and the fate of biocatalyst, and use of the appropriate analytical tests to support them. In the case of Merck, protein residues can be identified and tested by ELISA, 1D SDS–PAGE with silver stain and proteomic LC–MS/MS. This case study demonstrates the importance of a holistic analytical control strategy in HCP characterization for biocatalytic route synthesized API. The comprehensive analytical control strategy allows process chemists to design new commercial manufacturing process to remove residual proteins (HCP and enzymes) to insignificant levels (<10 ng/mg) in three representative batches of API [9]. The generic drug manufacturers have to be able to meet the standards set by the innovator.

We believe it is time for the FDA to act on this matter and to do so in a much more attention than NDA drug and chemical process drug.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

V. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: June 1, 2024. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Jingwei Pharmaceutical Company, Ltd. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

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REFERENCES

[1] https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-2010-greener-reaction-conditions-award
[2] (a) Savile, C. K.; Jacob, M.; Janey, J. M.; Mundorff, E. C.; Moore, J. C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, F. J.; Brands, J.; Devine, P. N.; Huisman, G. W.; Hughes, G. J. *Science* 2010, **329**, 305. (b) Desai, A. A. *Angew. Chem., Int. Ed.* 2011, **50**, 1974.
[3] Wells, A. S.; Finch, G. L.; Michels, P. C.; Wong, J. W.; *Org. Process Res. Dev.* **2012**, 16, 1986;
[4] https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021995Orig1s053lbl.pdf
[5] https://www.fda.gov/media/151821/download?attachment.
[6] Sarlo, K.; Kirchner, D. *Curr. Opin. Allergy Clin. Immunol.* **2002**, 2, 97.
[7] (a) Ferro, E, Michos, E, Bhatt, D. et al. *J Am Coll Cardiol.* **2020**, 76, 2522; (b) Docket No. FDA–2019–N–6084.

[8] Wells, A. S.; Wong, J. W.; Michels, P. C.; Entwistle, D. A.; Fandrick, K.; Finch, G. L.; Goswami, A.; Lee, H.; Mix, S.; Moody, T. S.; Pang, L.; Sato, R. K.; Turner, N. J.; Watson, T. J., *Org. Process Res. Dev.* **2016**, 20, 594.
[9] Wang, F., Li, X., Swanson, M., Guetschow, E., Winston, M., Smith, J. P., Hoyt, E., Liu, Z., Richardson, D., Bu, X., Jawa, V., & Variankaval, N. *Biotechnology and Bioengineering*, **2022**, 119, 2088–2104.