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In Re: Patent Term Extension
Application for
U.S. Patent No. RE44,599
Filed: September 17, 2014

June 27, 2023

ORDER TO SHOW CAUSE

This is an order to show cause based on the apparent ineligibility of U.S. Patent No. RE44,599 (the '599 patent) for patent term extension ("PTE") request under 35 U.S.C. § 156.

Factual Background

1. On November 12, 2013, the United States Patent and Trademark Office ("USPTO" or "Office") issued the '599 patent to Fowler *et al.* The patent is assigned to ICOS Corporation ("ICOS").[1]

2. On July 23, 2014 the Food and Drug Administration ("FDA") under § 505(b) of the Federal, Food, Drug and Cosmetic Act (21 U.S.C. § 355), approved the active ingredient ZYDELIG® (idelalisib) to Gilead Sciences, Inc. ("Gilead"), the Marketing Applicant.[2]

3. The FDA approved active ingredient ZYDELIG® (idelalisib) under the expedited regime called Accelerated Approval of New Drugs with the aim of providing treatment for relapsed chronic lymphocytic leukemia (CLL), 21 C.F.R. § 314.510.[3]

4. On September 17, 2014, ICOS filed PTE Applications under 35 U.S.C. § 156 to extend the term of the '599 patent based on the regulatory review period under § 505(b) of the Federal, Food, Drug and Cosmetic Act for the human drug product ZYDELIG® (idelalisib).[4] ICOS has obtained authorization to rely on the activities of Gilead for the purpose of obtaining term extension.[5]

5. On June 18, 2015, pursuant to the Memorandum of Understanding ("MOU") between the USPTO and the FDA,[6] the USPTO requested assistance from the FDA in confirming that active ingredient ZYDELIG® (idelalisib) was subject to a regulatory review period before its commercial marketing or use as required under 35 U.S.C. § 156(a)(4).

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[1] See the PTE application Attachment F1.
[2] See the PTE application Attachment E1.
[3] See the PTE application Attachment D.
[4] See the PTE applications page 2.
[5] See the PTE application Attachments B and C.
[6] See 52 Fed. Reg. 17830, May 12, 1987.

6. On November 4, 2015, the FDA confirmed that active ingredient ZYDELIG® (idelalisib) was approved on July 23, 2014.

7. On November 16, 2016, 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 ZYDELIG® (idelalisib) and publish the determination as a notice in the Federal Register.

8. On February 15, 2018, and February 23, 2018 the FDA published the RRP for ZYDELIG® (idelalisib) in the Federal Register Notices at Vol. 83 No. 32 starting at page no. 6861 and Fed. Reg. Vol. 83, No. 37 starting at page 8088 respectively.

9. On December 21, 2018, the FDA provided to the USPTO their final determination with respect to the RRP as published in the Federal Register Notices.

10. On May 26, 2022, the FDA published the revocation of active ingredient ZYDELIG® (idelalisib) as requested by Gilead in the Federal Register Notice at Vol. 87 No. 102, page no. 32031.

Analysis

Pursuant to 21 U.S.C. § 355, the FDA is mandated by Congress to review New Drug Application (NDA) filings. The data gathered during the clinical trials of NDA become part of the approval process. The goal of the NDA 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 drug product ZYDELIG® (idelalisib) was approved under the FDA's Accelerated Approval Requirement which relies on a surrogate endpoint or an intermediate clinical endpoint pending final FDA approval based on due diligence and further clinical data. *See*, 21 C.F.R. § 314.510.

According to the PTE application, the FDA initially authorized introduction of the active ingredient ZYDELIG® (idelalisib) into interstate commerce under the condition that in order to

[7] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.530, last visited June 27, 2023.

obtain final FDA approval certain endpoint benchmarks must be met, otherwise the approval for ZYDELIG® (idelalisib) will be withdrawn.[8]

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirements specified in your submission dated July 17, 2014. These requirements, along with required completion dates, are listed below.

Design and conduct a prospective trial and provide the full final report and data sets to evaluate dose reductions in patients who achieve a response or have stable disease in order to optimize the safety and efficacy of chronic administration of Zydelig in patients with follicular or small lymphocytic lymphoma. Include adequate PK sampling to provide dose-response data (for efficacy and safety).

Final Protocol Submission:	12/2014
Interim Report Submission:	12/2017
Trial Completion:	06/2019
Final Report Submission:	12/2019

According to the published Federal Register Notice of May 26, 2022, Gilead requested withdrawal "(revocation)" of its active ingredient ZYDELIG® (idelalisib).[9] The Notice, in part, provided that the required clinical data did not meet the required threshold to receive final approval and Gilead waived its oppurtunity for a hearing.[10]

On November 22, 2021, FDA met with Gilead to discuss the status of ZYDELIG (idelalisib) Tablets's accelerated approval for the follicular lymphoma indication and the SLL indication, including the continued need for postmarketing trials intended to verify clinical benefit in follicular lymphoma and small lymphocytic lymphoma. FDA raised withdrawal of approval during this discussion, explaining its intent to consult the Oncologic Drugs Advisory Committee (ODAC) on whether FDA should pursue withdrawal of the follicular lymphoma indication and the SLL indication. Subsequently, on December 17, 2021, following further communication with Gilead, FDA advised Gilead that voluntary withdrawal of approval for these indications would be appropriate under § 314.150(d) (21 CFR 314.150(d)). On January 10, 2022, Gilead submitted a letter requesting withdrawal of the follicular lymphoma indication and the SLL indication for ZYDELIG (idelalisib) Tablets and waiving its opportunity for a hearing. Gilead subsequently clarified, on February 23, 2022, that they were requesting the Agency withdraw approval of the follicular lymphoma indication and the SLL indication pursuant to § 314.150(d).

Therefore, under § 314.150(d), approvals of the follicular lymphoma indication and the SLL indication for ZYDELIG (idelalisib) Tablets are withdrawn as of May 26, 2022.

[8] See the PTE application Attachment E1.

[9] See 87 Fed. Reg. 32031, May 26, 2022.

[10] *Id.*, see 2nd full paragraph under "Supplementary Information"

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, ICOS is required to show cause with regard to its PTE applications for ZYDELIG® (idelalisib) and establish: (1) why the USPTO should not terminate the PTE applications based on the plain language of 35 U.S.C. § 156(c); and (2) why the PTE applications for the '599 patent should remain under consideration despite Gilead's express written request of withdrawal (revocation) of the active ingredient ZYDELIG® (idelalisib) and waiver of the opportunity for a hearing. In responding to the show cause request, ICOS should identify statutory language in 35 U.S.C. § 156 or case law that would support extension of the '599 patent that claims the product despite revocation of the active ingredient. Moreover, ICOS should explain how PTE applications for a withdrawn "revoked" of active ingredient ZYDELIG® (idelalisib) are 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:

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
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Attention: Beverly Friedman

RE: ZYDELIG® (idelalisib)
Docket No.: FDA-2015-E-2602
& FDA-2015-E-2604