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P.O. Box 6288
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In Re: Patent Term Extension
Application for
U.S. Patent No. 8,128,929
Filed: December 12, 2016

April 14, 2023

ORDER TO SHOW CAUSE

This is an order to show cause based on the apparent ineligibility of U.S. Patent No. 8,128,929 (the '929 patent) for patent term extension ("PTE") request under 35 U.S.C. § 156.

Factual Background

1. On March 6, 2012, the United States Patent and Trademark Office ("USPTO" or "Office") issued the '929 patent to Loizos *et al.* The patent is assigned to ImClone LLC ("ImClone").[1]

2. ImClone is a wholly-owned subsidiary of Eli Lilly and Company ("Lilly").[2]

3. On October 19, 2016 the Food and Drug Administration ("FDA") pursuant to § 351(a) of the Public Health Service Act, 42 U.S.C. § 262, approved the Biologics License Application (BLA), BLA-761038 for LARTRUVO® (olaratumab) to the Marketing Applicant Lilly.[3]

4. LARTRUVO® (olaratumab) (BLA-761038) was approved by the FDA under the expedited regime called Accelerated Approval Program with the aim of providing treatment to adult patients with soft tissue sarcoma (STS), 21 C.F.R. § 601.41.[4]

5. On December 12, 2016, Lilly filed a PTE Application under 35 U.S.C. § 156 to extend the term of the '929 patent based on the regulatory review period under § 351 of the Public Health services Act (PHSA) for the human biological product LARTRUVO® (olaratumab).[5]

6. On June 16, 2017, pursuant to the Memorandum of Understanding ("MOU") between the USPTO and the FDA,[6] the USPTO requested assistance from the FDA in confirming that LARTRUVO® (olaratumab) was approved pursuant to BLA-761038.

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[1] See the PTE application Exhibit B.
[2] See the PTE application page 2.
[3] See the PTE application page 8.
[4] See the PTE application page 5
[5] See the PTE application page 3.
[6] See 52 Fed. Reg. 17830, May 12, 1987.

7. On November 6, 2017, the FDA confirmed that LARTRUVO® (olaratumab) was approved pursuant to BLA-761038 on October 19, 2016.

8. On June 27, 2018, the Office pursuant to 35 U.S.C. § 156(d)(2(A)(ii) asked the FDA to determine the applicable regulatory review period (RRP) for LARTRUVO® (olaratumab) and publish the determination as a notice in the Federal Register.

9. On October 24, 2018, the FDA published the RRP for LARTRUVO® (olaratumab) in the Federal Register Notice at Vol. 83 No. 206 starting at page no. 53640.

10. On July 17, 2020, the FDA published the revocation of LARTRUVO® (olaratumab) as requested by Lilly in the Federal Register Notice at Vol. 85 No. 138, page no. 43587. Accordingly, Lilly requested the revocation of BLA-761038 and "waived" its opportunity for a hearing.

11. On July 28, 2020, Lilly in response to the Office's telephonic inquiry regarding the published notice of revocation of July 17, 2020 asserted that it still intends to pursue its PTE application for the '929 patent of LARTRUVO® (olaratumab).

12. On September 8, 2022, the FDA provided to the USPTO their final determination with respect to the RRP as published in the Federal Register.

Analysis

Pursuant to 21 U.S.C. § 301, the FDA is mandated by Congress to review BLA filings. The data gathered during the clinical trials of BLA become part of the approval process. The goal of the BLA approval process, *in part*, is to provide enough information to permit the FDA reviewer to determine whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.

The FDA has instituted the Accelerated Approval Program to allow for earlier approval of drugs that treat serious conditions, based on displaying proven efficacy at a designated future endpoint. An approved active ingredient under this program is still subject to final ratification by FDA officials where applicant is required to conduct studies to confirm the anticipated clinical benefit. If the confirmatory trial shows that the drug actually provides a clinical benefit then the FDA grants final approval for the drug. However, if the confirmatory trials do not verify the promised clinical benefit of a drug or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug, then the drug's approval may be withdrawn or the label indication of the drug adjusted. *See*, 21 C.F.R. § 314.530.[7]

The human biological drug product LARTRUVO® (olaratumab) was approved under the FDA's Accelerated Approval Requirement which relies on a surrogate endpoint or an intermediate

[7] At www. FDA.gov: Accelerated Approval, last visited April 4, 2023.

clinical endpoint pending final FDA approval based on due diligence and further clinical data. *See*, 21 C.F.R. § 601.41.

According to the PTE application, the FDA initially authorized introduction of LARTRUVO® (olaratumab) into interstate commerce under the condition that in order to obtain final FDA approval certain endpoint benchmarks must be met, otherwise the approval for LARTRUVO® (olaratumab) BLA-761038 will be withdrawn.[8]

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such a clinical trial with due diligence. If the postmarketing clinical trial fails to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 5, 2016. This requirement, along with required completion dates, is listed below.

3131-1 Conduct and submit the results of a multicenter, randomized clinical trial confirming the clinical benefit of olaratumab in combination with doxorubicin in patients with soft tissue sarcoma that is not amenable to surgery or radiation.

Final Protocol Submission:	June 2015 (completed)
Interim Analysis Submission:	June 2018
Trial Completion:	August 2019
Final Report Submission:	January 2020

According to the published Federal Register Notice of July 17, 2020, Lilly requested withdrawal "(revocation)" of its BLA for the human biological product LARTRUVO® (olaratumab).[9] The Notice, in part, provided that the required clinical data did not meet the required threshold to receive final approval and Lilly waived its oppurtunity for a hearing.

E. On January 18, 2019, Eli Lilly reported in a press release that the confirmatory study required as a condition of LARTRUO's accelerated approval, entitled "Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin Plus Olaratumab Versus Doxorubicin Plus Placebo in Patients With Advanced or Metastatic Soft Tissue Sarcoma" (ANNOUNCE trial), "did not meet the primary endpoints of overall survival in the full study population or in the leiomyosarcoma subpopulation." On September 27, 2019, Eli Lilly requested withdrawal (revocation), in writing, of the BLA for LARTRUVO (olaratumab) injection (BLA 761038) under § 601.5(a) (21 CFR 601.5(a)) because the ANNOUNCE trial failed to demonstrate improvement in overall survival for

[8] See the PTE application Exhibit K.

[9] See 85 Fed. Reg. 43587, July 17, 2020.

olaratumab in combination with doxorubicin compared to doxorubicin alone. In that letter, Eli Lilly waived its opportunity for a hearing. On February 25, 2020, the Agency issued a letter to Eli Lilly revoking the approval to manufacture and market LARTRUVO (olaratumab) injection (BLA 761038).

Therefore, under § 601.5(a), the Agency revoked the BLA for LARTRUVO (olaratumab) injection (BLA 761038), applicable as of February 25, 2020.

The right to extend the term of a patent is predicated on obtaining final FDA approval based upon regulatory review which is the result of the Drug Price Competition and Patent Term Restoration Act of 1984, Public Law 98-417, 98 Stat. 1585, commonly known as Hatch-Waxman Act. *See,* 21 U.S.C.§ 355(b), (j), (l); 35 U.S.C. § 156; and Manual of Patent Examination Procedure (MPEP) § 2750.

The PTE application is required to set forth an identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred. *See,* 37 C.F.R. § 1.740(a).

The patent term extension determination is made based on the representations contained in the PTE application. 35 U.S.C. § 156(c) provides "[t]he term of a patent eligible for extension under subsection (a) shall be extended by the time equal to the regulatory review period for *the approved product* which period occurs after the date the patent is issued". Further information may be required or inquiry made of applicant before a final determination is made on whether a patent is eligible for extension. *See* 37 C.F.R. § 1.750.

Requirement to Show Cause

Since there is no longer an approved product, Lilly is required to show cause with regard to its PTE application for LARTRUVO® (olaratumab) and establish: (1) why the USPTO should not terminate the PTE application based on the plain language of 35 U.S.C. § 156(c); and (2) why the PTE application for the '929 patent should remain under consideration despite Lilly's express written request of withdrawal (revocation) of BLA-761038 and waiver of the opportunity for a hearing. In responding to the show cause request, Lilly should identify statutory language in 35 U.S.C. § 156 or case law that would support extension of the '929 patent that claims the product despite revocation of the biologics license application. Moreover, Lilly should explain how a PTE application for a withdrawn "revoked" biologics license application is in compliance with requirements of 37 C.F.R. § 1.740.

Time Period For Response

Applicant has **TWO MONTHS** from the date of this letter to reply to this requirement. Extensions of time under 37 C.F.R. § 1.136 are available.

Any correspondence from applicant with respect to this matter should be submitted via the USPTO's EFS Web system and should be addressed as follows:

By mail: Commissioner for Patents
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Telephone inquiries related to this notice should be directed to the undersigned at (571) 272-0909.

/Ali Salimi/
Ali Salimi
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner for Patents

cc: FDA, CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

Attention: Beverly Friedman

RE: LARTRUVO® (olaratumab)
Docket No.: FDA-2017-E-5106