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February 8, 2024

Patrizia Cavazzoni, M.D., Director
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD, 20993-0002

Re: Application for Patent Term Extension
U.S. Patent Nos. 9,108,973 and 10,434,103
LYTGOBI (futibatinib)
Taiho Pharmaceutical Co., Ltd.
NDA No. 214801
Docket Nos. FDA-2024-E-0162 and FDA-2024-E-0163

Dear Director Cavazzoni:

We are writing on behalf of Taiho Pharmaceutical Co., Ltd. ("Taiho"), the owner of the patents listed above and applicant for patent term extension that was the subject of a January 24, 2024 letter from your office to the U.S. Patent and Trademark Office ("PTO") advising that Taiho's application for patent term extension was not submitted timely within the meaning of 35 U.S.C. 156(d)(1).[1] We are appending a copy of that letter as Exhibit A for your convenient reference.[2]

Contemporaneously with this letter, Taiho is submitting to the PTO a supplemented application for patent term extension which we respectfully submit establishes that Taiho's application for patent term extension was filed in a timely manner. We are appending a copy of that submission as Exhibit C for your convenient reference. Based on the supplemented submission and for the reasons stated below, we respectfully request that FDA now determine that Taiho's application for patent term extension was filed in a timely manner, and on that basis transmit a new letter to the PTO to that effect.

[1] Applications for patent term extensions have been submitted for both of the patents listed above. References herein to the application for patent term extension are intended to connote both applications.

[2] For clarity, please note that Taiho Oncology, Inc. ("TOI"), a subsidiary of Taiho, is the holder of the NDA listed above, and has authorized Taiho to rely on TOI's regulatory activities conducted before FDA in connection with FDA's review of the NDA for purposes of the patent term extension application. We are providing copies of the pertinent authorization documentation as Exhibit B for your convenient reference.

I. Introduction

FDA issued an initial approval notification letter for the NDA for LYTGOBI on September 30, 2022. However, that letter contained certain labeling errors. Rather than launch with an erroneous label, Taiho immediately called those errors to FDA's attention, and FDA issued a corrected approval notification letter on October 5, 2022. Taiho submitted its application for patent term extension on November 29, 2022. FDA has determined that the submission was untimely on the basis that the approval date was September 30, 2022 and the application for patent term extension was submitted one day later than 60 days after that date.[3]

As discussed more fully below, the basis for our request is that due to these errors in the initial approval notification letter, the date on which the "product received permission for commercial marketing" was in fact October 5, 2022, because had Taiho launched LYTGOBI under the September 30, 2022 letter, the drug product would have been misbranded under 21 U.S.C. section 352(a)(1) ("A drug or device shall be misbranded if ... its labeling is false or misleading in any particular"), and thus would not have had "permission for commercial marketing." Indeed, any such marketing prior to the October 5, 2022 letter would have been a prohibited act under the Food, Drug, and Cosmetic Act ("FDCA"). 21 U.S.C. section 331(a).

II. Background

LYTGOBI is a kinase inhibitor indicated for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements. This indication was approved under accelerated approval based on overall response rate and duration of response. The sponsor is currently fulfilling its post-marketing commitments.

LYTGOBI represents the first permitted commercial marketing of the product within the meaning of 35 U.S.C. sections 156(a) and 156(f)(1). LYTGOBI was subject to a regulatory review period before its commercial marketing or use within the meaning of 35 U.S.C. section 156(a)(4). As such, Taiho is entitled to apply for a patent term extension under the process set forth in 35 U.S.C. section 156 ("Section 156").

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[3] In addition to the grounds stated herein for requesting a determination that Taiho's application for patent term extension was submitted in a timely manner, namely, that the date on which the "product received permission for commercial marketing" within the meaning of Section 156 was October 5, 2020, Taiho believes that even if that date is determined to be September 30, 2022, in that event the application still would be timely submitted because the correct methodology for calculating the duration of the 60-day period stated in 35 U.S.C. section 156(d)(1) would have been to begin counting on that date (with the end of the first day being October 1, 2022) and find that the ensuing 60-day period ended on November 29, 2022. Taiho respectfully reserves the right to pursue that position in further detail if and when appropriate.

Section 156 requires that such an application for patent term extension be submitted within the 60-day period beginning on the date the product receives "permission for commercial marketing" from FDA. 35 U.S.C. section 156(d)(1). FDA issued an initial approval notification letter for LYTGOBI on September 30, 2020. FDA's determination that the application was untimely was based on the date of that letter as the start date for the calculation of the deadline. However, the September 30, 2022 letter contained labeling errors that would have rendered the product misbranded had it been marketed with that labeling. Taiho immediately informed FDA of the errors in FDA's letter, and in response FDA issued a corrected approval letter on October 5, 2020.

As set forth in more detail herein, it is Taiho's position that "permission for commercial marketing" was not effective under the September 30, 2022 FDA letter because the product would have been misbranded if marketed thereunder. Rather, "permission for commercial marketing" was only effective upon FDA's issuance of its corrected October 5, 2022 letter. Calculating the 60-day period as beginning on that date renders the application timely. In these circumstances, and as set forth in more detail below, Taiho respectfully submits that its application for patent term extension, as now supplemented, should be granted.

III. FDA'S September 30, 2022 Notification Letter Contained Labeling Errors That FDA Corrected on October 5, 2022

On September 30, 2022, FDA sent Taiho a letter entitled "ACCELERATED APPROVAL" indicating that the NDA review was complete and the NDA was approved. Attached to that letter was labeling information that included the labeling text for the Prescribing Information as well as carton and container label copy specifying storage conditions. We are appending a copy of that letter with attachments as Exhibit D for your convenient reference. That letter from FDA contained the following two errors with respect to labeling:

- Prescribing Information: The Initial U.S. Approval date was erroneously listed as "**YYYY.**"
- Carton Labels: The storage conditions were erroneously listed as "**Store below 30°C (86°F). Do not refrigerate or freeze.**"

See Exhibit D. FDA's letter specifically states, "***Content of labeling must be identical to the enclosed labeling.***" Thus, Taiho did not have the option unilaterally to correct FDA's mistake and place the correct information on the actual product labeling. In these circumstances, Taiho did not market the product with this erroneous labeling, but instead promptly notified FDA of the problem.

On October 3, 2022, Taiho sent FDA a letter pointing out the errors and proffering corrections in the erroneous areas. We are appending a copy of that letter as Exhibit E for your convenient reference. That letter from Taiho stated as follows:

The purpose of this submission is to correct two errors in the labeling documents attached to the Approval Letter as follows:

- Prescribing Information: The Initial U.S. Approval date has been changed from YYYY to 2022. A ***tracked changes*** and ***clean*** version are provided in Module 1.14.2.3, respectively.
- Carton Labels: a change in the storage condition was inadvertently carried over from a previous version, now corrected from "Store below 30°C (86°F). Do not refrigerate or freeze" to "Store LYTGOBI tablets at room temperature 20°C to 25°C (68°F to 77° F); excursions permitted between 15°C and 30°C (59°F to 86°F). [see USP Controlled Room Temperature]", to be consistent with the Prescribing Information.

See Exhibit D. Taiho submitted corrected versions of the subject sections of the labeling to the NDA for clarification to FDA. We are appending copies of those documents as Exhibit F for your convenient reference.

On October 5, 2022, FDA sent Taiho a letter entitled "Corrected Approval" which FDA stated "incorporates the correction of the error." We are appending a copy of that letter as Exhibit G for your convenient reference. As the record now stands, the publicly available approval package for LYTGOBI posted on FDA's web site ***Drugs@FDA Search*** (Drugs@FDA: FDA-Approved Drugs) only contains the "Corrected Approval" letter and shows its date as October 5, 2022. (Lytgobi (futibatinib), tablets (fda.gov))

IV. Under Section 156 "*The Date the Product Received Permission for Commercial Marketing*" Is When the Product First May Be Legally Marketed

Section 156(d)(1) specifies the time limitation for the submission of an application for patent term extension:

> To obtain an extension of the term of a patent under this section, the owner of record of the patent or its agent shall submit an application to the Director. ... [S[uch an application may only be submitted ***within the sixty-day period beginning on the date the product received permission*** under the provision of law under which the applicable regulatory review period occurred ***for commercial marketing or use*** ....

21 U.S.C. section 156(d)(1) (emphasis added). Thus, the first date of the 60-day period for submission of a patent term application is triggered by actual permission to go to market, which does not occur until the approval of the product by FDA is correct and complete.

LYTGOBI underwent a regulatory review period and received marketing authorization from FDA pursuant to the New Drug Application process set forth in FDCA section 505(b)(1). 21 U.S.C. section 355.

Drugs authorized for marketing under this provision are subject to section 502 of the FDCA, under which "misbranding" of a product is a prohibited act:

> A drug or device shall be ***misbranded*** if … its ***labelling*** is ***false*** … in ***any particular***.

21 U.S.C. section 352(a) (emphasis added); *see also* section 331(a) ("The following acts … are prohibited … introduction … into interstate commerce of any … drug … that is … misbranded.")

The above-described incorrect listing of the date of the product in the prescribing information and the incorrect listing of the storage conditions in the carton copy would have rendered the product misbranded. In an analogous case, a drug manufacturer listed the product name differently in the labeling than in the establishment registration database, and FDA found these circumstances to constitute misbranding:

> Our review determined that your firm has ***submitted a label*** for this drug that ***does not match the name of the listed drug***. As such, your firm is in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as explained below. Specifically, the ***label image*** you provided to FDA states "***triamcinolone 0.1 % ointment***," whereas the product name included in the ***drug listing submission*** is "***clotrimazole and betamethasone dipropionate cream***." These are different drug products with different active ingredients. Therefore, your firm has not fulfilled its listing obligations under section 510 (j) of the FD&C Act, which is a prohibited act under section 301(p), 21 U.S.C. 360(j) and 331(p). In addition, failure to properly list a drug with FDA also renders it misbranded under section 502(o) of the FD&C Act, and in violation of section 301(a) of the FD&C Act, 21 U.S.C. 352(o) and 331(a).

FDA Warning Letter to RPK Pharmaceuticals, Inc., No. MARCS-CMS 613400 (March 26, 2021) (RPK Pharmaceuticals Inc. - 613400 - 03/26/2021 | FDA)

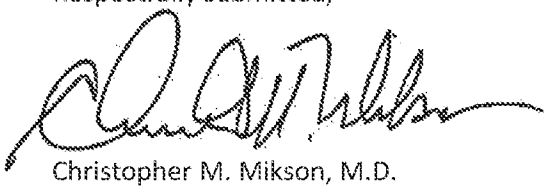
In this case, it is axiomatic that (a) the error in the approval date and (b) the inaccurate listing of the storage conditions for the product in the initial FDA notification were false. The statute does not provide any applicable exception for such a falsity. Accordingly, had Taiho marketed the product with labeling containing those errors, that labeling would have been false. In addition, leaving the errors in the statement of storage conditions in place would have resulted in the product being labeled to be stored at 32°F–86°F, rather than the correct 59°F–86°F. Given this 27-degree colder temperature range, and the notation in the initial carton labeling "***Do not refrigerate or freeze***," storing at the incorrectly-labeled conditions could have compromised product quality, possibly affecting safety and/or effectiveness of the product. Thus, regardless of the technicality of an initial notification letter stating approval on September 30, 2022, Taiho was prohibited under the FDCA from marketing LYTGOBI with false labeling, 21 U.S.C. sections 331(a) and 352(a)(1), and the actual, valid "permission for commercial

marketing" of LYTGOBI did not exist until FDA corrected the labeling language in its October 5, 2022 "Corrected Approval" letter.

V. Conclusion

Based on the supplemented patent term extension application being contemporaneously submitted to the U.S. Patent and Trademark Office and for the reasons stated above, we respectfully request that FDA now determine that Taiho's application for patent term extension was filed in a timely manner, and on that basis transmit a new letter to the PTO to that effect. To the extent FDA may have concerns, comments, or questions with respect to this request, we would respectfully request that FDA afford Taiho the opportunity for a meeting with FDA to discuss the pertinent issues.

Respectfully submitted,



Christopher M. Mikson, M.D.

Enclosure: Appendix of Exhibits
cc: Beverly Friedman (w/enclosure)

EXHIBITS NOT INCLUDED

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