August 17, 2022

Patrick Girondi
San Rocco Therapeutics LLC
308 E. Emily St.
Tampa, FL 33603

Sent via email to: megan@sanroccotherapeutics.com

Re: Docket No. FDA-2022-P-0704

Dear Mr. Girondi,

This letter responds to the citizen petition dated April 27, 2022, that San Rocco Therapeutics LLC (Petitioner) submitted to the Food and Drug Administration (FDA, the Agency, we) under docket number FDA-2022-P-0704 (the Petition), regarding a biologics license application (BLA) submitted by Bluebird Bio, Inc. (Bluebird) for betibeglogene autotemcel (beti-cel). In your Petition, you request that FDA conduct "a careful investigation of the BLA from Bluebird seeking a license for [b]eti-[c]el for the treatment of β-thalassemia." (Petition at 1.) The Petition also states that "FDA should withhold final approval of [b]eti-[c]el until [Petitioner's] patent infringement case against Bluebird is resolved or until after expiration of [Petitioner's] Patents."[1] (Petition at 9.)

This letter responds to the Petition in full. We have carefully reviewed the Petition and other information available to the Agency. Based on our review of these materials, and for the reasons described below, we conclude that the Petition does not contain facts demonstrating any reasonable grounds for the requested actions. In accordance with Title 21 Code of Federal Regulations (CFR) 10.30(e)(3), and for the reasons stated below, FDA is denying the Petition.

I. BACKGROUND

Bluebird submitted a BLA under section 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)) seeking approval of beti-cel for the treatment of patients with β-thalassemia who require regular red blood cell (RBC) transfusions. Beti-cel is a one-time autologous gene therapy product intended to treat transfusion dependent β-thalassemia (TDT). TDT is a rare hemoglobinopathy associated with life-long anemia requiring frequent RBC transfusions, complicated by organopathy related to iron overload, reduced quality of life, and shortened

[1] The Petition does not list withholding approval of beti-cel for these, or any other reasons, in its statement of the "Action Requested" (see Petition at 1; 21 CFR 10.30(b)(3)). However, to the extent that the Petition could be interpreted to request such an action, we address the request in section II.B of this letter.

survival. Allogenic hematopoietic stem cell transplantation using human leukocyte antigen matched related donors results in the best outcomes, but few patients have such donors available, and there continues to be a significant unmet need for patients with this disease. Following a thorough review, including consideration of recommendations from the June 9-10, 2022 meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee, FDA approved Bluebird's BLA for beti-cel (BLA 125717; ZYNTEGLO) for the treatment of adult and pediatric patients with ß-thalassemia who require regular RBC transfusions on August 17, 2022.

FDA approval of a BLA submitted under section 351(a) of the PHS Act is based on a demonstration that the product is safe, pure, and potent, a demonstration that the facility in which the product is manufactured, processed, packed, or held meets applicable standards, and the applicant's consent to inspection of the manufacturing facility.[2] The PHS Act generally does not contemplate any involvement by FDA in patent-related matters in the context of a BLA (such as the beti-cel BLA) submitted under section 351(a) of the PHS Act.[3]

II. DISCUSSION

In this section, we address Petitioner's requests.

A. Petitioner's Request for an Investigation of the BLA for Beti-cel

The Petition specifically requests a "careful investigation of the BLA from Bluebird seeking a license for [b]eti-[c]el for the treatment of β-thalassemia." (Petition at 1.) In describing the grounds for this request, the Petition argues that Bluebird's products "ha[ve] demonstrated repeated evidence of toxicity to date" and cites several potential safety concerns, including (1) "one patient exhibit[ing] a concerning clonal dominance[,]" (2) reports of certain malignancies and other adverse events occurring in clinical trials of Bluebird gene therapy products, and (3) use of beti-cel "for the treatment of β-thalassemia without an insulator[.]" (Petition at 5-7.) The Petition also cites concerns about the price of beti-cel and asserts that if FDA approves this product, then the Agency "will allow Bluebird to, without authority, make, use, offer to sell and sell [b]eti-[c]ell within the United States that infringes valid claims of U.S. patents during their patent exclusivity term — here, the [Petitioner's] Patents." (Petition at 7-9.)

As a threshold matter, by its own terms, the Petition does not purport to set forth all relevant factual information. Rather, Petitioner asks FDA to initiate an "investigation" and factfinding process, using the "utmost scrutiny" in reviewing Bluebird's BLA for beti-cel. (Petition at 1.) Therefore, we are denying your Petition to the extent that it requests, through the citizen petition

[2] See section 351(a)(2)(C) of the PHS Act.

[3] For biosimilar applications under section 351(k) of the PHS Act, Congress has established a mechanism by which certain patent disputes between a biosimilar applicant and a reference product sponsor may be identified and potentially resolved between these parties concurrent with the FDA review process, rather than after FDA approval of the product. See section 351(l) of the PHS Act and 35 U.S.C. 271(e)(2). These procedures are parallel to, but separate from, the FDA review process. The only express role for FDA related to biological product patents is described in section 351(1)(6)(C) of the PHS Act. That subsection directs a biosimilar applicant to provide the Agency with notice and a copy of certain patent infringement complaints. It then directs FDA to publish notice that it received the complaint in the Federal Register.

process, that FDA initiate an investigation. Under 21 CFR 10.30, citizen petitions can request that FDA issue, amend, or revoke a regulation or an order, or take or refrain from taking an administrative action,[4] and are to be resolved based on information in the administrative record.[5] An investigation is not an administrative action, and, as the Petition implicitly acknowledges, investigations necessarily require fact finding beyond what is presented in the current administrative record. For these reasons, we deny your request for a "careful investigation of the BLA from Bluebird seeking a license for [b]eti-[c]el for the treatment of β-thalassemia."

Although Petitioner's request for an investigation of the beti-cel BLA is not an appropriate subject of a citizen petition, we acknowledge the importance of carefully considering the risks and benefits of a product before approving a BLA. As noted above, FDA conducted a thorough review of BlueBird's BLA for beti-cel to determine if it met the requirements for licensure, including a demonstration that the product is safe, pure, and potent, as we do for any BLA that is filed.

B. Petitioner's Assertion that FDA Should Withhold Approval of the Beti-cel BLA Until Certain Patent-Related Actions Occur

Petitioner also asserts that FDA should "withhold final approval of [b]eti-[c]el until [Petitioner's] patent infringement case against Bluebird is resolved or until after expiration of [Petitioner's] Patents."[6] (Petition at 9). In support of this assertion, Petitioner states that "the timing of the FDA's final approval of [b]eti-[c]el should be based on the [Petitioner's] Patents, especially now that the FDA has been made aware that … [b]eti-[c]el infringes one or more valid claims of the [Petitioner's] Patents."[7] (Petition at 9). However, the Petition itself states that FDA should consider "the effect and status of [Petitioner's] Patents" in its determination regarding "final approval" of the beti-cel BLA because of "public policy reasons," (Petition at 9) rather than statutory or regulatory requirements.

FDA's biologics licensing regulations state that "[a] biologics license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research that the establishment(s) and the product meet the applicable requirements established in [FDA regulations in Chapter I of Title 21 of the Code of Federal Regulations].[8]" Therefore, the Agency must approve a BLA for a product that meets applicable statutory and FDA regulatory requirements for licensure. According to Petitioner, "[s]imilar to 21 CFR 314.107 *et seq*, the date of a settlement order or consent decree signed and entered by the court stating that the [Petitioner's] Patents are invalid, unenforceable or not infringed by [b]eti-[c]el should govern when the FDA issues its final approval on Bluebird's [b]eti-[c]el." (Petition at 9.) As this statement appears to acknowledge, however, the cited

[4] 21 CFR 10.30(b)(3).
[5] 21 CFR 10.30(j).
[6] As previously noted, we address this assertion to the extent it could be considered an "Action Requested" in the Petition. See 21 CFR 10.30(b)(3).
[7] We note that the PHS Act provides FDA with the authority to regulate the safety, purity, and potency of biological products, see generally section 351 et seq. of the PHS Act, whereas the federal courts are tasked with determining the outcome of litigation alleging patent infringement, see, generally, 35 U.S.C. 271.
[8] 21 CFR 601.4(a).

regulations do not apply to products licensed under the PHS Act.[9] In particular, 21 CFR 314.107, addresses applications for drug products submitted under section 505(b)(2) of the FD&C Act or abbreviated new drug applications submitted under section 505(j) of the FD&C Act, and does not apply to the beti-cel BLA submitted under section 351(a) of the PHS Act.[10] Therefore, the regulations cited by Petitioner do not prescribe requirements that beti-cel must meet to be licensed, and are not a basis for FDA to withhold approval of the beti-cel BLA. The Petitioner identifies no other statute or regulation as a basis for FDA to withhold approval of the beti-cel BLA on the grounds that there is unresolved patent litigation related to the product or that patents beti-cel allegedly infringes have not expired. Thus, the Petition fails to provide adequate legal grounds for requesting that FDA "withhold final approval of [b]eti-[c]el until [Petitioner's] patent infringement case against Bluebird is resolved or until after expiration of [Petitioner's] Patents",[11] and we deny Petitioner's request to do so.

III. CONCLUSION

FDA has carefully considered Petitioner's requests. For the reasons given in this letter, FDA denies the requests and therefore denies the Petition in its entirety.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff

[9] 21 CFR 314.1(b).
[10] Id.
[11] See 21 CFR 10.30(b)(3) (requiring citizen petitions to set forth the legal grounds on which the petition relies).