FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

August 08, 2023

23-653113

Robert Zamboldi
Site Head
Novartis Pharmaceuticals Corporation
220 E. Hanover Ave.
Morris Plains, NJ 07950

Dear Mr. Zamboldi:

The United States Food and Drug Administration (FDA) conducted an inspection of your firm, Novartis Pharmaceuticals Corporation (Novartis), located at 220 East Hanover Avenue, Morris Plains, NJ 07950, between November 28, 2022 and December 9, 2022. During the inspection, FDA investigators documented significant deviations from current good manufacturing practice (CGMP) requirements in the manufacture of your licensed biological product, Kymriah (tisagenlecleucel), including deviations from section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Title 21, Code of Federal Regulations (21 CFR), Parts 210 and 211.

At the close of the inspection, FDA issued a Form FDA-483, List of Inspectional Observations, which described significant CGMP deviations applicable to Kymriah. FDA identified additional significant deviations upon further review of the information collected during the inspection, as described below. These deviations include, but are not limited to, the following:

1. **Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)].** Specifically, your firm's sampling plan and test procedure for (b) (4) freezing bags ("Cryobags"), the primary container for Kymriah, are not appropriate to assure that Cryobags are "free of…particulate matter" as required by your acceptance criteria. Between December 2018 and the date of the inspection, you identified approximately one hundred (100) batches of Kymriah contaminated with foreign particulate matter, such as wood, cellulose, brass, and steel. In November 2020, your firm concluded the Cryobags were the most probable root cause. Although you implemented enhanced visual inspection of incoming Cryobags, your firm has continued to identify particulate matter in batches of Kymriah final product, which you have attributed to the Cryobags as recently as October 8, 2022.

2. **Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211.113(b)]; Failure to have control systems necessary to prevent contamination or mix-ups [21 CFR 211.42(c)].** Specifically, between October 2019 and the date of the inspection, you have had approximately one hundred (100) action level excursions for mold in ISO 5/Grade A and ISO 7/Grade B areas where Kymriah is manufactured. Contributing factors identified by your firm include gaps in procedures relating to cleaning and sanitizing of manufacturing areas, equipment cleaning and sanitizing, equipment transport, material handling, personnel gowning, cleanroom behavior, and handwashing and sanitation as well as failure to follow some of these procedures. You implemented at least 15 corrective and preventive actions (CAPA) to address mold, including most recently on October 12, 2022. Despite these CAPAs you have continued to recover mold in your Grade A manufacturing area, as recently as October 21, 2022, and in your Grade B manufacturing area, as recently as November 18, 2022.

3. **Failure to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity that they are purported or represented to possess [21 CFR 211.100(a)].** Specifically,

   (a) You have not validated your (b) (4) procedure performed when foreign particulate matter is identified in single-bag batches of Kymriah with respect to identity, strength, purity, and quality. The (b) (4) process has been performed on approximately (b) (4) Kymriah batches since 2019.

   (b) Your procedure for removing particulates detected in Kymriah in final product does not provide assurance that all particulates, including particulates that are not easily visible, can be identified and removed such that the final product, delivered through intravenous infusion, is free from contamination with foreign particulate matter. You have identified “sterility issue[s]” and “thrombosis issue[s]” as potential risks associated with particulate contamination.

We acknowledge receipt of your letters dated December 28, 2022, February 28, 2023, April 28, 2023, and July 14, 2023 responding to FDA’s inspectional observations (Form FDA-483). We have reviewed these responses and have the following comments:

1. Your responses do not address whether your most recent CAPA implemented on October 12, 2022, which you describe as “holistic,” has been effective against Grade B mold recoveries. Provide an overview of any action level excursions and trends, not limited to mold, in the Grade A and Grade B areas since October 12, 2022, the root causes identified, and any additional CAPAs initiated.

2. Your December 2022 response indicates that Novartis was “required to use a limited number of bags produced before the CAPAs were implemented, to meet patient needs.” Your response explains that Novartis received the first shipment of bags manufactured after CAPAs were implemented (i.e., post-CAPA bags) in January 2022 and a second shipment of post-CAPA bags in December 2022. Your response does not specifically address whether Kymriah batches found to have particulates after January 2022 were manufactured using pre-CAPA or post-CAPA bags. According to information obtained during the inspection, at least one batch of Kymriah was filled using a bag manufactured in

July 2022. Report on the foreign particulate event rate since the inspection, and the effectiveness of your CAPAs implemented to prevent foreign particulates in Kymriah.

3. Your July 2023 response states that Novartis has identified a secondary supplier for final product cryopreservation bags and that these bags will be implemented as an "alternate consumable." Please clarify if you intend to continue to use the (b) (4) bags for Kymriah. Explain any studies performed to evaluate the new bags prior to implementation as well as your plans for reporting this change to FDA. Provide an update on your timeline for implementation.

4. Your December 2022 response states that you will revise the relevant procedure to "remove the section relating to (b) (4) and to specify that each bag of drug product in which particulate matter is identified must be rejected." Clarify what actions you have taken to date or plan to take in the future if particulate is identified in one-bag batches of Kymriah.

   Additionally, your (b) (4) process is a reprocessing procedure that required submission of a supplement in accordance with 21 CFR 601.12. Explain your failure to file a supplement to the Kymriah BLA and any actions taken to prevent similar, future oversights.

5. Your December 2022 response sets a December 15, 2023, target date for revising your procedure for visual inspection of filled containers to include a (b) (4) Please provide justification for this timeline.

6. Your December 2022 response states, "All remaining units of pre-CAPA bags were quarantined on December 27, 2022, and will no longer be used in the manufacture of Kymriah." Provide your specific plans for the quarantined (b) (4) bags.

Neither this letter nor the observations noted on the Form FDA-483, which were discussed with your firm at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies that may be associated with your products. It is your responsibility to ensure full compliance with the FD&C Act, PHS Act, and all applicable regulations.

We request that you respond in writing within thirty (30) calendar days from your receipt of this letter, outlining the specific steps you have taken or plan to take to correct the noted deviations and prevent their recurrence. Include any documentation necessary to show that the matters have been addressed. If you do not believe your product is in violation of the FD&C Act, PHS Act, or applicable regulations, include your reasoning and any supporting information for our consideration.

Your response should be emailed to Amy Graf, Compliance Officer, Office of Biological Product Operations – Division 2, U.S. Food and Drug Administration at Amy.Graf@fda.hhs.gov, or sent to 300 River Place Drive, Suite 5900, Detroit, MI 48207. If you have any questions, please contact Amy Graf via email or at (313) 393-2034.

Regulatory Meeting Request

Further, we request your attendance at a Regulatory Meeting, to be held in person, at FDA's White Oak Campus on one of the following dates: October 3, 2023, at 2:00 PM Eastern Time or October 4, 2023, at 12:00 PM Eastern Time. During this meeting, be prepared to discuss our

comments above and your corrective actions to the deficiencies noted in this letter. Please contact Amy Graf, using the information above, with your date preference, a list of attendees including names, titles, and company name, as well as any presentation materials you may have by September 15, 2023.

Sincerely,

Karlton T. Watson -S

Digitally signed by Karlton T. Watson -S
Date: 2023.08.08 08:55:53 -05'00'

Karlton T. Watson
Program Division Director
Office of Biological Products Operations – Division 2