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NIH Meeting on Norvir/Ritonavir March-In Request
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Introduction

Essential Inventions has asked the Department of Health and Human Services (DHHS) to exercise its march-in rights in six patents held by Abbott Laboratories that are used in the manufacture and sale of ritonavir, a drug used to treat AIDS. Essential Inventions also has a separate petition asking DHHS to exercise march-in rights in the Columbia University patent on Xalatan, a drug used for the treatment of glaucoma. These petitions ask the government to protect the public, under the particular provisions set out in the Bayh-Dole Act.

Policy Basis for Norvir March-In Request

In December 2003, Abbott Laboratories increased the price of ritonavir by 400 percent. The price increase was not uniform. Some US public sector programs will not face the 400 percent price increase. No foreign consumers will face the 400 percent price increase. Abbott did not increase the price of Kaletra, an Abbott fixed dose combination product that combines ritonavir and lopinavir. As a consequence of the discriminatory price increase, US employers/insurers/consumers who buy ritonavir with private sector insurance will pay five to ten times more than employers/insurers/consumers in other high-income countries. US insurers will place pressure on patients to switch to the Kaletra fixed dose combination. Non-Abbott drug developers will be effectively excluded as a first line treatment on most formularies, reducing potential markets and undermining incentives for R&D.

The 400 percent price increase for a treatment for a deadly disease comes eight years after Ritonavir was introduced into the US market, having already generated billions of dollars in revenue to Abbott (for Norvir, the standalone product, and Kaletra, the co-formulated fixed dose combination). Patients living with AIDS, and employers and insurers that pay for AIDS treatments, are all concerned that the very aggressive price hike by Abbott will encourage other companies to sharply increase prices for AIDS drugs.

Table 1
Retail Price of Norvir in Six Countries
(Monthly: sixty 100 milligram tabs)

Australia	\$ 52.04
Belgium	\$ 58.91
Canada	\$ 58.97
Germany	\$ 111.91
Italy	\$ 132.00
USA (CVS, Washington, DC)	\$ 642.90

Table 2
Retail Price of Norvir Boost, Before and After Price Increase
Annual average wholesale cost

Boehringer-Ingelheim/Tipranavir 400 milligrams/day	Before	\$ 3,129	
	After	\$16,644	
	Difference		\$12,515
Merck/Crixivan 200 milligrams/day	Before	\$1,564	
	After	\$7,822	
	Difference		\$6,258
Abbott/Kaletra 200 milligrams/day	Difference		\$0

The fundamental questions posted by the Norvir march-in request are the following:

Is it appropriate for Abbott to increase the price of ritonavir, a government funded invention, by 400 percent in one day, after the company has already earned billions on the drug? Is it appropriate for Abbott to price ritonavir, a government-funded invention, 5 to 10 times higher in the United States than in other high-income countries? It is appropriate for Abbott to price ritonavir, a government-funded invention, 5 times higher when the drug is used in combination with non-Abbott owned protease inhibitors, than the price when ritonavir is used in connection with Abbott’s own protease inhibitor lopinavir.

If DHHS determines that the answer to any of these three questions is no, it should grant the march-in request.

Legal Basis for March-In

In the terms of the Act, the first ground for the march-in is that the “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.”¹ The Act defines “practical application” as the utilizing of the invention in such a way “that its benefits are to the extent permitted by law or government regulations available to the public on reasonable terms.”²

Abbott is not making the product available to the public on “reasonable terms.” It is not reasonable to raise the price of an essential life saving drug by 400 percent. It is not reasonable to price an essential life saving drug 5 to 10 times more in the United States than in Europe, Canada or other high-income countries. It is not reasonable to charge 5 times more just because ritonavir is used with a competitor’s protease inhibitor.

These acts are not reasonable. They are outrageous pricing abuses.

The second ground is that the “action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees.”³ There is evidence in the record that the price increases for ritonavir is creating hardships on persons living with AIDS. There is also evidence that the recent price increase is having a harmful impact on the pipeline for new AIDS drugs, by reducing the expected market share for Abbott’s competitors. Indeed, if Abbott charges different prices for ritonavir depending upon which drugs it is used with, and discriminates against its competitors, it is unlikely that there will be significant new investment in AIDS drugs that require ritonavir as a boosting agent. This is the most serious threat to the health and safety needs of persons living with AIDS.

The NIH has received letters in opposition to this petition that assert that the Bayh-Dole march-in provisions were not intended to address abuses of patent rights that concern the pricing of drugs.⁴ It is difficult to imagine how the term making “available to the public on reasonable terms” would exclude prices. Professor Jerome Reichman of Duke University Law School has looked at this issue for us, and will present in a separate statement his views on how the term “available to the public on reasonable terms” should be interpreted.

Any fair reading of the legislative history of the Bayh-Dole Act and also the pre-Bayh-Dole Act debates over the patenting of federally funded inventions reveal longstanding concerns over the potential for abuses stemming from monopoly pricing of inventions.⁵

¹ 35 U.S.C. § 203(a)(1).

² 35 U.S.C. § 201(f).

³ 35 U.S.C. § 203(a)(2).

⁴ Joseph P. Allen, President National Technology Transfer Center, letter to Mark Rohrbaugh, March 31, 2004. Norman J. Latker, letter to Mark Rohrbaugh, April 14, 2004.

⁵ American Association for the Advancement of Science (AAAS), *The Protection by Patents of Scientific Discoveries: Report of the Committee on Patents, Copyrights, and Trademarks*. New York: Science Press, 1934; Robert Weissman, “Public Finance, Private Gain: The Emerging University-Business-Government Alliance and the New U.S. Technological Order,” Undergraduate thesis, Harvard University, 1989; Peter S. Arno & Michael H. Davis, “Why Don’t We Enforce Existing Drug Price Controls? The Unrecognized and Unenforced Reasonable Pricing Requirements Imposed upon Patents Derived in Whole or in Part from Federally Funded Research,” 75 *Tulane L. Rev.* 631, 640, 656 (2000); David C. Mowery, Richard Nelson,

As described in some detail in the attached memo prepared by David Halperin, the legislative approval of the Bayh-Dole was clearly tied to the existence of the march-in provision as a general safeguard to protect the public from abusive pricing of federally funded inventions, including medicines.⁶

We do not claim the NIH is required to exercise federal march-in rights on every federally funded patent, or even for many federally funded patents. Nor is the NIH obligated to exercise its royalty free rights in the patents. The federal government has broad discretion to act, but also broad discretion to not act. The NIH has never used a march-in petition to grant licenses to patents on drugs. But even the possibility of a march-in proceeding may have influenced licensing practices in the past, not only for drugs, but for the licensing of patents on stem cell lines or other research tools.

Whatever the NIH does in this proceeding will influence the terms under which future products are made available to the public. If the NIH decides, for example, that government funded inventions should not be priced higher in the United States than in other high income countries, it will be a straightforward rule that patent owners can both understand and easily follow. Likewise, the NIH could adopt policy guidance on other practices that should be avoided, such as the Abbott effort to charge far more for a drug if used with a competitor's product, or decisions to sharply increase prices on highly profitable products.

On the other hand, if the NIH denies the petition, the opposite signal will be sent to patent owners. The facts in the Abbott case are so extreme that a "sky is the limit" or "anything goes" precedent will have been sent. This will likely lead to even more aggressive pricing on federally funded inventions, and perhaps even for medicines in general.

Government Role in Development of Ritonavir.

Ritonavir was initially developed on a US government grant to Abbott. The NIH not only provided Abbott with approximately \$3.5 million to finance Abbott's discovery and development of ritonavir, but the NIH also undertook its own research on ritonavir, employing Dr. John Erickson, a former Abbott researcher who played an instrumental role in obtaining the initial NIH grant to Abbott. Abbott acknowledges US government rights in six of the key patents for ritonavir.

Abbott claims that the US contribution to the development of ritonavir was small compared to Abbott's. Abbott deliberately under-estimates the economic value of NIH contributions in the early stages of development, and ignores the continued US government investment in research on ritonavir.

To fairly evaluate that the economic value of the \$3.5 million grant to Abbott, one must recognize the risky nature of the public investment. The odds of success for investments

Bhaven N. Sampat and Arvids A. Ziedonis, *Ivory Tower and Industrial Innovation: University-Industry Technology Transfer Before and After the Bayh-Dole Act*, Stanford Business Books, 2004.

⁶ David Halperin, "the Bayh-Dole Act and March-In Rights," 2001.

in pre-clinical research are low. Most NIH funded grants to develop AIDS drugs are unsuccessful. Only a few such grants lead to a commercial product. The pharmaceutical industry itself frequently emphasizes that risk must be considered when calculating investment costs. Often we are told that every compound has only a 1 in 5,000 chance of commercial success. This is more a polemic than an actual estimate, but consider for a moment if this were the true risk. The risk-adjusted value of the US government investment would then be \$3.5 million multiplied by 5,000, or \$17.5 billion. And this does not even include the adjustments for inflation and the cost of capital that industry economists typically include in cost estimates. There is no good estimate of the actual risks in the initial investment stage, but in any reasonable analysis it would be significant. Joseph DiMasi and his colleagues have estimated the cost of pre-clinical research, adjusted for risk and capital costs, to be approximately \$335 million.⁷ This is a good starting point for thinking about the value of the initial NIH investment in ritonavir.

Abbott claims to have spent hundreds of millions on the development of ritonavir, but this is a “trust us” number. We have almost no details from Abbott. The initial FDA approval of ritonavir was based upon clinical trials that involved 1,583 patients. This is less than 30 percent of the number of patients the DiMasi study says are average for new drug approvals. The trials were also relatively short, and the FDA approval time for Norvir was extremely short -- only 70 days.⁸ When trials and FDA approval times are shorter, company costs are generally lower -- certainly in terms of the cost of capital. These objective data are evidence that Abbott’s costs for clinical development were below average.

Subsequent to FDA approval, the NIH continued to pour money into ritonavir R&D. The NIH has sponsored a large number of post market clinical trials involving ritonavir, and has given out dozens of grants.

Abbott’s role has also been important. Ritonavir has been a successful collaboration between the NIH and Abbott. It has also been a highly profitable collaboration for Abbott, as reflected both in its sales of Norvir and the sales of ritonavir as a component of Kaletra. Ritonavir has generated billions of dollars for Abbott. And the US government has received zero royalties from ritonavir.

Patent Landscape for Ritonavir

Ritonavir is sold in different formulations and presentations. For each presentation, Abbott has registered differed patents in the *FDA Orange Book*. If the NIH grants licenses to Abbott’s six ritonavir patents to Essential Inventions, we will consider our options for providing generic versions of ritonavir. We have asked several patent lawyers and experts to review the patent landscape for ritonavir to determine if it is possible to produce and market a generic version of ritonavir if we are successful in obtaining the

⁷ Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, "The price of innovation: new estimates of drug development costs," *Journal of Health Economics* 22 (2003) 151–185.

⁸ The request for FDA marketing approval was December 21, 1995. The FDA approval for ritonavir was March 1, 1996.

march-in licenses. We believe this is feasible. Our priority is for the 100 milligram tablet. The following is an excerpt from an analysis by the Daniel Ravicher of the Public Patent Foundation on the capsule formation of ritonavir:⁹

PUBPAT has undertaken a review of the patents pertaining to Abbott Laboratories' ritonavir drug products. In total, there are 5 patents listed by Abbott in the Orange Book for its approved ritonavir capsule product. Of those 5, the Ritonavir Petition would, if granted, provide access to 4, leaving only one patent, U.S. Patent No. 6,232,333 ("333 patent"), as a potential barrier to making an effective generic ritonavir capsule product. Table 1 below sets forth the Orange Book patent listing for Abbott's ritonavir capsule product and also indicates which of those patents are subject to the Ritonavir Petition.

Patent No.	Listed for Abbott's Ritonavir Capsule	Subject to the Ritonavir Petition
5,541,206	YES	YES
5,635,523	YES	YES
5,648,497	YES	YES
5,846,987	YES	YES
6,232,333	YES	NO
Table 1: Orange Book Listed Patents for Abbott's Ritonavir Capsule		

The '333 patent, unlike each of the other 4 patents listed for Abbott's ritonavir capsule, does not claim the active ingredient, ritonavir, itself. Rather, it merely claims a pharmaceutical composition containing ritonavir. Upon initial review, we have serious doubts about the validity of the '333 patent and its applicability to an effective generic ritonavir product. One issue regarding the '333 patent's validity is that its Abstract and Specification purport to teach an invention providing "improved bioavailability." Yet, no such limitation is present in any of the '333 patent's claims. Such a missing limitation means that the scope of the claims is much broader than what the patent otherwise purports to cover. This breadth of the claims increases the likelihood that they are invalid.

Regardless, the existence of the '333 patent in no way detracts from the importance or utility of the Ritonavir Petition. Access to the technology claimed in the 4 other patents that pertain to ritonavir is absolutely necessary to making an effective ritonavir capsule product available to the American public on fair terms. Further, a potential producer of a generic ritonavir product is much more likely to challenge the '333 patent if it

⁹ April 29, 2004. Daniel Ravicher letter to Mark Rohrbaugh, "Analysis of Patents Relevant to the Ritonavir Petition."

stands alone as the sole patent at issue than if the other 4 patents must also be dealt with. This is especially true since the '333 patent has such glaring validity issues and may be much more easily designed around than the other 4 patents since it does not cover the active ingredient ritonavir itself.

Proposed Remedy Includes Novel R&D Mandate

The march-in remedy proposed by Essential Inventions includes a novel proposal for the creation of an R&D Fund for AIDS treatments, funded by generic suppliers of ritonavir. Essential Inventions has proposed a mandatory R&D contribution of \$.004 per milligram (typically \$292 per year per patient), but the NIH could choose any figure. This R&D mandate would be in addition to the payment of reasonable royalties to Abbott. The structure of the R&D Fund management would be left to the NIH, but it could include either public or private sector management of the R&D fund, and different approaches to managing the intellectual property rights of the Fund. The proposal is modeled after an R&D mandate that the NIH imposed on Bristol-Myers in the early 1980's in connection with the Bristol-Myers marketing of cisplatin, a US government funded cancer drug. It is important to Essential Inventions that the exercise of the march-in right does not undermine investments in R&D, and the mandate that generic producers contribute to the R&D Fund is a mechanism to ensure that R&D levels are increased to socially desirable levels.

Concluding Comments

In the 24 years since the Bayh-Dole Act has passed, it has attracted a broad base of support among policy makers and researchers. The Act is also subject to criticism over a wide range of issues, including the tensions between sharing information and claiming property rights in research, and concerns over unjust pricing of some government-funded technologies. It is important that the bargain struck in the Bayh-Dole Act be considered fair to taxpayers.

The Norvir march-in case will be an important precedent, no matter what the outcome. For those who defend the policy of giving patent rights to grant recipients and contractors, and allowing patent owners much flexibility in using exclusive rights, there is an important issue. Is it sustainable in the long run to treat the taxpayers as if their only interest in the patents is to ensure that products are commercialized, regardless of the terms? The failure to use the march-in clause, ever, for any set of facts, will create the impression that the Act has been captured by those who profit from the commercialization of the taxpayer funded research. In the long run, this may undermine support for the broader policy of giving grant recipients title of US government funded research.