NATIONAL INSTITUTES OF HEALTH OFFICE OF THE DIRECTOR DETERMINATION IN THE CASE OF NORVIR® MANUFACTURED BY ABBVIE

On October 25, 2012, the National Institutes of Health (NIH) received a request on behalf of Knowledge Ecology International, the American Medical Students Association, the U.S. Public Interest Research Group, and the Universities Allied for Essential Medicines (all referred to collectively as "Requestors") asking the NIH to exercise its Bayh-Dole Act march-in rights under 35 U.S.C. § 203 and to take other agency actions on six patents that are owned and used in the manufacture of AbbVie's[1] drug ritonavir and marketed as Norvir® ("Request").

The Requestors and AbbVie provided additional information for six questions that the NIH requested information on concerning the use of and access to Norvir® (Attachment 1). The NIH carefully considered available information, including all the information provided in the Request, the responses to the questions, information provided by AbbVie, as well as publicly available information directed to the reasonable use of and access to Norvir®. For the reasons provided below, the NIH declines to initiate a march-in investigation.

Patent Landscape for Ritonavir

The six patents at issue, U.S. Patent Nos. 5,541,206, 5,635,523, 5,648,497, 5,674,882, 5,946,987, and 5,886,036, claim inventions directed to the treatment of patients with HIV/AIDS and made by AbbVie with funding by the NIH ("Subject Patents"). These Subject Patents have expiration dates between December 29, 2012, and July 15, 2014. In addition, the Food and Drug Administration ("FDA") granted AbbVie six-months of pediatric exclusivity beginning at the expiration of each patent. AbbVie owns an additional 11 patents that were not made with Government-funding and thus are not subject to Bayh-Dole and the rights reserved for the Government, such as march-in and the Government's use license. The Subject Patents and the additional AbbVie patents are used in the manufacture of three different formulations of Norvir® (tablet, soft gel capsule, and oral solution), according to the FDA's Electronic Orange Book. Of the listed patents specified in the FDA's Orange Book for which the Government has no rights, the patents for the soft gel Norvir® tablet expire by November 22, 2020; for the Norvir® tablet by February 25, 2025; and for the oral solution of Norvir® by December 26, 2016.[2] As such, the NIH understands that the earliest the FDA could approve any generic version of Norvir® oral solution is after December 26, 2016, absent any other actions by AbbVie or another company. Additionally, if AbbVie initiates litigation under the Hatch-Waxman Act and does not prevail, a generic company could possibly receive FDA approval. Currently, there are at least three generic manufacturers, Roxane Laboratories, Inc., Hetero USA, Inc., and Mylan, Inc., seeking

[1] As of January 1, 2013, AbbVie is a new independent biopharmaceutical company composed of Abbott's former proprietary pharmaceutical business, including Norvir®. The six Norvir® patents in question are now owned by AbbVie, as are all of the other patents used for the manufacture of Norvir®. Even though the Request names Abbott Laboratories and Abbott Laboratories participated in the 2003 request for march-in, AbbVie is the current owner of the subject patents and is referred to throughout this determination.

[2] These dates include the FDA's six-month extensions.

early approval of a generic version of a Norvir® formulation through the filing of an Abbreviated New Drug Application (ANDA) for which AbbVie has instituted patent infringement actions under the Hatch-Waxman Act framework. These proceedings are expected to determine the validity and/or infringement of the Subject Patents and the 11 AbbVie patents by proposed generic formulations.

Summary of 2004 NIH March-In Request on Ritonavir

The Subject Patents were first reviewed in response to a 2004 march-in request that asserted a significant price increase initiated by Abbott in 2003 for Norvir® raised issues of practical application, pricing, and health and safety needs. In 2004, after holding a public meeting and receiving written comments, the NIH determined that "it [did] not have information that leads it to believe that the exercise of march-in rights might be warranted . . . within the meaning of 35 U.S.C. § 203." See In the case of Norvir, Manufactured by Abbott Laboratories, Inc. at page 6 (July 29, 2004) ("2004 Norvir® Position Paper").

The current Request relates to the pricing of Norvir® and the same three issues considered and decided in 2004, which were also addressed more generally in the Determination in the Case of Petition of Cell Pro, Inc. (1997), and in the Position Paper in the Case of Xalatan® (2004). (See http://www.ott.nih.gov/policies-reports). Additionally, the Requestors ask that the NIH use its Government use license and/or use the Government's march-in rights to adopt "two general policy rules regarding the commercialization of federally-funded inventions, and apply those rules in the case of six patents claimed for the manufacture and sale of the drug ritonavir under the federal government's authority to grant licenses to third parties in cases of abuses of patent rights."

Statutory Authority and Criteria

The stated policy and objective of the Bayh Dole Act is:

> [T]o use the patent system to promote the utilization of inventions arising from federally supported research or development; . . . to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government, and protect the public against nonuse or unreasonable use of inventions; . . . . (35 U. S.C. § 200).

Toward this goal, the Bayh-Dole Act provides a Federal agency with march-in authority in certain limited circumstances, to ensure that a federally funded invention is available to the public. More specifically:

> With respect to any subject invention in which a small business firm or nonprofit organization has acquired title under this chapter, the Federal agency under whose funding agreement the subject invention was made shall have the right, in accordance with such procedures as are provided in regulations promulgated hereunder to require the contractor, an assignee, or exclusive licensee of a subject invention to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible

applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee, or exclusive licensee refuses such request, to grant such a license itself, if the Federal agency determines that such—

(1) 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;
(2) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees;
(3) action is necessary to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees; or
(4) action is necessary because the agreement required by section 204 has not been obtained or waived or because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of its agreement obtained pursuant to section 204. (35 U.S.C. § 203(a))

With respect to the use of march-in, the regulations state at 37 C.F.R. § 401.6(b):

> Whenever an agency receives information that it believes might warrant the exercise of march-in rights, before initiating any march-in proceeding, it shall notify the contractor in writing of the information and request informal written or oral comments from the contractor as well as information relevant to the matter.

Based on the available information, a Federal agency can either initiate march-in procedures set forth at 37 C.F.R. § 401.6(c) or notify the contractor that it will not pursue march in rights.[3] Consistent with 35 U.S.C. § 203(a) with respect to any subject invention, a Federal agency is authorized to:

> require the contractor, an assignee or exclusive licensee of a subject invention to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee, or exclusive licensee refuses such request, to grant such a license itself.

Analysis of the Bayh-Dole Criteria and the Request for NIH to use its March-In Authority for Ritonavir

(1) ***35 U.S. C. § 203 (a)(1) "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."***

[3] See 37 C.F.R. § 401.6(b).

The Request asserts that AbbVie failed to achieve practical application of Norvir® because of its high, differential pricing structure between publicly funded and private sector health care plans. As set forth in the NIH's prior march-in determinations, including the NIH 2004 determination for Norvir®, practical application is evidenced by the "manufacture, practice, and operation" of the invention and the invention's "availability to and use by the public . . . ." (2004 Norvir® Position Paper). Norvir® has now been on the market as an FDA approved drug since 1995. As in 2004, Norvir® is used primarily as a booster to increase the effectiveness of protease inhibitors. According to the FDA approved labels, Norvir® is used as a co-administered drug with five other protease inhibitors on the market. The Requestors have provided no information, and no information was identified to suggest, that ritonavir is in short supply either as a standalone drug, co-formulated with AbbVie's lopinavir labeled as Kaletra®, or co-administered with other HIV anti-retroviral medications owned by competing pharmaceutical companies.

In addition, the Request states that on November 18, 2011, Matrix Laboratories received FDA approval for a co-formulated product of ritonavir and atazanavir. The FDA approval was granted as part of the United States President's Emergency Plan for AIDS Relief (PEPFAR) as a co-formulated drug for sale only in Africa and Least Developed Countries. While not available as a co-formulated product in the United States, Europe, or other developed countries, atazanavir is marketed by Bristol Myers Squibb as Reyataz® and can be co-administered with ritonavir. Finally, the Requestors acknowledge that the FDA on August 27, 2012, approved "the Gilead drug, cobicistat, ("COBI"), a protease inhibitor similar to ritonavir...." COBI, as reported in the Request, "is part of a four drug fixed dose combination." The Requestors note that as a result, "a competing 'boosting' drug now exists in cobicistat...." The Requestors also state that even though COBI has received FDA approval, "it must still be evaluated for effectiveness and appropriateness across larger populations than those who participated in clinical trials."

AbbVie's record of manufacture and ritonavir's availability and use around the world demonstrate that AbbVie has achieved practical application of the Subject Patents as required under Bayh-Dole.

(2) *35 U.S. C. § 203 (a)(2) "action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or other licensees*

A second consideration under Bayh-Dole is whether march-in is warranted to alleviate health or safety needs which are not reasonably satisfied by the contractor (35 U.S.C. § 203(a)(2)). Under this prong, the Requestors assert that AbbVie's prices for the private sector health care plans negatively affect public health, correlating Norvir® prices to poor compliance and deferred or interrupted treatment. As noted above, Norvir® is available as a single drug as well as in co-administration or co-formulation with other anti-retroviral drugs. The price for Norvir® has not increased since 2003. In addition, AbbVie states that Norvir® is provided free under its Patient Assistance Program, regardless of income, to those patients who have been prescribed the drug and have no prescription drug insurance coverage. AbbVie states that it provides access to Norvir® at no cost or at reduced prices for eligible patients. (See http://abbvie.com/responsibility/patients-first/patient-assistance-programs.html)

0Responding to a similar argument in 2004, the NIH determined that "Norvir® has been approved by the FDA as safe and effective and is being widely prescribed by physicians for its approved indications." What has changed since 2004 is the availability of new formulations and combination therapies using ritonavir. No new information was provided or identified to suggest AbbVie has failed to "reasonably satisfy" the health and safety need standard of the Bayh-Dole march-in statute.

> **(3) *35 U.S. C. § 203 (a)(3) "actions is necessary to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees"***

The third assertion is that action by the NIH is necessary to meet requirements for public use specified by Federal regulations, and such requirements are not reasonably satisfied by the contractor as required under 35 U.S.C. § 203(a)(3). In support, the Request cites the implementing regulations and requirements of the American with Disabilities Act (ADA) and the Patient Protection and Affordable Care Act (PPACA). This Bayh-Dole criterion is applicable when a statute or regulation, e.g., a safety or standards regulation, specifically requires the use of a patented technology, and the patent owner is not willing to grant licenses to third parties required to use it in their products. The cited statutes and implementing regulations do not specify a requirement for public use of Norvir® but rather deal with more general access and insurance issues. The NIH concludes that, these statutes do not apply as a basis for consideration of march-in because the ADA and PPACA do not specifically require the use of ritonavir.

Additional Government Actions Requested for the Rights to use the Subject Patents

> **(1) *Request for use of the Government's use license.***

The Requestors alternatively ask the NIH to utilize its non-exclusive, nontransferable, irrevocable, paid up license to "practice or have practiced for or on behalf of the United States [the] subject invention throughout the world," also referred to as a confirmatory or Government-use license. The statutory basis to use the Government use license is found at 35 U.S.C. §202(c)(4) and states, in part, that a federal funding agency has a nonexclusive license to practice or have practiced for or on behalf of the United States any subject invention throughout the world.[4] The NIH has authority to act directly or by contract to "secure, develop and maintain, distribute, and support the development and maintenance of resources needed for research."[5] As such, the NIH is a research institution not a drug manufacturer. Even if the NIH were to exercise

[4] 25 U.S.C. § 202 recites: With respect to any invention in which the contractor elects rights, the Federal agency shall have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world: *Provided*, That the funding agreement may provide for such additional rights, including the right to assign or have assigned foreign patent rights in the subject invention, as are determined by the agency as necessary for meeting the obligations of the United States under any treaty, international agreement, arrangement of cooperation, memorandum of understanding, or similar arrangement, including military agreements relating to weapons development and production.

[5] 42 U.S.C. § 284(b)(1)(F).

its Government license for the patents based on Government funded inventions, it would not address the majority of the patents listed for the drug formulations that are not Government-owned. Finally, there is already a statutory mechanism, the Hatch-Waxman Act, to address barriers to generic entry by permitting companies to begin developing generic versions of brand name drugs prior to the expiration of patents. In such circumstances, the generic could be ready to be considered for FDA approval upon the expiration of exclusivity for the brand name drug. As discussed above, Hatch-Waxman proceedings have been instituted for at least three generic companies. The use of the Government's use license in this case is not warranted.

(2) *Request for NIH to Issue Rules Related to Pricing Disparities between the United States and other Developed Counties.*

The Requestors proposed two rules under which the NIH would grant contracts or open licenses for NIH-funded inventions. Rule 1 would establish a rebuttable assumption that U.S. prices of a drug arising from an NIH-funded invention are not reasonable where the U.S. prices for a drug are higher than seven of the ten largest countries, as measured by gross national product (GNP), among the countries determined by the World Bank to be high income or where the U.S. prices are 10 percent higher than reference countries. Absent rebuttal of the presumption, the rule would then permit the Secretary of Health and Human Services ("HHS") to award contracts or grant licenses to competitors to supply the drug to the U.S. consumer. Rule 2 would require the Secretary of HHS to grant licenses to third parties to use the NIH-funded inventions, "subject to the payment of a reasonable royalty and appropriate field of use, if a product based on those patented inventions:

(a) Is a drug, drug formulation, delivery mechanism, medical device, diagnostic or similar invention, and
(b) Is used or is potentially useful to prevent, treat, or diagnose medical conditions or diseases involving humans, and
(c) Its co-formulation, co-administration, or concomitant use with a second product is necessary to effect significant health benefits from the second product, and
(d) The patent holder has refused a reasonable offer for a license."

Under the Requestor's Rule 1, the comparison of prices for drugs that are available in the United States would be to prices of the same drugs that are available in high income countries around the world such as Norway, Italy, France, Canada, Australia, the Netherlands, New Zealand, and the United Kingdom. It is not appropriate to assess the price of one drug out of the context of a country's entire health care delivery and drug pricing/reimbursement system. Moreover, the United States does not have a delivery system like any of these other country comparators.

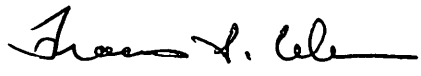
With respect to Requestors' Rules 1 and 2, the statutory authority for the NIH to consider using its march-in authority, as set out above, is directed to "any subject invention" if one of the four Bayh-Dole march-in criteria are met. We do not think that the AbbVie pricing policies and pricing disparities between the United States and other countries trigger any of the four Bayh-Dole march-in criteria.

Conclusion

The NIH is sensitive to the impact of the pricing of drugs and their availability to patients. As in 2004, when similar pricing and availability issues were raised and discussed at public hearings, the NIH's role in the present case is limited to compliance with the Bayh-Dole Act, including its march-in criteria, outlined and discussed in detail (above).

Drug pricing and patient access are broad and challenging issues in the United States. The NIH continues to agree with the public testimony in 2004 that the extraordinary remedy of march-in is not an appropriate means of controlling prices of drugs broadly available to physicians and patients.

In conclusion, as set forth in this determination, the information and justification provided in the Request, as well as publicly available information, do not support re-consideration of the NIH determination to decline to initiate a march-in proceeding for the Subject Patents used by AbbVie in the production of Norvir® and other combination products. As stated in previous march-in considerations, the general issue of drug pricing is appropriately addressed through legislative and other remedies, not through the use of the NIH's march-in authorities. The exercise of the Government's use license to the Subject Patents is not appropriate in this case. Finally, the NIH declines to set the rules proposed by the Requestors directing the initiation of such proceedings based on certain price disparities between the United States and other developed countries.



Francis S. Collins, M.D., Ph.D.
Director, NIH

11/1/13

Date

NATIONAL INSTITUTES OF HEALTH (NIH) QUESTIONS ON MARCH-IN REQUEST FOR RITNOVIR

FOR REQUESTERS

KNOWLEDGE ECONOLOGY INTERNATIONAL, THE AMERICAN MEDICAL STUDENTS ASSOCIATION, THE U.S. PUBLIC INTEREST RESEARCH GROUP and THE UNIVERSITIES ALLIED FOR ESSENTIAL MEDICINES

In considering the march-in request on six subject inventions identified in the march-in request for ritonavir, the NIH has the following six questions.

1. Are you aware of any supply availability issues with respect to ritonavir, alone or as part of a combination drug that were not included in your march-in request? _____Yes _____No

   If yes, please provide supporting information.

2. Are you aware of any patents not identified in your march-in request that are necessary for the administration of ritonavir? _____Yes _____No

   If yes, please provide supporting information.

3. Apart from the asserted status that all of the identified patents are directed to a subject invention, please explain your rationale for each patent's inclusion in your request.

4. In your march-in request you assert that march-in action by the NIH is necessary under the implementing regulations and requirements of the American with Disabilities Act (ADA) and the Patient Protection and Affordable Care Act (PPACA). Please identify the specific implementing regulations and requirements for the ADA and the PPACA that are directed to ritonavir.

5. Was the differentiation in pricing for ritonavir that was provided in the march-in request for ritonavir by itself or for ritonavir in combination with other drugs?

6. Is there any supplemental information that you would like to submit to the NIH that was not included in your original march-in request? _____Yes _____No

   If yes, please provide your supplemental information.