EXELIXIS®

1851 Harbor Bay Parkway
Alameda, CA 94502

650.837.7000 MAIN
650.837.8205 FAX
www.exelixis.com

March 27, 2023

BY ELECTRONIC FILING (http://www.regulations.gov)

William N. Parham, III
Director, Paperwork Reduction Staff
Office of Strategic Operations and Regulatory Affairs
Room C4-26-05
7500 Security Boulevard
Baltimore, MD 21244-1850

RE: Agency Information Collection Activities: Proposed Collection; Comment Request [CMS 10844]

Dear Mr. Parham:

Exelixis appreciates the opportunity to respond to the Centers for Medicare & Medicaid Services (CMS) notice entitled "Agency Information Collection Activities: Proposed Collection; Comment Request" (ICR), which relates to the Agency's implementation of protections for "small biotech drugs" under the Inflation Reduction Act (IRA) "Drug Price Negotiation Program" (Program).[1]

Exelixis is an innovative, research-based pharmaceutical company that focuses exclusively on accelerating the discovery, development, and commercialization of new medicines for difficult-to-treat cancers. We are committed to serving patients in desperate need of more effective cancer therapies. Our discovery efforts have resulted in two available products that are marketed by Exelixis: CABOMETYX® (cabozantinib) tablets and COMETRIQ® (cabozantinib) capsules. Exelixis has a long-standing commitment to research and development (R&D), year-over-year making significant investments to deliver the next generation of medicines that raises the standard of care for patients with cancer. Before we had a commercialized product, we spent between 73 percent and 87 percent of operating expenses on R&D (nearly $2.3 billion). In 2022, Exelixis invested approximately 55 percent of its revenue for the year in R&D, and we anticipate investing approximately 56 percent of our revenue in R&D in 2023.[2]

We recognize that CMS recently issued initial guidance on the Program (Initial Guidance).[3] The Initial Guidance clearly states that CMS is *not* soliciting comments on Section

[1] 88 Fed. Reg. 4184 (Jan. 24, 2023).
[2] Exelixis Announces Fourth Quarter and Full Year 2022 Financial Results and Provides Corporate Update (Feb. 7, 2023), *available at* https://ir.exelixis.com/news-releases/news-release-details/exelixis-announces-fourth-quarter-and-full-year-2022-financial.
[3] Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191-1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitation of Comments ("Initial Guidance"), CMS (March 15, 2023), https://www.cms.gov/files/document/medicare-drug-price-negotiation-program-initial-guidance.pdf.

30, which addresses foundational issues such as the small biotech carveout and the definition of a qualifying single source drug. Because CMS is not soliciting comments on these critically important topics under the Initial Guidance, we are submitting commentary on the small biotech carveout in response to this ICR.

As further explained below, despite a record of clear Congressional intent to preserve the ability of small biotechnology companies to continue their development of innovative medicines, Exelixis is concerned that the absence of definitive guidance from CMS on the scope of the small biotech carveout creates uncertainty as to whether that provision will safeguard the innovation of companies, like Exelixis, that it was intended to assist. In particular, Exelixis urges CMS to make clear that pursuant to the definition of qualifying single source drug set forth in the Initial Guidance—under which all dosage forms, strengths, and formulations that share the same active moiety and the same New Drug Application (NDA) holder are considered together— a qualifying single source drug must qualify as a small biotech drug for *all* of its formulations, provided the NDA holder retains ownership of these formulations (and thus they continue to constitute the same qualifying single source drug). We believe a contrary approach would be inconsistent with the statutory obligation to calculate a single "maximum fair price" (MFP) for each qualifying single source drug, and inconsistent with Congress' intent to protect R&D incentives for small biotechnology companies.

I. Congress Intended to Protect R&D Incentives for Small Biotechnology Companies

A key principle underlying the IRA is to protect incentives for small biotechnology companies. In the lead-up to the IRA's predecessor, the Build Back Better Act, Senate Finance Committee Chair Ron Wyden released a set of "Principles for Drug Pricing Reform."[4] The principles set forth a mission: to "mak[e] prescription drug prices more affordable while encouraging innovation and scientific breakthroughs."[5] Significantly, the principles recognized the unique and critical role of small biotechnology companies, stating that "[t]he research that led to these medical advances can largely be traced back to small biotechnology companies that take on a disproportionate share of the risk of R&D."[6] Therefore, Chair Wyden indicated that drug pricing reforms should be "tailored to the scale of these companies, as well as other factors that affect their access to capital."[7]

All of the subsequent drafts of the drug pricing reform legislation—including the IRA, as enacted—reflect Chair Wyden's commitment to protect small biotechnology companies. For example, one of the key provisions that Congress included in the IRA to protect small biotech manufacturers is the small biotech carveout. This carveout excludes "small biotech drugs" from the Program for three years, after which such drugs will have a temporary floor on the MFP

[4] Chairman Ron Wyden, Principles for Drug Pricing Reform 1 (June 2021), *available at* https://www.finance.senate.gov/imo/media/doc/062221%20SFC%20Drug%20Pricing%20Principles.pdf.
[5] *Id.* at 1.
[6] *Id.* at 3 (emphasis added).
[7] *Id.*

determined under the Program.[8] Additionally, under the Part D redesign provisions of the IRA, certain smaller manufacturers (known as "specified manufacturers" and "specified small manufacturers") will have their manufacturer discounts phased-in over a five-to-seven-year period.[9]

II. CMS Should Interpret the New Formulations Exclusion from the Small Biotech Carveout Consistent with the Statute and Congressional Intent

Under the small biotech carveout, a "small biotech drug" is defined as "a qualifying single source drug" that satisfies certain Medicare expenditure thresholds.[10] The IRA further states that "a new formulation, such as an extended release formulation, of a qualifying single source drug shall not be considered a [small biotech drug]."[11] CMS is not soliciting comment on section 30 of the Initial Guidance, which addresses the small biotech carveout and other foundational issues related to selection under the Program. We are deeply concerned that CMS' decision to skip over the step of providing stakeholders an opportunity to comment before issuing final guidance deprives stakeholders of an important process protection and creates avoidable programmatic risk. Neither the Initial Guidance nor the ICR addresses the new formulation exclusion to the small biotech carveout at all, leaving manufacturers without a clear understanding of how CMS will determine whether their drugs qualify as small biotech drugs. Nevertheless, if CMS maintains the definition of qualifying single source drug set forth in the Initial Guidance, we believe that the statute requires a qualifying single source drug to qualify as a small biotech drug for *all* of its formulations, provided the NDA holder retains ownership of these formulations. In addition to securing other intended effects, this outcome will also protect the R&D incentives that drive investment in innovation like that demonstrated by Exelixis in its development of COMETRIQ® and CABOMETYX®.

A. The MFP, and thus the Small Biotech Carveout, Applies Equally to All Formulations of the Same Qualifying Single Source Drug

Under the statute, the scope of a "qualifying single source drug" is significant at every stage of the Program. A qualifying single source drug that meets certain criteria is a negotiation-eligible drug,[12] and a negotiation-eligible drug that meets certain criteria is a selected drug.[13] CMS is required to establish a single MFP for each selected drug, as well as to "establish[] . . . procedures to compute and apply [that] maximum fair price across different strengths and dosage forms of a selected drug and not based on the specific formulation or package size or package type of such drug."[14] Therefore, the statute establishes a chain under which a single MFP

[8] Social Security Act (SSA) §§ 1192(d)(2)(A); 1194(d).
[9] SSA § 1860D-14C(g)(4)(B)-(C).
[10] SSA § 1192(d)(2)(A).
[11] SSA § 1192(d)(2)(C).
[12] SSA § 1192(d)(1).
[13] SSA § 1192(b).
[14] SSA § 1196(a)(1)-(2).

ultimately is determined for each qualifying single source drug that is selected under the Program.

The Initial Guidance defines a "qualifying single source drug" to include all dosage forms, strengths, and formulations of a product that share the same active moiety and the same NDA holder.[15] Because a single MFP will apply across all of these formulations, if CMS maintains the definition of qualifying single source drug set forth in the Initial Guidance, Exelixis believes a qualifying single source drug must qualify as a small biotech drug for *all* of its formulations, provided the manufacturer retains ownership of the NDA of all of these formulations (and thus all formulations continue to constitute the same qualifying single source drug) and the qualifying single source drug meets the Medicare expenditure thresholds set forth in SSA § 1192(d)(2)(A).

B. Applying the Small Biotech Carveout to all Formulations of the Same Qualifying Single Source Drug Furthers the Innovation Incentives Underlying this Provision

As Congress recognized when enacting the IRA, small and mid-size biotechs, like Exelixis, play an increasingly larger role in discovering innovative medicines. This involves overwhelming challenges and inherent risks of failure at each step of the discovery, development, regulatory, and commercialization process. For example, during most of Exelixis' nearly 30-year history, the company operated without product revenue, taking significant risks to sustain formidable research facilities and clinical trials. Exelixis was founded in 1994, focused initially on early-stage scientific research before shifting exclusively to cancer. We used an industry-leading high throughput drug discovery process to identify compounds with therapeutic potential and advance them through preclinical and clinical development. As is typical, a large majority of these drug candidates failed. But, some succeeded, of which the most promising was cabozantinib. FDA approved COMETRIQ® (cabozantinib) capsules in 2012 to treat a small population of patients with a rare thyroid cancer.[16] We suffered a catastrophic event in late 2014 after two phase 3 registrational cabozantinib clinical trials failed in prostate cancer. These events forced us to restrict spending immediately, reduce our workforce by more than 70 percent, and focus our limited financial resources on two important and difficult-to-treat indications – kidney and liver cancer. Fortunately for seriously ill cancer patients and the company, cabozantinib demonstrated positive results in two large global pivotal trials, and CABOMETYX® (cabozantinib) tablets was approved in 2016.[17]

CABOMETYX® is Exelixis' primary commercial product, and it is the culmination of decades of high-risk investments in cutting-edge science. We estimate that Exelixis invested over $2 billion on the *separate* development of CABOMETYX®, including internal and external work required to perform discrete clinical trials on each drug and efforts to achieve regulatory

[15] Initial Guidance at 8.

[16] Drugs@FDA: FDA-Approved Drugs, New Drug Application (NDA): 203756, *available at* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=203756.

[17] Drugs@FDA: FDA-Approved Drugs, New Drug Application (NDA): 208692, *available at* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208692.

approvals. The significant time and expense to conduct additional clinical trials to obtain a new NDA for important and difficult-to-treat cancer indications is the sort of investment that Congress sought to protect and encourage through the small biotech carveout.

If CMS were to interpret the small biotech carveout to apply only to certain formulations of a qualifying single source drug — in spite of the statutory language to the contrary — CMS would also be undermining Congress' intent to protect small biotech R&D incentives. Such an outcome would impose a heavy and irrational penalty on manufacturers that invest in improvements to the formulation of their existing products while also seeking new indications to benefit different patient populations, rather than just seeking FDA approval for new indications using the same, and perhaps less advantageous, formulation.[18] Such a result would undermine innovation and frustrate the express goals of Congress in enacting specific protections for small biotech drugs. If CMS nevertheless intends to move forward with this interpretation, we believe it is imperative that CMS issue guidance and provide an opportunity for stakeholders to submit comments before finalizing its interpretation.

III. Conclusion

Over the company's 29-year history, Exelixis' employees and investors have become accustomed to the natural turbulence of the biotechnology industry. We have also come to appreciate the tremendous influence that government incentives (and disincentives) can have upon biotech investment decisions, and how those decisions ultimately enhance or impede innovation. With the small biotech carveout provisions of the IRA, Congress recognized and expressed a desire to preserve the ability of small biotechnology companies to continue to make outsized contributions to medical innovation. It is therefore critically important that CMS carefully consider the impact of its policies on smaller biotechs, like Exelixis, that drive a significant share of medical innovation. We urge the Agency to clarify that a qualifying single source drug will qualify as a small biotech drug for *all* of its formulations, provided the NDA holder retains ownership of these formulations. Such an outcome is mandated by the statute and consistent Congress' intent to maintain incentives for innovation, particularly by small biotechnology companies, and will help achieve Congress' goal of encouraging such businesses to invest further in the next generation of lifesaving treatments.

* * *

[18] Such a result would be an unprecedented disincentive to develop superior formulations and operate quite differently, for example, than the new formulations provision of the Medicaid rebate statute. Prior to the Affordable Care Act amendments to the Medicaid rebate statute, manufacturers could potentially reduce their Medicaid rebate liability by launching new formulations of certain covered outpatient drugs. The Affordable Care Act amendments removed this incentive for launching a new formulation, but they did not *penalize* manufacturers for launching new formulations. Affordable Care Act § 2501(d) (as amended by Health Care and Education Reconciliation Act of 2010 § 1206(a)) (codified at SSA § 1927(c)(2)(C)).

Thank you again for the opportunity to comment on CMS's implementation of the small biotech carveout. We would be happy to answer any questions that CMS may have regarding the topics we address herein.

Sincerely,

Michael M. Morrissey, Ph.D.
President and Chief Executive Officer
Exelixis, Inc.