I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 21, 2023 Signature: /Whitney Escalanti/
(Whitney Escalanti)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:

Kerry W. Fowler et al.

Patent No.: RE44,599

Issued: November 12, 2013

For: QUINAZOLINONES AS INHIBITORS OF HUMAN PHOSPHATIDYLINOSITOL 3-KINASE DELTA

Assignee: Gilead Sciences, Inc.

Unit: Office of Patent Legal Administration

Advisor: Ali Salimi

RESPONSE TO ORDER TO SHOW CAUSE PURSUANT TO 37 CFR 1.750

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

Commissioner:

Applicant provides the following response to the Order to Show Cause pursuant to 37 CFR 1.750, dated June 27, 2023 ("the Order").[1]

As described below, Applicant believes that the Order rests on a basic factual error regarding the approval status of ZYDELIG (idelalisib) oral tablets (100 and 150 mg). In particular, the Order incorrectly states that the US Food and Drug Administration ("FDA" or "the Agency") withdrew approval of ZYDELIG (idelalisib) in May 2022. In fact, FDA withdrew approval of two of the three indications for which ZYDELIG (idelalisib) had initially been approved. ZYDELIG (idelalisib) remains approved for use "in combination with rituximab, for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate therapy due to other co-morbidities."[2]

[1] The US Patent and Trademark Office ("USPTO" or "the Office") also issued an Order to Show Cause with regard to patent term extension applications for U.S. Patent RE44,638 related to the approval of ZYDELIG (idelalisib). Applicant has provided a separate response to that Order to Show Cause in the file for U.S. Patent RE44,638.

[2] NDA 205858, Approval Letter (Feb. 18, 2022), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/205858s016lbl.pdf.

On this basis, the pending applications for patent term extension ("the PTE applications") should not be terminated, and Applicant respectfully requests that the USPTO promptly issue a final determination on the pending applications.

In addition, Applicant would like to take this opportunity to address several issues raised by the Order. First, the Order repeatedly characterizes the Accelerated Approval pathway as "conditional" or otherwise short of final approval. This characterization represents an incorrect interpretation of the eligibility requirements for patent term extension under 35 USC 156.

Finally, Applicant respectfully requests that the USPTO promptly issue a final determination on the pending PTE applications related to ZYDELIG (idelalisib). These applications have been pending for more than nine years. There is no apparent justification for such delay, particularly where the USPTO has granted dozens of patent term extensions based on products approved – and PTE applications submitted – more recently than ZYDELIG (idelalisib).

I. Statement of Facts

FDA Approved Two New Drug Applications for ZYDELIG (idelalisib) on the Same Day

FDA initially approved ZYDELIG (idelalisib) in July 2014 following review of two NDAs submitted by Gilead Sciences, Inc. ("Gilead"): NDA 205858 and NDA 206545.

The first ZYDELIG NDA (NDA 205858) was submitted on September 11, 2013, and granted final approval by FDA on July 23, 2014, for the following indications:

- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies ("the FL indication"); and

- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies ("the SLL indication").[3]

The FL and SLL indications were approved under FDA's Accelerated Approval pathway. Generally, FDA's Accelerated Approval pathway authorizes the Agency to grant final approval to drugs for serious conditions that fill an unmet medical need based on evidence of an effect on a surrogate endpoint or an intermediate clinical endpoint.[4]

The second ZYDELIG NDA (NDA 206545) was submitted on December 6, 2013, for the following indication:

[3] *See* NDA 205858, Approval Letter (July 23, 2014) at 1, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205858Orig1s000ltr.pdf.

[4] *See generally* 21 USC 356(h); 21 CFR 314.500 – 314.560.

- In combination with rituximab, for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate therapy due to other co-morbidities ("the CLL indication").[5]

NDA 206545 was given a priority review and granted final approval by FDA on July 23, 2014 – the same date as final approval of NDA 205858.[6] FDA did not use its Accelerated Approval pathway as the basis for granting final approval of the CLL indication.

At the time of the final approval of the two NDAs, FDA "administratively closed" NDA 206545. FDA therefore directed Gilead to make all future submissions and correspondence to NDA 205858. Both NDAs continue to be listed in FDA's Drugs@FDA database, although the Agency has not updated the listing for NDA 206545 since its initial approval.[7] FDA's Orange Book publication contains a single listing for ZYDELIG (idelalisib) under NDA 205858.[8]

Timely Submission of Applications for Patent Term Extension

Following approval of the ZYDELIG NDAs, Applicant timely submitted four patent term extension applications, seeking extension of two patents: U.S. Patent No. RE44,599 ("the '599 Patent") and U.S. Patent No. RE44,638 ("the '638 Patent").

Specifically, on September 17, 2014, Applicant submitted two PTE applications for each patent, based on the two regulatory review periods for the two NDAs approved on July 23, 2014. Those four PTE applications can be found in the following public dockets maintained by FDA, as well as in the relevant USPTO file for each patent:

- Docket No. FDA-2015-E-2604: PTE application seeking extension of the ***'599 Patent*** based on the approval of ***NDA 205858***;

- Docket No. FDA-2015-E-2619: PTE application seeking extension of the ***'638 Patent*** based on the approval of ***NDA 205858***;

- Docket No. FDA-2015-E-2615: PTE application seeking extension of the ***'599 Patent*** based on the approval of ***NDA 206545***; and

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[5] *See* NDA 206545, Approval Letter (July 23, 2014), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/206545Orig1s000ltr.pdf.

[6] *Id.*

[7] *See* Drugs@FDA: FDA-Approved Drugs, *available at* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=205858; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=206545.

[8] *See* Approved Drug Products with Therapeutic Equivalence Evaluations (known as "the Orange Book") (43rd ed. 2023) at 3-243, *available at* https://www.fda.gov/media/71474/download?attachment.

- Docket No. FDA-2015-E-2602: PTE application seeking extension of the ***'638 Patent*** based on the approval of ***NDA 206545***.

Each of these four PTE applications remains pending, notwithstanding that FDA issued its Final Determination of the Regulatory Review Period for each of the applications in December 2018.[9] Since that time, the Office has, to the best of our knowledge, taken no action with regard to the four pending applications.

Voluntary Withdrawal of the FL and SLL Indications

Based on the Accelerated Approval of the FL and SLL indications in 2014, FDA directed Gilead to conduct certain post-marketing trials to verify the clinical benefit of ZYDELIG for these indications.[10] In 2021, Gilead and FDA met to discuss the status of the FL and SLL post-marketing trials.[11] Following these discussions, Gilead requested withdrawal of approval of the FL and SLL indications, by letter of January 10, 2022.[12] Gilead also waived its right to a hearing.[13] In January 2022, Gilead also submitted a supplement to NDA 205858 to revise the labeling for ZYDELIG to reflect the voluntary withdrawal of the FL and SLL indications.

In a May 2022 Federal Register Notice ("the FR Notice"), FDA announced the withdrawal of approval of the FL and SLL indications.[14]

II. The Order to Show Cause

On June 27, 2023, the USPTO issued an Order to Show Cause pursuant to 37 CFR 1.750 "based on the apparent ineligibility of U.S. Patent No. RE44,599 for patent term extension."[15]

In particular, the Order to Show Cause asserted that the ZYDELIG drug product had been withdrawn and, on that basis, directed Applicant to show cause with regard to the eligibility of the pending PTE applications:

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[9] *See, e.g.*, Letter from FDA to USPTO Regarding Patent Nos. RE44599 and RE44638 (Dec. 21, 2018), Docket Nos. FDA-2015-E-2604-0007 and FDA-2015-E-2619-0007 (informing USPTO that "FDA considers the regulatory review period determination to be final" with regard to NDA 205858).

[10] NDA 205858, Approval Letter (Feb.18, 2022) at 3, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/205858s016lbl.pdf.

[11] *See* Gilead Sciences, Inc.; Withdrawal of Approval of Indications for Relapsed Follicular Lymphoma and Relapsed Small Lymphocytic Lymphoma for ZYDELIG (Idelalisib) Tablets, 87 FR 32031 (May 26, 2022).

[12] *Id.*

[13] *Id.*

[14] *Id.*

[15] Order to Show Cause at 1.

> 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 [*sic*] active ingredient ZYDELIG® (idelalisib) are in compliance with requirements of 37 C.F.R. § 1.740.

III. ARGUMENT

A. The USPTO should not Terminate the Pending PTE Applications Related to the Approval of ZYDELIG (idelalisib), Because the Approval of ZYDELIG (idelalisib) has not been Withdrawn

Since its initial FDA approval in July 2014, ZYDELIG (idelalisib) has at all times been an "approved product" for purposes of 35 USC 156(c) and therefore eligible for patent term extension. On that basis alone, the pending PTE applications arising from the final approval of ZYDELIG (idelalisib) should not be terminated and should instead remain under consideration by the USPTO.

1. FDA has Withdrawn Approval of Two Indications for ZYDELIG (idelalisib), *not* the Entire Product or the ZYDELIG "Active Ingredient"

Based on the statement of facts in the Order to Show Cause, the USPTO appears to misunderstand the scope of FDA's May 2022 FR Notice. Specifically, the Office has characterized the FR Notice as providing for the withdrawal of ***all ZYDELIG products*** or ***the active ingredient in ZYDELIG***. For example, the Order to Show Cause states that "[a]ccording to the published Federal Register Notice of May 26, 2022, Gilead requested withdrawal '(revocation)' of its active ingredient ZYDELIG® (idelalisib)."[16]

That is not accurate. In fact, the FR Notice announced that Gilead had voluntarily agreed to withdraw final approval of ***two of the three approved indications for ZYDELIG***:

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[16] *Id.* at 3. It is unclear why the term "(revocation)" appears in quotation marks here. That term does not appear in the FR Notice cited by the Office in the Order to Show Cause. Instead, it appears that the term "revocation" comes from USPTO's own statement of the factual record: "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."

> 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).[17]

As FDA made clear at the conclusion of the FR Notice, the withdrawal of these two indications had no impact on the ongoing final approval of ZYDELIG (idelalisib) for the CLL indication:

> 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. ***Withdrawal of approval of these indications does not affect any other approved indication for ZYDELIG (idelalisib) Tablets***.[18]

As the FR Notice makes clear, ZYDELIG continues to be an approved drug product; it is presently listed in Drugs@FDA and in the Orange Book's Prescription Drug Products List. As the most recent labeling available on Drugs@FDA shows, ZYDELIG (idelalisib) continues to be approved for the CLL indication:

> Zydelig is indicated, in combination with rituximab, for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.[19]

As the Order to Show Cause notes, 35 USC 156(c) conditions eligibility for patent term extension on, *inter alia*, the existence of an "approved product."[20] In short, ZYDELIG is – and has been at all times since the initial approval of NDAs 206545 and 205858 in July 2014 – an FDA-approved drug product. Accordingly, ZYDELIG's ongoing approval clearly satisfies the basic statutory requirements described in the Order to Show Cause. On this factual basis alone, the PTE applications related to the final approval of ZYDELIG (idelalisib) should not be terminated and should therefore remain under consideration for patent term extension.

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[17] 87 FR at 32031 (emphases added).

[18] *Id.* (emphases added).

[19] Prescribing Information, NDA 205858 (Feb. 18, 2022) at Section 1, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/205858s016lbl.pdf.

[20] *See, e.g.*, Order to Show Cause, In Re: Patent Term Extension Application for U.S. Patent No. RE44,599 (June 27, 2023) at 4.

B. The Order to Show Cause Mischaracterizes the FDA's Accelerated Approval Pathway and the Eligibility for Patent Term Extension of Drug Products Approved under this Pathway

As described in the Statement of Facts, two of the three indications for ZYDELIG were initially approved under FDA's Accelerated Approval pathway. FDA's Accelerated Approval pathway is a "final approval" and represents the "permission for commercial marketing" required by the PTE statute's eligibility criteria. In fact, as shown below, the USPTO has routinely granted patent term extensions for products – like ZYDELIG – approved under this pathway, even where those approvals have been withdrawn.

1. Approval of the FL and SLL Indications under FDA's "Accelerated Approval" Pathway Satisfies the Patent Term Extension Eligibility Criteria

The Order to Show Cause appears to mischaracterize the legal status of drug products approved under FDA's Accelerated Approval pathway. In particular, the Order to Show Cause repeatedly and mistakenly characterizes FDA's approval of ZYDELIG in July 2014 as something less than "final approval":

- "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."[21]

- 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 obtain final FDA approval*** certain endpoint benchmarks must be met, otherwise the approval for ZYDELIG® (idelalisib) will be withdrawn."[22]

- "If the confirmatory trial shows that the drug actually provides a clinical benefit ***then the FDA grants final approval*** for the drug."[23]

However, FDA's Accelerated Approval is not, as the Office contends, conditional or "subject to final ratification." Instead, Accelerated Approval is a "final approval" sufficient to satisfy the relevant requirements in 35 USC 156(c).

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[21] Order to Show Cause at 2 (emphases added).

[22] *Id.* at 2-3 (emphases added). In support of this statement, the Office cited Exhibit E1 of the PTE application, which is the FDA Approval Letter for NDA 205858. Nothing in that letter states that postapproval requirements must be fulfilled to obtain "final approval."

[23] *Id.* at 2 (emphases added).

a. FDA's Accelerated Approval Pathway is a "Final Approval" Permitting Commercial Marketing

Generally, Accelerated Approval is a statutory authority pursuant to which FDA may grant final approval to a drug (or biological product) for a serious or life-threatening condition:

> "[u]pon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."[24]

As FDA has repeatedly made clear, "[d]rugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval"[25]:

> Under accelerated approval, FDA can rely on a particular kind of evidence, such as a drug's effect on a surrogate endpoint, as a basis for approval. FDA carefully evaluates such evidence to ensure that any remaining doubts about the relationship of the effect on the surrogate to clinical benefit are resolved by additional postapproval studies or trials.[26]

It is true that drug products approved pursuant to the Accelerated Approval pathway must comply with certain postapproval requirements. For example, drug products approved under the Accelerated Approval regime may be subject to additional postapproval studies "to verify and describe the predicted effect on a irreversible morbidity or mortality or other clinical benefit."[27] In some cases, FDA requires that a sponsor of a drug approved under Accelerated Approval submit its promotional materials to the Agency prior to public dissemination of the materials.[28] Under the Accelerated Approval statute and regulations, failure to comply with FDA's postapproval requirements may be grounds for withdrawal of the approval of the product under expedited procedures.[29]

Nevertheless, the imposition of postapproval requirements does not render an Accelerated Approval "conditional" or otherwise different than a "final approval." The

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[24] 35 USC 156(c)(1)(A).

[25] *Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014) (citing 21 USC 355(d)), available at https://www.fda.gov/media/86377/download.

[26] *Id.* at 19 (citing 57 FR 58942 at 58948).

[27] 35 USC 156(c)(2)(A).

[28] *Id.* at 156(c)(2)(B).

[29] 35 USC 156(c)(3).

Accelerated Approval provisions are not unique in authorizing FDA to impose postapproval requirements or to provide for withdrawal of approval if a company fails to fulfill those requirements. For example, several other provisions of the Food, Drug, and Cosmetic Act (FDCA) authorize FDA to impose postapproval study requirements – including requirements to conduct additional clinical trials.[30] Similarly, the FDCA grants FDA authority to withdraw approval of drug products for numerous reasons, ranging from new safety issues to failure of the NDA holder to submit required patent information.[31]

The Office's apparent confusion regarding Accelerated Approval may stem from FDA's own use of informal terms to describe such approvals. For example, FDA commonly differentiates between "Accelerated Approval" and "regular approval" or "traditional approval."[32] These informal terms have no basis in the statute or regulations, but are instead simply used to signify the termination of postapproval requirements under the Accelerated Approval pathway.[33]

Notwithstanding the Agency's use of such informal terms, approval of an NDA under FDA's Accelerated Approval pathway is equivalent to, and carries the same legal status as, an approval under the "traditional" – that is, not Accelerated Approval – pathway.

b. ZYDELIG is – and has been since July 2014 – an "Approved Product" Sufficient to Qualify for Patent Term Extension

Nothing in the PTE statute supports the idea of treating an approval of an NDA under FDA's Accelerated Approval pathway differently than any other NDA approval granted by the Agency. In fact, the term "final approval" does not appear in the PTE statute or regulations.

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[30] *See, e.g.*, 21 USC 355c (authorizing FDA to require postapproval studies in pediatric populations); 21 USC 355(o) (authorizing FDA to impose postapproval studies and/or clinical trials to assess certain safety risks).

[31] *See generally* 21 USC 355(e).

[32] See, e.g., FDA, Verified Clinical Benefit | Cancer Accelerated Approvals, *available at* https://www.fda.gov/drugs/resources-information-approved-drugs/verified-clinical-benefit-cancer-accelerated-approvals ("This listing includes accelerated approvals (AAs) for malignant hematology and oncology indications with postmarketing trials that have verified clinical benefit and for which traditional approval has been subsequently granted for the specific indication.").

[33] *See, e.g.*, "FDA approves pralsetinib for non-small cell lung cancer with RET gene fusions" (August 9, 2023), *available at* https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pralsetinib-non-small-cell-lung-cancer-ret-gene-fusions ("Pralsetinib was previously granted accelerated approval for the NSCLC indication on Sept. 4, 2020, based on initial overall response rate (ORR) and duration of response (DOR) in 114 patients enrolled in the ARROW trial (NCT03037385), a multicenter, open-label, multi-cohort trial. The conversion to regular approval was based on data from an additional 123 patients and 25 months of additional follow-up to assess durability of response.").

Instead, the statute generally refers only to an "approved product," whose meaning is expressly described in 35 USC 156(a).

In the case of a drug like idelalisib, the term "product" is defined to mean "a drug product," which is, in turn, defined to mean "the active ingredient of…a new drug" (as that term is used in the FDCA).[34] In addition, the PTE statute provides that the term "approved product" is used throughout 35 USC 156 to refer to a "product" that has met two eligibility criteria for obtaining a patent term extension:

- The product "has been subject to a regulatory review period before its commercial marketing or use; and
- "[T]he permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred."[35]

Thus, eligibility for patent term extension depends in pertinent part on being an "approved product."

The approval of ZYDELIG on July 23, 2014, is indisputably a final approval. Specifically, ZYDELIG was granted final approval by FDA on July 23, 2014, for three indications, following the Agency's review of two NDAs. FDA employed its Accelerated Approval pathway to grant final approval to ZYDELIG for the FL and SLL indications. What is more, FDA also granted final approval to ZYDELIG for the CLL indication under the agency's traditional approval pathway – that is, not pursuant to the Accelerated Approval pathway.[36]

As noted, FDA and the USPTO already determined that Zydelig "was approved on July 23, 2014" and, on such basis, determined that the PTE was (1) timely filed within sixty-days and (2) calculated the review period for the PTE term, ending on the approval date of July 23, 2014.[37] To find now that Zydelig was not approved for PTE purposes creates a divergent meaning(s) under 35 USC 156, which is wholly unsubstantiated and violative of the plain language doctrine. Even assuming *arguendo* that an Accelerated Approval was in fact

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[34] 35 USC 156(f)(1)(A),(f)(2).

[35] 35 USC 156(a)(4),(5).

[36] Even if an Accelerated Approval were somehow ineligible for PTE – which as described above is plainly not the case under the governing law and regulations – the USPTO's Order to Show Cause does not acknowledge that ZYDELIG was approved for the CLL indication under the "traditional approval" pathway, not the Accelerated Approval pathway. *See* Approval Letter, NDA 206545 (July 23, 2014), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/206545Orig1s000ltr.pdf.

[37] See Determination of Regulatory Review Period for Purposes of Patent Extension; ZYDELIG—New Drug Application dated Feb. 22, 2018), https://www.regulations.gov/document/FDA-2015-E-2602-0006.

"conditional" as the USPTO states, 35 USC 156 explicitly use the term "conditional approval" in the context of filing fees, thereby demonstrating that Congress knew how to reference a "conditional approval" if it wanted to and chose not to for the issue at hand.[38]

Accordingly, ZYDELIG is an "approved product" supporting the eligibility of the '599 Patent for extension.

2. Longstanding USPTO Practice Confirms that Drug Products Approved under the Accelerated Approval Pathway are Eligible for PTE

Consistent with the legal framework just described, the USPTO has a longstanding practice of recognizing that drug and biological products approved under the FDA's Accelerated Approval pathway are eligible for patent term extension. In fact, the USPTO has awarded extended patents covering drug and biological products whose initial approval was pursuant to FDA's Accelerated Approval pathway on numerous occasions, even where the approval was subsequently withdrawn for failure to fulfill the postmarketing requirements:

- For example, FDA approved NDA 205353 for FARYDAK (panobinostat). This NDA was granted final approval under the Accelerated Approval pathway for the "use…in combination with bortezomib (BTZ) and dexamethasone (Dex), for the treatment of patients with multiple myeloma (MM), who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent."[39] According to publicly available sources, the sponsor of NDA 205353 submitted an application for patent term extension on April 23, 2015, seeking extension of US Patent No. 6,833,384. PTO issued a final Patent Term Extension Certificate for this patent on January 29, 2021. The approval for this product was withdrawn pursuant to a Federal Register notice on March 24, 2022.[40]

- Similarly, FDA approved BLA 761069 for IMFINZI (durvalumab) on May 1, 2017. That approval was granted under the Accelerated Approval pathway for "the treatment of patients with locally advanced or metastatic urothelial carcinoma who: have disease progression during or following platinum-containing chemotherapy. [or] have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-

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[38] *See 35 USC 156(h)(i)* "if the Secretary of Health and Human Services provides notice to the sponsor of an application or request for approval, conditional approval, or indexing of…"

[39] Approval Letter, NDA 205353 (February 23, 2015) at 1, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/205353Orig1s000ltr.pdf.

[40] Secura Bio, Inc.; Withdrawal of Approval of New Drug Application for FARYDAK (Panobinostat) Capsules, 10 Milligrams, 15 Milligrams, and 20 Milligrams (Mar. 24, 2022), 87 FR 16742, Docket No. FDA-2022-N-0352.

containing chemotherapy.[41] The sponsor of BLA 761069 submitted an application for patent term extension on June 28, 2017, seeking extension of US Patent No. 9,493,565. PTO issued a final Patent Term Extension Certificate on September 3, 2020. Subsequently, the approval for this indication was withdrawn pursuant to a labeling supplement approved on February 19, 2021.[42]

- Finally, the USPTO issued a final Patent Term Extension Certificate for US Patent No. 6,888,027 on September 27, 2021. That PTE was granted based on the approval of NDA 206256 for BELEODAQ (belinostat) on July 3, 2014 – ***a mere twenty days earlier than the ZYDELIG NDAs***. The initial approval of BELEODAQ for "the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)" was made pursuant to the Accelerated Approval pathway based on a surrogate endpoint. According to FDA's most recent database, the sponsor of BELEODAQ has not yet completed its required confirmatory postapproval trial.[43] That trial was initially projected to be completed on January 31, 2021 – six months before the PTE certificate was awarded.[44]

There are many other examples of the Office extending patents based on the regulatory review of products approved under FDA's Accelerated Approval pathway.

3. 35 USC 156 does not Require that a Drug Product Maintain Final Approval to be Eligible for Patent Term Extension

Finally, the PTE statute does not require that an applicant maintain final approval of its drug or biological product – only that it have obtained approval. As noted above, the PTE statute conditions eligibility for patent term extension on a drug product being "subject to a regulatory review period before its commercial marketing or use" and that "permission for the commercial marketing or use of the product being the first received permission for commercial marketing or use under the provision of law under which the applicable regulatory review occurred."[45]

As the FARYDAK and IMFINZI precedents show, withdrawal of approval does not render a drug or biological product ineligible for patent term extension. FDA approvals may be withdrawn for commercial reasons or for reasons related to the safety and efficacy of the

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[41] Prescribing Information, BLA 761069 (May 1, 2017) at Section 1, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf.

[42] *See* Approval Letter, BLA 761069/S-029 (Feb. 19, 2021), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761069Orig1s029ltr.pdf.

[43] CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint As of June 30, 2023, *available at* https://www.fda.gov/media/151146/download?attachment.

[44] See FDA, Postmarket Requirements and Commitments database (search term: Product = "BELEODAQ"), *available at* https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

[45] 35 USC 156(a)(4),(5); 37 CFR 1.720(e).

product. In either case, the marketing status of a drug or biological product has – and should have – no impact on the eligibility of a patent for extension on the basis of FDA's regulatory review of that product.

Consistent with these examples, ZYDELIG would be eligible for PTE even if the entire product had been withdrawn – which, as we have shown above, it has not.

C. The USPTO should Promptly Grant the ZYDELIG PTE Applications, because they have been Pending for More than Nine Years

Applicant respectfully requests that the USPTO promptly make a final determination on the four pending PTE applications related to FDA approval of ZYDELIG (idelalisib). These applications have been pending for more than nine years, since their submission in September 2014.

There appears to be no reason for such a lengthy and arbitrary delay. As some of the examples already cited in this Response make clear, many other products approved around the same time as ZYDELIG have already received final PTE determinations, including the vast majority of eligible drug and biological products approved in 2014. Indeed, ***many products approved years after ZYDELIG have already received patent term extension***. Finally, numerous patents have been extended based on regulatory review of products approved under the Accelerated Approval pathway – even where postmarketing trials have not been completed or the indication(s) have been withdrawn.

As noted above, it is a fundamental tenet of administrative law that a government agency must not treat similarly situated parties differently, absent a rational basis for doing so. Here, there appears to be no basis – certainly the USPTO has provided none in the Order to Show Cause– for the unnecessary delay in making a final determination on the PTE applications arising from the FDA approval of ZYDELIG (idelalisib) in July 2014. As noted in our Statement of Facts, the USPTO long ago sought and obtained all of the information needed from FDA to make a final determination on the eligibility of these patents for extension.

CONCLUSION

In view of the foregoing, Applicant has provided this Response to the Office's Order to Show Cause in order to demonstrate that ZYDELIG (idelalisib) remains an approved product eligible for patent term extension, notwithstanding the withdrawal of two indications approved under FDA's Accelerated Approval pathway. Applicant respectfully requests that the Office promptly issue a final determination regarding the eligibility of the '599 Patent for patent term extension. If the Office believes a telephone conference would expedite grant of the PTE application, please contact the undersigned at the number provided.

Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes the Commissioner to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 07-1250 (Docket No. 616082000831), from which the undersigned is authorized to draw.

Dated: November 21, 2023

Respectfully submitted,

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