September 24, 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

CITIZEN PETITION

Alvotech USA Inc. ("Alvotech") submits this citizen petition pursuant to 21 C.F.R. §§ 10.30 and 10.31 and Section 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA") to request that the Commission of Food and Drugs take certain actions to ensure that the U.S. Food and Drug Administration ("FDA" or "the Agency") is licensing under the Public Health Service Act ("PHSA") safe and effective interchangeable biosimilar versions of the biological product Ustekinumab.

I. ACTIONS REQUESTED

Alvotech respectfully requests that FDA refuse to license any biosimilar version of Ustekinumab as interchangeable with the brand-name reference product that is manufactured using a Chinese hamster ovary ("CHO") cell-line system—and in particular Ustekinumab-ttwe—unless and until the Agency has evaluated and concluded that the differences in sialyation between the proposed interchangeable biosimilar and the reference product, Stelara (ustekinumab), do not have the potential to adversely affect half-life and clinical effectiveness—particularly with respect to therapeutic response durability.

II. STATEMENT OF GROUNDS

A. Legal Background

1. Biological and Biosimilar Product Licensure

As a result of their complexity and the inherent variability of living organisms, the process by which biological products are manufactured is of critical importance, and generally cannot be as precisely controlled as the manufacturing process of chemically synthesized small molecule drugs. Minor changes in the manufacturing process of a biological product can lead to variations that significantly modify the product's stability, activity, specificity, or antigenic properties, thus affecting the product's safety or effectiveness profile for an intended or approved indication.

As a practical matter, the requirements for showing the safety and effectiveness of a biologic drug are similar, if not identical, to those that apply to non-biologic drugs approved under the FDCA. Thus, while the statutory provision applicable to biological products refers to the requirement that the product be "safe, pure, and potent," PHSA § 351(a)(2)(C)(i)(I), FDA has interpreted that provision as requiring the same type of evidence of safety and effectiveness, including adequate and well-controlled clinical investigations showing the product's effectiveness, that is required by statute for non-biologic drugs.

The Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), Patient Protection and Affordable Care Act, Pub. L. No. 111-148, Title VII, Subtitle A, 124 Stat. 119, 804-21 (2010), has ushered in a new era of biological product competition. The BPCIA amended the PHSA to establish a pathway, under section 351(k), for the licensure of "biosimilar" and "interchangeable" biological products of a "reference product" licensed under PHSA § 351(a). The statute defines each of these terms and specifies the general content and standards for FDA licensure.

A biological product is biosimilar to a reference product, which is "the single biological product licensed under [PHSA § 351](a) against which a biological product is evaluated in an application submitted under [PHSA § 351](k)," PHSA § 351(i)(4), if it is "highly similar" to the reference product relied on for licensure "notwithstanding minor differences in clinically inactive components," and if there are no "clinically meaningful differences" between the products with respect to safety and effectiveness. *Id.* § 351(i)(2)(A)-(B). FDA has issued various guidance documents setting forth the factors and tests that may be used to determine whether products meet the statutory requirements of "highly similar" and "clinically meaningful differences." *See* FDA, Biosimilars Guidances, at https://tinyurl.com/ynapmy56.

A Section 351(k) BLA, also referred to as an "abbreviated BLA" or "aBLA," must include information demonstrating that the proposed product is biosimilar to a reference product based on data from analytical studies, animal studies, and clinical studies, *see* PHSA § 351(k)(2)(A)(i)(I), unless FDA determines that such information is not necessary. *See id.* § 351(k)(2)(A)(ii). To the extent the mechanism of action of the reference product is known, the proposed biosimilar product must utilize the same mechanism(s). *See id.* § 351(k)(2)(A)(i)(II).

The showing needed to demonstrate biosimilarity (as well as interchangeability, discussed below) to a reference product is usually more rigorous than the bioequivalence standard used for generic drugs under the FDCA. Rather than demonstrating mere equivalence in terms of bioavailability, FDA, under the Agency's totality-of-the-evidence approach, may require a comparison of the proposed biosimilar and the reference product with respect to structure, function, animal toxicity, human

pharmacokinetics and pharmacodynamics, clinical immunogenicity, and clinical safety and effectiveness.

FDA has adopted a stepwise approach for applicants to demonstrate the biosimilarity of their proposed product to the reference product. The approach begins with extensive structural and functional characterization of both the biosimilar and reference products to help determine what additional studies, such as animal or clinical studies, may be needed. At each step, FDA recommends that a biosimilar applicant evaluate the extent to which there may be "residual uncertainty" about biosimilarity and use that uncertainty to guide next steps in the development program. *See* FDA, Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 7 (Apr. 2015) ("The purpose of a biosimilar development program is to support a demonstration of biosimilarity between a proposed product and a reference product, including an assessment of the effects of any observed differences between the products, but not to independently establish the safety and effectiveness of the proposed product. FDA recommends that sponsors use a stepwise approach to developing the data and information needed to support a demonstration of biosimilarity. At each step, the sponsor should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify next steps to try to address that uncertainty.").

2. Interchangeable Biosimilar Licensure

In addition to demonstrating biosimilarity to a reference product, an applicant may also seek to obtain a designation of interchangeability. This can be done through either the submission of an original aBLA or a supplement to a licensed aBLA for a highly similar product. *See* PHSA § 351(k)(2)(B).

A biological product is licensed as "interchangeable" with a reference product if it is biosimilar and can be expected to produce the same clinical results as the reference product in any given patient. *See id.* § 351(k)(4)(A). In addition, for a product administered more than once to a patient, there must be no greater risk to the patient in switching from the reference product to the proposed interchangeable version than would be involved in remaining on the reference product. *See id.* § 351(k)(4)(B). As FDA recently explained, "the switching standard is intended to provide added assurances regarding safety and efficacy in cases where the decision to switch a patient's treatment from the reference product to the interchangeable biosimilar is not made by the prescribing healthcare provider." FDA, Draft Guidance for Industry, Considerations in Demonstrating Interchangeability With a Reference Product: Update, at 3 (June 2024).

Although FDA initially determined "that applications or supplements seeking a determination of interchangeability include data from a switching study or studies to help provide the added assurance with respect to any immunogenicity risk associated with

switching or alternating between the reference product and the proposed interchangeable biosimilar," *id.*, the Agency has since backed away from and evolved this position. FDA's current position is that "[a]pplicants may choose to provide an assessment of why the comparative analytical and clinical data provided in the application or supplement support a showing that the switching standard set forth in [PHSA § 351(k)(4)(B)] has been met," and that "[a]ny such assessment should include any other information the applicant considers relevant to support a showing that the risk, in terms of safety and diminished efficacy, from alternating or switching between the reference product and the proposed interchangeable product is not greater than the risk of using the reference product without such alternation or switch." *Id.*

B. Factual Background

1. Stelara (Ustekinumab) Injection

Ustekinumab is a human immunoglobulin isotype class G subclass 1 kappa monoclonal antibody that acts as an antagonist of interleukin ("IL")-23 and IL-12 that is available in two parenterally-administered presentations, 45 mg/0.5 mL and 90 mg/mL for subcutaneous use and 130 mg/26 mL for intravenous use. Each presentation is separately licensed: BLA 125261 was initially licensed on September 25, 2009, and BLA 761044 was initially licensed on September 23, 2016.

Both Stelara presentations are licensed for multiple indications, including for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, active psoriatic arthritis, moderately to severely active Crohn's disease, and moderately to severely active ulcerative colitis; and for pediatric patients 6 years and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, and active psoriatic arthritis.

Stelara is produced by using a mouse hybridoma ("Sp2/0") host cell line, which allows for more efficient sialylation of the molecule as compared to, for example, production using Chinese hamster ovary ("CHO") cells using recombinant DNA technology. As discussed further below, the level of sialyation (sialic acid) may be critical to the therapeutic effect of Ustekinumab.

2. Biosimilar and Interchangeable Biosimilar Ustekinumab

FDA has licensed three highly similar biosimilar versions of Stelara:

- BLA 761373 for Samsung Bioepis Co., Ltd.'s ("Samsung's") Pyzchiva (ustekinumab-ttwe) subcutaneous injection, 45 mg/0.5 mL and 90 mg/mL (licensed on June 28, 2024);

- BLA 761425 for Samsung's Pyzchiva (ustekinumab-ttwe) intravenous injection, 130 mg/26 mL (licensed on June 28, 2024); and

- BLA 761343 for Alvotech's Selarsdi (ustekinumab-aekn) subcutaneous injection, 45 mg/0.5 mL (licensed on April 16, 2024).

FDA has also licensed two interchangeable biosimilar versions of Stelara:

- BLA 761285 for Amgen Inc.'s ("Amgen") Wezlana (ustekinumab-auub) subcutaneous injection, 45 mg/0.5 mL and 90 mg/mL (licensed October 31, 2023); and

- BLA 761331 for Amgen's Wezlana (ustekinumab-auub) intravenous injection,130 mg/26 mL (licensed October 31, 2023).

With the exception of Pyzchiva, each highly similar biosimilar and interchangeable biosimilar version of Stelara—including Stelara itself—is produced by using a Sp2/0 host cell line or a glyco-engineered CHO cell-line system. Only Ustekinumab-ttwe (Pyzchiva) is produced using CHO cells and without glycan-engineering. Additionally, other proposed biosimilars to Stelara manufactured in CHO, such as Celltrion's CT-P43 (Steqeyma in the European Union ("EU"), may be under review by FDA.

Due to a period of first interchangeable exclusivity, FDA is unable to license additional interchangeable biosimilar versions of Stelara until the first interchangeable exclusivity period expires. However, once the first interchangeable exclusivity passes, FDA is expected to act quickly to license additional interchangeable biosimilar versions of Stelara. Indeed, Samsung's development and commercialization partner Sandoz announced in July 2024 that "FDA provisionally determined that Pyzchiva® would be interchangeable with the reference medicine as it is currently subject to an unexpired period of exclusivity for the first interchangeable biosimilar biological products." Sandoz Press Release, FDA approves biosimilar Pyzchiva® (Ustekinumab-ttwe), to be commercialized by Sandoz in US (July 1, 2024), at https://tinyurl.com/bdeuf5a5.

3. The Significance of Sialylation (Sialic Acids) to Ustekinumab

One difference between the production of monoclonal antibodies using Sp2/0 versus CHO cell line is the efficient addition of sialic acids on the glycosylation structures by Sp2/0. That does not occur with CHO-based manufacturing. And it is a significant difference in terms of biological product interchangeability.

Among the many glycan constituents, sialic acid plays a critical role in extending circulatory half-life by masking the terminal galactose that would otherwise be recognized by the hepatic asialoglycoprotein receptor ("ASGPR"), resulting in clearance of the biotherapeutic from the circulation. The circulatory half-life of recombinant therapeutic proteins is an important pharmacokinetic attribute because it determines the dosing frequency of these drugs, translating directly to treatment cost. Thus, recombinant therapeutic glycoproteins such as monoclonal antibodies have been chemically modified by various means to enhance their circulatory half-life (*e.g.*. Ustekinumab biosimilar Wezlana (also known as ABP654) is expressed in glycol-engineered CHO cell-line).

C. Argument

1. Pharmacokinetic and Clinical Impact from Lower Sialylation

The potential pharmacokinetic differences resulting from significantly lower sialylation in a biosimilar Ustekinumab raise concerns about the suitability of that biosimilar for interchangeable designation. These differences could impact dosing, efficacy, and safety profiles in ways that may not be fully captured by standard studies supporting biosimilarity determinations. This is particularly so now that FDA is no longer generally requiring switching studies for purposes of obtaining licensure as an interchangeable biosimilar.

Low sialylation of therapeutic proteins can significantly impact their pharmacokinetics ("PK"), particularly in terms of circulation time, immune clearance, and overall efficacy. Here are some key impacts of low sialylation on PK:

- Reduced Serum Half-Life: Low sialylation can lead to a decreased half-life of therapeutic proteins in circulation. Sialic acid residues are crucial for stabilizing glycoproteins in the bloodstream, and their absence can result in faster clearance by the liver and kidneys. Reduced sialylation can enhance the recognition by the immune system, leading to increased phagocytosis and clearance by macrophages. This is particularly relevant for monoclonal antibodies like Ustekinumab, which are designed to have extended half-lives.

- Increased Clearance Rate: Reduced sialylation can enhance the recognition by the immune system, leading to increased phagocytosis and clearance by macrophages. This is particularly relevant for monoclonal antibodies like Ustekinumab, which are designed to have extended half-lives.

Given these potential impacts on PK characteristics of Ustekinumab biosimilars with significantly lower levels of sialylation, the clinical effects of CHO-derived

biosimilars may be different over prolonged periods than the reference product and those biosimilars manufactured in Sp2/0. These effects may include:

- Altered Efficacy: Changes in the PK profile due to low sialylation can ultimately affect the therapeutic efficacy of the protein. For example, faster clearance can lead to suboptimal drug levels and reduced therapeutic effects. While there is no full agreement on the minimal Ustekinumab plasma levels associated with sustained efficacy, studies confirm that maintaining trough levels above certain thresholds is essential for optimal therapeutic response.

- Immunogenicity Differences: Proteins with low sialylation can elicit a stronger immune response, potentially leading to the development of anti-drug antibodies. This can reduce the drug's effectiveness and increase the risk of adverse effects.

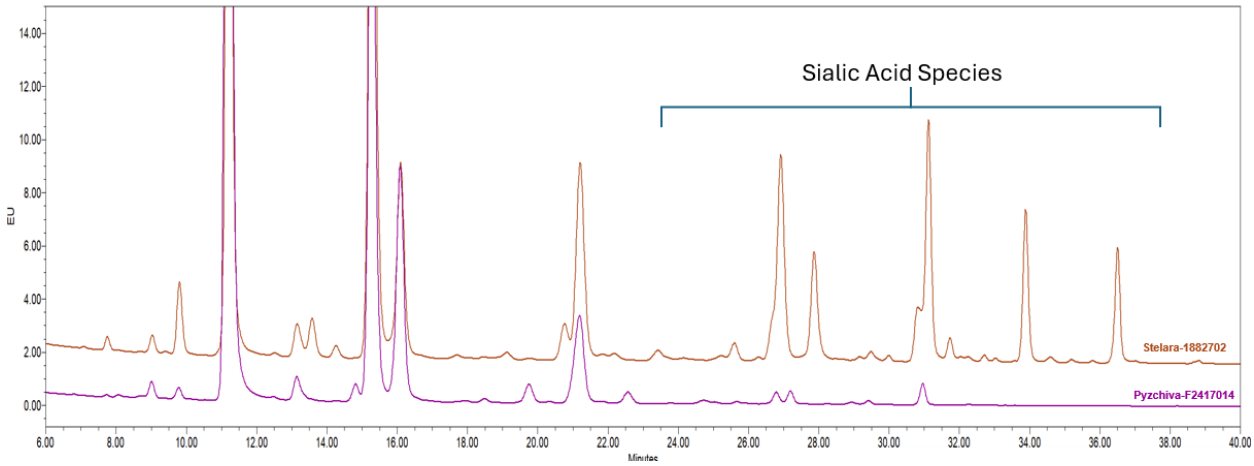
- Patient Variability: Given that glycosylation patterns influence a drug's interaction with various receptors and its distribution in the body, a biosimilar with lower sialylation may behave differently in subsets of patients, challenging the expectation of producing the same clinical result in any given patient (Shade and Anthony, 2013).

The altered clinical effectiveness profile further complicates the assessment of true interchangeability. Until the clinical implications of these pharmacokinetic alterations are thoroughly understood and addressed, it would be prudent for FDA to withhold interchangeable status for Ustekinumab produced using CHO-based manufacturing. Further studies specifically designed to assess the impact of significantly decreased sialylation on real-world interchangeability and clinical outcomes should be required before such a designation is considered. The current evidence supports this conclusion.

2. Evidence of Sialic Acid Content Differences

The sialic acid content in Stelara and Pyzchiva lots were measured by Ultra Performance Liquid Chromatography ("UPLC") analysis of RapiFluor-MS labelled released glycans. The overlay of the N-glycosylation profiles of representative Stelara and Pyzchiva lots, shown in **Figure 1** below, demonstrates the lack of sialic acid structures in Pyzchiva, compared to Stelara.

Figure 1. **N-glycan profiles of Stelara and Pyzchiva demonstrating lack of sialic acid structures in Pyzchiva**



Further, the abundance of the sialic acid structures was estimated based on the area under the curve of each of the detectable sialic acid species in Stelara and Pyzchiva lots. The data generated from two Pyzchiva 90 mg/mL PFS, one Stelara 90 mg/mL PFS, one Pyzchiva 130 mg/26 mL vial and one Stelara 130 mg/26 mL vial lots analyzed side-by-side was compared against the historical quality ranges (Min-Max) derived from Stelara using the same analytical method. The results of that analysis are reported in Table 1 below. The distribution of sialic acid content across multiple batches of Stelara and Pyzchiva are shown in Figure 2 below.

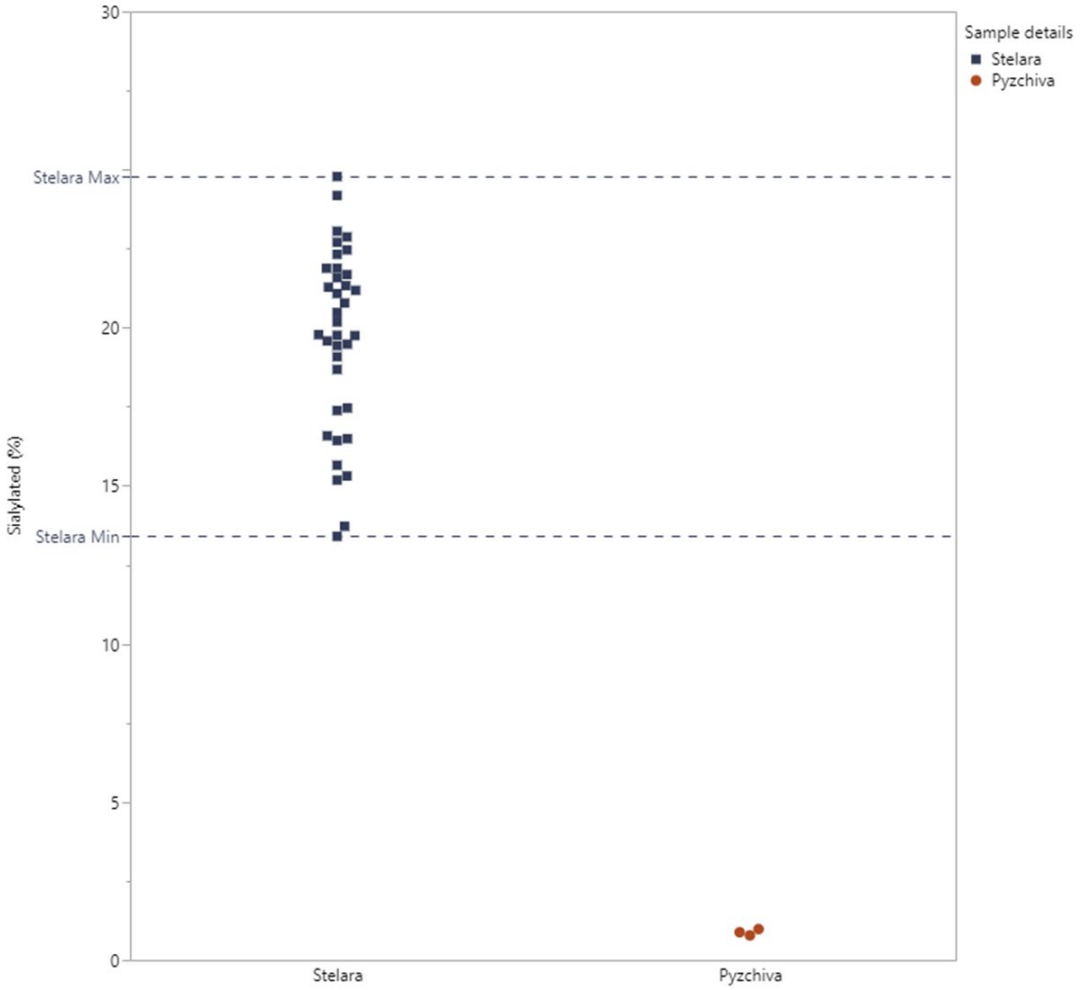
The sialic acid content (% sialylation) in ***the three Pyzchiva lots analyzed were 15-25 times lower than the US Stelara batches***.

Table 1: **Sialic acid content (% sialylation) in Stelara and Pyzchiva**

Historically Measured Stelara	Data from Lots Analyzed Side-by-side				
	Stelara		Pyzchiva		
(N=36)	1882702	JIS402	F241702	F2417008	F2417014
13.4-24.8	24.6	24.5	0.9	0.8	1.0

(N) indicates the number of lots used to derive minimum and maximum range

Figure 2: **Sialic acid content (% sialylation) in Stelara and Pyzchiva**



The potential pharmacokinetic differences resulting from lower sialylation raise significant concerns about CHO-based interchangeable Ustekinumab. As discussed above, these differences could impact dosing, efficacy, and safety profiles in ways that may not be fully captured by standard interchangeability studies. As such, FDA should withhold interchangeable status for Ustekinumab produced using CHO-based manufacturing until the Agency has received additional data and information assuring the safety and effectiveness of such products as interchangeable with Stelara.

D. Conclusion

For the foregoing reasons, FDA should refuse to license any biosimilar version of ustekinumab produced using CHO-based manufacturing as interchangeable with Stelara unless and until the Agency has evaluated and concluded that the differences in sialyation between the proposed interchangeable biosimilar and Stelara do not have the potential

to adversely affect half-life and clinical effectiveness (and particularly with respect to therapeutic response durability).

III. ENVIRONMENTAL IMPACT

The undersigned claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have an effect on the environment.

IV. ECONOMIC IMPACT

An economic impact statement will be submitted at the request of the Commissioner.

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: September 16, 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 person or organizations: Alvotech. 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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