September 14, 2017

Andrew Bremberg
Assistant to the President and the Director of the Domestic Policy Council
The White House
Washington, DC

Keagan Lenihan
Senior Adviser to HHS Secretary Tom Price
Department of Health and Human Services
Washington, DC
Via: Keagan.lenihan@hhs.gov

Re: Zinbryta Patent Issues

Dear Mr. Bremberg and Ms. Lenihan:

We write to you today with regard to the excessive price of an important drug for multiple sclerosis called daclizumab, co-marketed by Biogen and AbbVie as Zinbryta at prices roughly 3 to 4 times higher in the United States than in other high income countries. The patent for Zinbryta was licensed from the NIH, and under the Bayh-Dole Act there are three specific actions the United States government can and should utilize to authorize affordable competition, or to force Biogen to lower its price. These include: (1) making use of the government's royalty-free rights in the patent; (2) utilizing the "march-in" right to license the patent to a third party; and/or (3) terminating the exclusive license.

Amidst a crisis of out-of-control drug prices, this is an instance where the federal government has the power to act without the need for any additional statutory authority.

Background on Daclizumab

Multiple sclerosis is a disease of the nervous system affecting an estimated 400,000 patients in the United States, and approximately 2.5 million patients worldwide, with no known cure. The disease can cause muscle weakness, blurred vision, chronic pain, and any of a number of other symptoms, and can lead to an inability to walk, and to death.

Zinbryta was developed with technologies licensed by the Department of Health and Human Services to Biogen.[1] The drug was approved by the Food and Drug Administration in May 2016 as a self-administered monthly injectable used for the treatment of relapsing forms of multiple sclerosis in patients who failed to respond to two or more previous therapies.[2]

The FDA touted the importance of this drug, saying that "Zinbryta provides an additional choice to patients who may require a new option for treatment."[3]

Biogen has priced this drug at more than $90,000 per year, per patient; the price per syringe (the recommended dosage of 150 mg/ml) is approximately $7,500 every four weeks.[4] The high price for this drug has drawn attention and criticism, including in an investigation initiated by Representatives Cummings and Welch in August 2017 that noted that the average cost of MS drugs in 2004 averaged $16,050 per patient in 2004, and questioned whether anticompetitive behavior was a factor in today's high-priced MS drugs, including Zinbryta.[5]

The high price of this drug is all the more objectionable considering the fact that Zinbryta represents a new indication for an old drug previously marketed by Roche as Zenapax. Zenapax was approved by the FDA in 1997 as a prophylaxis of acute organ rejection in patients receiving renal transplants, to be used as a part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.[6] The drug was designated as an orphan drug, thus affording Roche a 50% tax credit on qualifying clinical trials for the drug, and exclusive rights in the test data that expired in 2004.

Roche voluntarily discontinued the manufacture of Zenapax in 2009, stating that its decision to do so "has been taken in view of available alternative treatments and the diminishing market demand for ZENAPAX and is not due to any safety issue."[7]

<u>The Government Has Significant Leverage Under the Bayh Dole Act To Lower The Price of Daclizumab</u>

Under the Bayh Dole Act, the Government retains significant rights when licensing federally-owned inventions, including leverage when a licensee prices the invention excessively in breach of its obligation of reasonable pricing under the law.

---

[1] https://www.ott.nih.gov/hhs-licensed-products-approved-fda
[2] https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm504000.htm
[3] *Id.*
[4] https://www.goodrx.com/zinbryta
[5] https://www.bloomberg.com/news/articles/2017-08-17/house-democrats-start-probe-into-multiple-sclerosis-drug-prices
[6] https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=67692
[7] https://www.fda.gov/downloads/drugs/drugsafety/drugshortages/ucm194907.Pdf

Under 35 U.S.C. § 203(a), the government may utilize what are referred to as "march-in" rights to require that Biogen license the patent to a third party, or could itself license the patents upon a determination that one of four conditions necessitates the government's action. Among those four, § 203(a)(1) provides for use of the march-in rights when "action is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve **practical application** of the subject invention in such field of use." [Emphasis added.]

"Practical application" is a defined term under 35 U.S.C. § 201(f) to include an affirmative obligation for reasonable pricing:

> "The term 'practical application' means to manufacture in the case of a composition or product, to practice in the case of a process or method, or to operate in the case of a machine or system; and, in each case, under such conditions as to establish that the invention is being utilized and that its benefits are to the extent permitted by law or Government regulations **available to the public on reasonable terms**. [Emphasis added.]

As we have pointed out in a separate document, "reasonable terms" has been interpreted by United States courts as well as a variety of international jurisdictions and fora to include price.[8]

Under 35 U.S.C. § 209(d), licenses of federally-owned inventions are required to contain provisions that specify certain rights that the government retains. Under § 209(d)(1), for example, the government retains a perpetual royalty-free license to use or authorize use on the government's behalf at any time: "...a nontransferable, irrevocable, paid-up license for any Federal agency to practice the invention or have the invention practiced throughout the world by or on behalf of the Government of the United States."

Perhaps most significantly, under § 209(d)(3) the statute requires provisions that authorize the government to terminate a license under various circumstances, including if the funding federal agency determines that:

> (A) the licensee is not executing its commitment to achieve practical application of the invention, including commitments contained in any plan submitted in support of its request for a license, and the licensee cannot otherwise demonstrate to the satisfaction of the Federal agency that it has taken, or can be expected to take within a reasonable time, effective steps to achieve practical application of the invention.

Thus, the government may simply terminate the license if the invention is not being made available to the public on reasonable terms, without having to concern itself with the time-consuming rights of administrative appeal that would apply to the use of march-in rights

[8] https://www.keionline.org/sites/default/files/KEI-March_10_2017-3rd-Comments-Zika.pdf

under 35 U.S.C. § 203(b), or be limited in any way by potential disputes over what constitutes "use on the government's behalf" in using the royalty-free right in the patent. Indeed, the termination option would provide enormous leverage, because it would make Zinbryta an infringing product and allow HHS to do whatever it wanted with the patent, including licensing the rights either exclusively or non-exclusively to companies willing to sell the product at affordable and reasonable prices.

Test data issues

There may be entry barriers for a biosimilar competitor involving rights to rely upon test data, but here again the government has options.

The U.S. government or a biosimilar competitor could always conduct trials, knowing that the safety of the drug was established in its previous use, and the efficacy was already approved for a different indication.

We also note that at least one of the trials Abbott used to register the drug for the new indication was conducted under NIH CRADA 27-2010/0, by the NIH's National Institute of Neurological Disorders and Stroke (NINDS).

Table 1: NIH CRADA 027-2010/0

CRADA Title	Execution Date, Company	Abstract
Use of Daclizumab High Yield Process (DAC HYP) to Treat Multiple Sclerosis	2010-04-06, Abbott Biotherapeutics Corp.	Under a Cooperative and Research Development Agreement, the National Institute of Neurological Disorders and Stroke will conduct a Phase 1, open-label, single armed study to investigate the mechanism of action and long-term safety and efficacy of Facet Biotech/Biogen Idec's Daclizumab High Yield Process (DAC HYP) in patients with High Inflammatory Multiple Sclerosis.

Moreover, according to clinicaltrials.gov, there are another 48 clinical studies using daclizumab that were funded by the NIH or another federal agency, 20 by non profit organizations, and additional studies by several other drug companies.

Zinbryta is Priced Higher in the United States than Other High Income Countries

While the United States funded the development of Zinbryta, and even holds the patent that protects the monopoly, Biogen and Abbvie are charging far more in the United States than in other high-income countries. Table 2 provides the GDP, GNI per capita, prices and reimbursement status for the United States and 10 other countries with per capita income of at least 75 percent of the United States.

Table 2: GDP, GNI Per capita and prices and reimbursement status for Zinbryta in the United States and 10 countries

Country	GDP in millions USD (2016, World Bank)	GNI per Capita in USD (2016, World Bank)	Price of 150mg of Zinbryta in USD	Per capita income as percent of US	Price as percent of US	Ratio of US price to country price
Norway	$370,557	$82,330	$2,670	147%	36%	2.8
Switzerland	$659,827	$81,240	$1,954	145%	26%	3.8
Denmark	$306,143	$56,730	$2,654	101%	36%	2.8
United States*	**$18,569,100**	**$56,180**	**$7,390**	**100%**	**100%**	**1.0**
Sweden	$511,000	$54,630	$1,737	97%	24%	4.3
Australia	$1,204,616	$54,420	$1,794	97%	24%	4.1
Netherlands	$770,845	$46,310	$1,742	82%	24%	4.2
Finland	$236,785	$44,730	$1,754	80%	24%	4.2
Canada***	$1,529,760	$43,660	$1,906	78%	26%	3.9
Germany	$3,466,757	$43,660	$2,556	78%	35%	2.9
UK**	$2,618,886	$42,390	$2,102	75%	28%	3.5

Source: calculations by Adam Buick, on September 14, 2017.

* US price is for Goodrx coupon price.
** UK price does not reflect further confidential discounts, which may be true in other jurisdictions.
*** Market price submitted to CADTH by manufacturer, December 2016.

The United States prices are 2.8 to 4.3 times higher than any of the reference countries. The U.S. price is 2.8 times higher than Norway and Denmark and 3.8 times higher than Switzerland, even though all three of these countries have higher per capita incomes than the United States, and the U.S. taxpayers funded the relevant discovery and own the patent.

There is no reason to accept a foreign price, even from a country of a similar per capita income, as reasonable. But in our opinion, it is unreasonable for Biogen/Abbvie to charge higher prices in the United States than in other large economies with a per capita income at least 50 percent of the United States.

In this case, prices in the U.S. are not only higher — they are 180 to 330 percent higher than every high income country where KEI could obtain pricing data. The pricing of Zinbryta is contrary to statutory requirement of the Bayh-Dole Act to make the inventions available to the public on reasonable terms. A failure by HHS to address the discrimination against U.S. residents in pricing harms everyone who buys or reimburses the drugs, including all U.S.

taxpayers, all employers who pay for health benefits, and many persons living with multiple sclerosis who face daunting co-payments, who are underinsured, or who never get the drug because of its high cost.

Conclusion

We request that the Department of Health and Human Services use one or more of the three options at its disposal under the Bayh Dole Act to lower prices of this important MS drug, including:

> (1) under 35 U.S.C. § 209(d)(1), utilizing the royalty-free license in the government-owned patent to authorize generic competition;
> (2) under 35 U.S.C. § 203(a), utilizing the "march-in" rights to license the drug to a third party; or
> (3) 35 U.S.C. § 209(d)(3), terminating the exclusive NIH license to Abbott/Biogen on the ground that the company is failing to abide by its obligation to make to invention "available to the public on reasonable terms".

Specifically, this letter should be seen as request to exercise march-in rights under 35 U.S.C. § 203(a), and/or to terminate the license under 35 U.S.C. § 209(d)(3), on the grounds that charging U.S. residents 2.8 to 4.3 times more than residents in other high income countries is on its face unreasonable, and in violation of the requirement in 35 U.S.C. § 201(f) to make the invention covered by the license "available to the public on reasonable terms." We also urge DHHS to use the royalty-free right in the patents to exercise leverage and freedom to operate whenever it faces challenges in implementing its section 203 or 209 rights.

We believe that terminating the exclusive license may be the best option, because it will provide the most leverage and the most flexibility in terms of obtaining alternative supplies of the product. But a credible threat to use any of these three options will be sufficient to force Biogen and AbbVie to lower its price of Zinbryta, at least to the prices that the companies already charge in other countries with incomes similar to the United States.

The Trump Administration has made numerous public pronouncements regarding the need to fight high drug prices, a policy point supported by overwhelming public opinion. In this instance, the government has all of the leverage it needs to take strong, decisive action to benefit multiple sclerosis patients, consumers, and taxpayers.

We request a meeting at your earliest convenience to discuss this matter further.

Sincerely,

James Love
Director
Knowledge Ecology International
james.love@keionline.org

Andrew S. Goldman, Esq.
Counsel, Policy and Legal Affairs
Knowledge Ecology International
+1.202.332.2670
andrew.goldman@keionline.org