PETITION TO USE AUTHORITY UNDER BAYH-DOLE ACT TO PROMOTE ACCESS TO RITONAVIR, SUPPORTED BY NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES CONTRACT NO. AI27220

1. Executive Summary

Essential Inventions, Inc. requests the Secretary to exercise Bayh-Dole March-In rights and grant an open license to use six patents related to the manufacture of ritonavir. The grounds for the request are that the patent owner charges unreasonable prices for Norvir/ritonavir, harming the public. The license should be open to any qualified application, grant the right to make, use, import, export and sell ritonavir, either as a standalone protease inhibitor or as a component of a fixed dose combination treatments. The license should include a five percent royalty to the patent owner, calculated on the basis of the generic sale price for standalone ritonavir products. The open license should also require every manufacture of generic ritonavir to contribute to an R&D Fund for AIDS. Essential Inventions recommends an R&D contribution $.004 milligram, which would generate $29.2 million per year for each 10,000 patients using a 200 milligrams per day of Norvir to boost protease inhibitor regimes.

2. Essential Inventions, Inc.

Essential Inventions, Inc. (EII) is a private, not-for-profit corporation organized under the laws of the District of Columbia in January 2004. Essential Inventions was formed to support the creation of and access to essential inventions, including medicines.

3. Request for licenses to patents on ritonavir

Essential Inventions seeks licenses under the Bayh-Dole Act that would allow it and others to supply ritonavir in the U.S. and abroad to treat HIV/AIDS. Specifically, this petition requests that you authorize any supplier of pharmaceuticals to use the following patents in order to manufacture, import, export or sell ritonavir. (U.S. Patent Nos.):

5541206
5635523
5648497
5674882
5846987
5886036

Each patent covers a product or process necessary to manufacture ritonavir, an important protease inhibitor used to treat HIV/AIDS.

4. Background on ritonavir

4.1. Discovery and commercial development of ritonavir

4.1.1. Government role in funding pre-clinical research and development

The National Institutes of Health has been instrumental in funding the discovery of treatments for HIV/AIDS, beginning with its support of the first tests to establish the efficacy of antiretroviral treatment in 1984. The National Cooperative Drug Discovery Groups (NCDDGs) were established by the NIH's National Institute for Allergies and Infectious Diseases (NIAID) in 1986 to financially support cooperative research between academic and industry-based investigators. Grants by NCDDG-HIV led to the development of protease inhibitors and other antiretroviral medicines, including through a multi-year grant to Abbott Laboratories scientists.

Abbott Laboratories received NIAID grant 5U01AI027220-050002 (referred to as AI027220) in 1988. The objective of the grant was to study the biochemistry of HIV protease enzymes to investigate whether medicines could be created to block the enzyme and thereby inhibit the spread of AIDS to new cells. Early research under the grant to Abbott was promising, with the development of an intravenous protease inhibitor in the first several years of the award. The grant continued to fund research and development of protease inhibiting compounds at Abbott through 1993 "to test its interaction with known aspartic proteinase inhibitors" and "to investigate additional means of inhibiting the protease." Abbott acknowledged that work in performance of this grant lead to the invention in each of the patents subject to this petition.

4.1.2. Initial clinical testing of ritonavir

Abbott's investment in the clinical development of ritonavir was modest. The initial FDA approval was based upon three clinical trials with 1,583 patients -- less than 30 percent of the number of patients that the Tufts Center for the Study of Drug Development claims is average for new "big pharma" drug approvals.[1] At $10,000 per patient, a figure considerably above the average cost of trials reported by Contract Research Organizations for AIDS trials, the cost of Abbott's pre-approval clinical trials for ritonavir can be estimated to be about $15 million.[2]

The time between discovery and marketing of ritonavir was extraordinarily brief. Ritonavir was approved for marketing in 1996, four years after Abbott received the NIAID federal grant, and less than one year after the key patents were filed. None of the clinical trials used for the FDA approval of Ritonavir lasted more than 48 weeks, also far below average for the industry. The FDA review of the ritonavir NDA was expedited and decided in just 70 days.[3]

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[1] Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, *Journal of Health Economics* 22 (2003) 151-185.

[2] James Love, "Evidence Regarding Research and Development Investments in Innovative and Non-Innovative Medicines," Consumer Project on Technology. September 22, 2003.

[3] Compare this to the average durations of clinical trials or FDA approvals. Kaitin and Healy of the Tufts Center for the Study of Drug Development examined data from 1996-1998 US FDA new drugs approvals, calculating mean clinical and approval times for eight therapeutic classes of drugs. For all products, the average duration for the clinical phase was 70.3 months (5.9 years), and the average FDA approval period was 16.3 months.

4.1.3. Use of ritonavir in Highly Active Antiretroviral Treatment (HAART)

i. Highly Active Antiretroviral Treatment (HAART)

By 1996, it was known that use of ARVs in single medicine or dual-drug therapy frequently led to the development of resistance of HIV to the treatment, but that use of three or more ARVs together, known as Highly Active Antiretroviral Therapy (HAART), could dramatically reduce the incidence of drug resistance. A HAART regime, sometimes called a "cocktail," typically consists of a "backbone" of two nucleoside analogue reverse transcriptase inhibitors (NRTIs)[4] plus a one or more additional drugs, such as a non-nucleoside reverse transcriptase inhibitor (NNRTI)[5] or a protease inhibitor (PI).

Different patients require different combination therapies and medicines depending on a host of factors including whether the patient has developed resistance to some medications, side effects of a particular medicine, pregnancy, interactions with other drugs and affect of drugs with different illnesses. No single ARV is directly and completely substitutable for other ARVs for every patient.

ii. Ritonavir as a standalone protease inhibitor

Norvir/ritonavir was initially marketed as a standalone protease inhibitor in a HAART regime with a dose of six 100 mg capsules twice a day (1200 mg /day). This dose is rarely used, however, because it is associated with a number of frequently occurring adverse side effects.

iii. Ritonavir as a "booster" for other protease inhibitors

The most common use of ritonavir is now in a low dose (100mg once or twice-daily) as a "booster" for other protease inhibitors (normally in conjunction with two NRTIs to create a HAART regime). A low dose of ritonavir can slow the ability of liver enzymes to break down the companion protease inhibitor, thus "boosting" the level of the companion drug in the bloodstream. This can make the other protease inhibitor more effective against HIV. It

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Mean clinical and approval phase times for NCEs approved 1996 to 1998, grouped by therapeutic class

	Clinical Phase	Approval Phase	Total
Endocrine (n=9)	96.1	10.6	106.7
Neuropharmacologic (n=15)	87.5	19.2	106.7
Andneplastic (n=11)	80.9	16.2	97.1
Cardiovascular (n=25)	69.2	18.3	87.5
Respiratory (n=7)	65.6	26.4	92.0
Antiinfective (n=13)	63.3	16.3	79.6
Anesthetic/Analgesic (n=9)	57.9	17.7	75.6
AIDS antiretrovials (n=9)	40.1	4.6	44.7
Average (n=110)	70.3	16.3	86.6

Source: Kenneth I. Kaitin and Elaine M. Healy, "The New Drug Approvals of 1996, 1997, and 1998; Drug Development Trends in the User Fee Era," *Drug Information Journal*, Vol. 34, pp. 1-14, 2000.

[4] Usually a two drug combination of the following NRTIs: zidovudine (AZT), lamivudine (3TC), stavudine (d4T) or didanosine (ddI), such as AZT+3TC, d4T+3TC or ddI+d4T.

[5] NNRTIs include nevirapine and efavirenz.

also makes it possible to use lower doses – or less frequent daily doses – of the improved medicine.

Abbott has introduced a fixed dose combination product named Kaletra, which combines 133 milligrams of lopinavir and 33 milligrams of ritonavir. A typical dose of Kaletra is six pills per day. Kaletra is the only protease inhibitor fixed dose combination that includes ritonavir. Kaletra is now the largest selling protease inhibitor.

4.1.4. Federal Research on ritonavir

The federal government continues to invest significantly in research and development of ritonavir, including into its efficacy as a booster for other protease inhibitor regimes. The NIH CRISP database[6] lists 574 federal grants to study ritonavir. ClinicalTrials.Gov identifies 26 clinical trials planned or currently recruiting patients that involve ritonavir. Of these, 21 are sponsored by US government agencies; Abbott is the sponsor of only one; and four are sponsored by other drug companies (including two small firms).

4.2. Abbott's Pricing of Norvir/ritonavir

4.2.1. Abbott's pricing of Norvir

Norvir was first introduced into the market as a standalone protease inhibitor, and despite the US government funding of the pre-clinical discovery of Norvir, the product was priced roughly the same as other drugs in this class. As of last fall, the annual cost of typical doses of standalone protease inhibitors were estimated as follows:

Table 1: Fall 2003, Average Wholesale Price of Unboosted Protease Inhibitors

Drug	*Presentation*	*Unit Cost*	*Units/day*	*Annual Cost*
Fortovase	200 mg	$1.39078	18	$9,137
Invirase	200 mg	$2.49596	9	$8,199
Crixivan	400 mg	$3.03542	6	$6,648
Reyataz*	200 or 150 mg	$13.80	2	$10,074
Lexiva	700 mg	$10.00	4	$14,600
Agenerase	150 mg	$1.53238	16	$8,949
Viracept	250 mg	$2.5222	10	$9,206
Kaletra	133/33 mg	$3.90833	6	$8,559
Norvir	100 mg	$2.1432	12	$9,387

**price the same for both presentations.*

As noted above, several protease inhibitor regimes can be combined with low doses (100 to 200 mg per day) of ritonavir, increasing the effectiveness of the treatment, and also reducing the dose of the non-ritonavir PI required for treatment. In most cases, this resulted in substantial savings to the patient.

[6] Computer Retrieval of Information on Scientific Projects. http://crisp.cit.nih.gov/

Table 2: Reduction in cost of base Protease Inhibitor

Base Protease Inhibitor	*Presentation*	*Unit Cost*	*Units/day when unboosted*	*Base Units after boost / Units for Norvir boost*	*(Fall 2003) Reduction in cost of base inhibitor*
Fortovase	200 mg	$1.39078	18	10 / 2	$ 4,061
Invirase	200 mg	$2.49596	18	10 / 2	$ 7,288
Crixivan	400 mg	$3.03542	6	4 / 2	$ 2,216
Reyataz*	200 or 150 mg	$13.80	2	2 / 1	0
Lexiva	700 mg	$10.00	4	2 / 2	$7,300
Agenerase	150 mg	$1.53238	16	8 / 2	$4,475
Viracept	250 mg	$2.5222	10	Cannot be boosted	
Kaletra	133/33 mg	$3.90833	6	Already boosted	

*price the same for both presentations.

Abbott recently announced enormous price hikes for Norvir. For the most important presentation, the 100 mg gel tablets, Abbott has increased the price from $2.1432 per tab to $10.71575 per tab. For a patient using ritonavir/Norvir as a full protease inhibitor regime this increases the price from $9,387 to $46,935 per year, for this single drug. However, the more important impact will be to greatly increase the cost of ritonavir/Norvir as a boosting agent for other protease inhibitors. Five of the protease inhibitors (Fortovase, Invirase, Crixivan, Reyataz, and Agenerase) are boosted with two 100 milligram tabs of Norvir per day. The annual cost of this boost will increase fivefold from $1,565 to $7,822. The increase in price is $6,258 per year. For Lexiva, which uses only a single 100 milligram tab boost, the annual cost increases from $782 to $3,911, an increase in price of $3,129. For at least one new protease inhibitor under development, the optimal dose of a Norvir booster may be 400 milligrams per day, for which Abbot would now charge $15,644, an increase in price of more than $12 thousand per year.

For the most common boosting dose of 200 milligrams per day, Novir will be priced just below the median price of standalone unboosted protease inhibitors.

4.2.2. Impact of Abbott Price Increases on Cost on Protease Inhibitor Regimes

Abbott did not pass on the price increases for Norvir to its own product Kaletra. Among the optimized regimes, Kaletra is now the least expensive. For many patients, Norvir is medically an essential component of six of the seven protease inhibitors now used in HAART Treatment. Abbott has effectively raised the price of its rival's products, giving patients, insurance companies and other payers a compelling reason to switch patients to Kaletra, even if it is not the best choice from a medical point of view.

Table 3: Annual cost of Base Protease Inhibitor Plus Norvir Boost				
Base Protease Inhibitor	*Presentation*	*Unit Cost*	*Units for Base / Units for Norvir Boost*	*Annual cost of PI Base plus Norvir boost*
Fortovase	200 mg	$1.39078	10 / 2	$12,899
Invirase	200 mg	$2.49596	10 / 2	$16,933
Crixivan	400 mg	$3.03542	4 / 2	$12,254
Reyataz*	200 or 150 mg	$13.80	2 / 1	$14,065
Lexiva	700 mg	$10.00	2 / 2	$15,123
Agenerase	150 mg	$1.53238	8 / 2	$12,297
Viracept	250 mg	$2.5222	10 / no boost	$9,206
Kaletra	133/33 mg	$3.90833	6 / already boosted	$8,559
*priced the same for both presentations.				

4.3. Abbott's profits for Ritonavir/Norvir sales

Ritonavir/Norvir has been profitable for Abbott. FDA approval was announced in March 1996. By the end of 2001, Norvir had generated cumulative sales of more than $1 billion -- more than sixty times the estimated cost of pre-approval outlays. Even without a price increase, securities analysts estimate Norvir will generate more than $2 billion over the next ten years.

5. Legal Analysis

Abbott's pricing of ritonavir is unreasonable, anticompetitive and threatens the health and safety of people with AIDS. The Department of Health and Human Services has the authority to use the march-in provisions of the Bayh-Dole Act to remedy Abbott's abuse of its patent rights, and increase access to a needed medicine.

5.1. Statutory background of the Bayh Dole Act

The Bayh-Dole Act in 1980, Pub. L. 96-517, §6, liberalized the circumstances under which recipients of federal funds could elect to retain title to inventions conceived in the performance of Federal contracts, subject to specific government rights to use the patent or license its use to others.[7] Congress believed that allowing contractors to elect to retain title to any subject invention would "use the patent system to promote the utilization [and commercialization] of inventions arising from federally supported research or development." 35 U.S.C. § 200. At the same time, Congress intended "to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the

[7] The original Act was limited to nonprofit or small businesses. Executive Order 12591, 52 Fed.Reg. 13414 (1987) extended the benefits of Bayh-Dole to all government contractors, including larger businesses.

Government and protect the public against nonuse or unreasonable use of inventions." 35 U.S.C. § 200.

Section 203(a) of the Bayh-Dole Act authorizes the Government to take steps to ensure that inventions are licensed to the public on "terms that are reasonable under the circumstances".[8] The agency may require the contractor to issue licenses on reasonable terms or, if the contractor fails to do so, the agency may grant the license itself on such terms as it finds to be reasonable.

5.2. The patents cover "subject inventions" under the Bayh-Dole Act

The Bayh-Dole Act, 35 U.S.C. § 200 et seq, authorizes the Federal government to grant licenses to any party to use any patented invention "conceived or first actually reduced to practice in the performance of work under a [Federal] funding agreement." 35 U.S.C. § 202(a); 35 U.S.C. 201(e).

As described above, ritonavir was conceived and reduced to practice in performance of NIAID grant AI027220. The Federal regulations implementing the Bayh-Dole Act require that contractors identify all inventions conceived or reduced to practice in the performance of a federal grant by including, on all patent applications and any patent issuing, the statement: "This invention was made with government support under (identify contract) awarded by (identify the Federal agency). The government has certain rights in the invention." 34 C.F.R. § 401.14(f)(4). Each of the ritonavir patents subject to this petition contains the required identification, stating: "This invention was made with Government support under contract number AI27220 awarded by the National Institute of Allergy and Infectious Diseases (NIAID). The Government has certain rights in this invention."

5.3. The inventions are subject to government march-in under section 203

The "march-in rights" in Section 203(a) authorize the funding agency to require the patent assignee or exclusive licensee to grant a license "to a responsible applicant or applicants, upon terms that are reasonable under the circumstances." If the assignee or exclusive licensee refuses such request, the agency may grant the license itself if it determines that one of several grounds for a march-in exists.

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[8] Section 203(a) states:
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 204.5

The first ground for a march-in is 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." 35 U.S.C. § 203(a)(1). The Act defines "practical application" as including "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." 35 U.S.C. § 201(f). A second ground exists if "action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees." 35 U.S.C. § 203(a)(2). Both of these grounds exist in the case of Abbott's marketing practices with respect to Norvir.

5.4. Norvir is not being made available to the public on reasonable terms

5.4.1. Under section 203, "reasonable terms" includes a reasonable price

i. The clear language of the Bayh-Dole Act requires reasonable pricing of government supported inventions

As professors Peter Arno and Michael Davis demonstrate through a survey of case law, the ordinarily understood meaning of the words "reasonable terms" in U.S. law includes reasonable prices:

> In the United States in similar contexts, the words "reasonable terms" have uniformly been interpreted to include price. In *Byars v. Bluff City News Co.*, the United States Court of Appeals for the Sixth Circuit, recognizing that establishing "reasonable terms" is necessary to remedy a monopolistic market, noted that "[t]he difficulty of setting reasonable terms, especially price, should be a substantial factor" in how to proceed. Similarly, in *American Liberty Oil Co. v. Federal Power Commission*, the United States Court of Appeals for the Fifth Circuit, interpreting a statute that allows the Federal Power Commission to establish "reasonable terms and conditions," concluded that this meant that the "price . . . must be reasonable." In *Commercial Solvents Corp. v. Mellon*, the United States Court of Appeals for the D.C. Circuit addressed prices under a statute that demanded "reasonable terms as to quality, price and delivery"; this language shows that the word "terms" includes, as a matter of common sense, the element of price. In *United States v. Mississippi Vocational Rehabilitation for the Blind*, the United States District Court for the Southern District of Mississippi similarly interpreted a statute that allowed organizations to operate vending machines on "reasonable terms" at the Stennis Space Center. Such reasonable terms, the court implied, include "prices and vending operations.". . . In *United States v. United States Gypsum Co.*, the United States District Court for the D.C. Circuit held that "reasonable terms and conditions" includes prices. Finally, in *South Central Bell Telephone Co. v. Louisiana Public Service Commission*, the Louisiana Supreme Court considered the meaning of "reasonable terms" and concluded that, although such things as timing and performance might be important, the most important and central factor is, of course, price.[9]

[9] 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, 660-661 (2001) (internal citations omitted).

ii. The legislative history evidences an intent to require that government supported inventions be priced reasonably.

The legislative history demonstrates that Congress intended the "reasonable terms" language in section 203 to include reasonable pricing. Throughout the hearings and other legislative history of the Bayh-Dole Act, "Congress's concern with march-in rights focused exclusively on maintaining competitive conditions, controlling profits, and doing so through price control."[10] This consensus was recorded in the Senate's Committee Report on the bill, which explained that march-in rights were intended to insure that no "windfall profits" or other "adverse effects result from retention of patent rights by these contractors."[11] Notably, the proposal by the Electronic Industry Association that "practical application" be rewritten to mean "that the invention is being worked *or* that its benefits are available to the public either on reasonable terms or through reasonable licensing" was rejected.[12] To meet the practical application definition, the invention must both be practiced *and* available to the public on reasonable terms.

5.4.2. Abbott's price of Norvir as a standalone protease inhibitor is not reasonable

Essential Inventions, Inc. maintains that Abbott's price for ritonavir, both before and after the recent fivefold increase in price, is not reasonable. A reasonable price is one that it is "[f]air, proper, or moderate under the circumstances."[13] One relevant circumstance includes the substantial public investment in the development of ritonavir which decreased both the cost and risk associated with the development of ritonavir. Even before the increase in price, Abbott had priced Norvir higher than several standalone protease inhibitors, none of which were invented on a government grant. With the price increase, the cost of Norvir as a standalone protease inhibitor skyrocketed to $46 thousand, three to five times as high as other standalone protease inhibitors that were not invented on a government grant.

5.4.3. Abbott's price increase for Norvir/ritonavir as a booster is an anticompetitive abuse of its patent rights

Even stronger evidence of the unreasonable price of Norvir is the discriminatory application of the price increase against Abbott's rivals. By dramatically increasing the cost of Norvir to boost non-Abbott protease inhibitor regimes, while not increasing the price of Kaletra, Abbott

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[10] Arno and Davis at 659; *see* Government Patent Policy: Hearings Before the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology, 96th Cong. 1st Session at 48 (1979) (statement of Harry F. Manbeck, General Patent Counsel for General Electric Company, that "if [a contractor] fails to supply the market adequately at a fair price, then there is reason for requiring it to license both the background patents and the patents stemming from the contract work."); *see id.* at 317 (statement of Mr. Manbeck that march in rights are "part of the answer to the so-called windfall situation").

[11] S. Rep. No. 96-480 at 30; *accord* The University And Small Business Patent Procedures Act, Hearings Before the Senate Committee on Judiciary, 96th Cong., 1st Sess., 1979, at 44 (statement of Senator Bayh that the march-in provisions were meant to control the ability of "the large, wealthy, corporation to take advantage of Government research and thus to profit at taxpayers' expense.").

[12] Patent Policy: Hearings on S.1215 Before the Subcommittee on Science, Technology and Space of the Senate Committee on Commerce, Science and Transportation, 96th Cong. at 221 (1979) (statement of Peter F. McCloskey, President, Electronic Industry Assn.) (emphasis added).

[13] *Black's Law Dictionary*.

clearly seeks to shift market share to Kaletra, even when Kaletra is not the best treatment for patients.

There is no other booster that can be used as a substitute for ritonavir. From a medical point of view, ritonavir/Norvir is an essential component of protease inhibitor treatment for many patients. The Abbott price increases are clearly an abuse of its patent rights.

It has been established since the Supreme Court's decisions in *International Salt* and *Motor Picture Patents* that a patent holder illegally restrains competition by tying the offer of preferential terms for a patented product to purchase of another product.[14] Abbott is effectively tying price discounts on ritonavir to the purchase of Kaletra.

5.4.4. Action is needed to protect the public's health needs.

It is clear from the legislative history of the Bayh-Dole Act that the march-in clauses were intended to protect the public health needs, and when appropriate, to promote competition by providing a speedy remedy for any anticompetitive use of patent rights on subject inventions.[15] High prices and related terms of sale that inhibit competition are not "reasonable" under section 203.

Action by the government in this case is necessary to alleviate the harm to the public, which includes excessive pricing, biases in prescribing practices that are contrary to optimal medical treatments, increasing barriers to treatment, and reduced incentives for development of new protease inhibitors that work best when combined with ritonavir.

Using Bayh-Dole March-in rights to remedy these problems is both appropriate, and more efficient than use of other mechanisms, such as antitrust litigation, which is time consuming and expensive. The US government has the authority to bring this matter to a rapid conclusion. Here are some of the negative consequences of not acting.

5.4.5. Rationing of access to HAART

Even before the price increases, Abbott's prices for ritonavir far exceeded that necessary to commercialize the federally funded invention, and the high prices for Norvir contributed to the rationing of treatment to people with AIDS in this country.

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[14] *International Salt v. United States*, 332 U.S. 392, 395-96 (1947) (describing tying as a per se "restraint of trade for which its patents afford no immunity from the anti-trust laws");*accord Motion Picture Patents Co. v. Universal Film Mfg. Co.*, 243 U.S. 502 (1917); *see also Kodak v. Image Technical Services*, 504 U.S. 451, 479 n.29 (1992) ("The Court has held many times that power gained through some natural and legal advantage such as a patent, copyright, or business acumen can give rise to liability if 'a seller exploits his dominant position in one market to expand his empire into the next.'").

[15] *See* Patent Policy: Hearings on S.1215 Before the Subcommittee on Science, Technology and Space of the Senate Committee on Commerce, Science and Transportation, 96th Cong. 150 (1979) (statement of James E. Denny, Assistant General Counsel for Patents, U.S. Energy Research and Development Agency, that march-in rights are appropriate "where the contractor is misusing the invention to the detriment of competitive market forces."); Patent and Trademark Law Amendments of 1980: Hearings Before a Subcommittee of the House Committee on Government Operations at 102 (1980) (statement of Ky P. Ewing, Assistant Attorney General for the Antitrust Division, that "'march in' provisions should help assure that the availability of exclusive rights . . . does not disrupt competition in the marketplace").

The impact of high prices for AIDS drugs can be seen in the financial strains experienced by AIDS Drug Assistance Programs (ADAPs), which provide HIV/AIDS related prescription drugs to uninsured and underinsured individuals.[16] ADAP medicine expenditures increased 12% last year, while the national ADAP budget increased just 8%. As of November 2003, fifteen ADAPs had closed enrollment to new clients or limited access to ARVs and other treatments.

Table 4: Fifteen State ADAP programs with waiting lists and/or access restrictions as of November 2003

Alabama	capped enrollment, 141 on waiting list
Arkansas	capped enrollment
Colorado	capped enrollment, 130 on waiting list
Idaho	capped enrollment, monthly expenditure cap
Indiana	capped enrollment, 47 on waiting list
Kentucky	capped enrollment, 140 on waiting list
Montana	capped enrollment, 1 on waiting list
Nebraska	capped enrollment, 30 on waiting list
North Carolina	capped enrollment, 96 on waiting list
Oklahoma	Reduced formulary and annual expenditure cap
Oregon	Reduced formulary, lowered financial eligibility, imposed cost-sharing, 24 on waiting list
South Dakota	capped enrollment, 49 on waiting list
Washington	Lowered financial eligibility criteria, reduced formulary, imposed cost-sharing
West Virginia	capped enrollment, 21 on waiting list
Wyoming	Reduced formulary, lowered financial eligibility

Six more states anticipate the need to implement program restrictions during FY2003 which began April 1, 2003.[17] Across the U.S., 600-800 people are "wait listed" for enrollment into ADAPs each month, denying them medicines they need.

Purchase of protease inhibitors accounts for about 25% of ADAP medicine costs, and about half of those expenditures are for Kaletra or Norvir/ritonavir. Decreasing the price of accessing ritonavir would significantly assist ADAPs meet their financial demands, reducing the number of people denied access to medicines because of an inability to pay.

High prices for AIDS medicines also impose enormous burdens on those who obtain medicines privately. Employers who provide insurance bear the costs of high drug prices, and increasingly employers seek ways to reduce these costs, such as greater use of contactors, who do not receive health care insurance, or through employment discrimination aimed at persons living with AIDS.

[16] People with AIDS in need of highly active antiretroviral therapy (HAART) are disproportionately represented among the poor and unemployed who rely on the public sector for their medicine needs. About 30% of patients on HAART have some form of private insurance, 50% rely on Medicaid, a small number have access to Medicare and about 20% have no form of public or private insurance coverage. ADAPs purchase about 25 percent of all AIDS medications in the U.S.

[17] Alaska, New Hampshire, New Mexico, Oklahoma, Texas, Washington.

5.4.6. Suboptimal use of ritonavir boosters

Abbott's aggressive and anticompetitive price increases for Norvir/ritonavir will lead predictably to biases in prescribing medicines. The new prices create incentives for patients and third party payers to use the least expensive regimes. Under-utilization of ritonavir/Norvir as a booster or the overuse of Abbott's Kaletra will have an adverse impact on the efficacy and safety of protease inhibitor regimes used to treat AIDS patients.

5.4.7. Negative Impact on R&D for Protease Inhibitors that would be best used in combination in ritonavir.

The Abbott price increases have reduced incentives by competitors to develop new protease inhibitors that would be best used in combination with ritonavir. For instance, tipranavir, Boehringer-Ingelheim's new protease inhibitor now in development, needs to be boosted with 400 milligrams of Norvir/ritonavir, double the average used for most protease inhibitors. The cost of the Norvir boost would be more than $16 thousand dollars. This increase in the cost of the booster will destroy Boehringer's market share for first line regimes, and discourage Boehringer and other firms from developing products that may be very important for "salvage" patients, who have already developed resistance to existing protease inhibitors.

6. Remedy requested

The Bayh-Dole Act authorizes the Secretary of the Department of Health and Human Services to require that Abbott issue licenses under "terms that are reasonable under the circumstances" and, if Abbott refuses the request, to grant such licenses itself. 35 U.S.C. § 203(a). We request that you use this authority to require Abbott to issue an open license for use of the ritonavir patents subject to this complaint. The terms of the license should include a reasonable royalty to Abbott as well as a contribution to a research and development fund to support discovery of new HIV/AIDS medicines.

6.1. Open license

6.1.1. Definition of an open license

An open license is a non-exclusive license that is available to any supplier willing to meet standard non-discriminatory terms.

An open license is similar to the "licenses of right" concept that appears in the patent law of many Commonwealth countries. In the US, examples of voluntary open licenses include IBM's policy of open licensing of patents in the information technology field,[18] or many well-

[18] http://www.ibm.com/ibm/licensing/patents/practices.shtml. (accessed January 27, 2004). "IBM has an open approach to patent licensing for products in the Information Technology (IT) field, and is generally willing to grant nonexclusive licenses under reasonable and nondiscriminatory terms and conditions to those who in turn, respect IBM's intellectual property (IP) rights. An exception to this open licensing practice is for patents directed to ornamental designs. These address the "look" of a product and are not normally licensed. IBM also has patents relating to products outside of the IT field, such as apparatus patents that cover machinery used to manufacture IT products. These may be available for licensing at IBM's discretion. For products in the IT field that practice an IBM patent, the royalty rate follows the guideline of one percent of the selling price of that

known technology patent pools. An example of open non-voluntary licensing is the Microsoft compulsory license of computer protocols, which is a court supervised remedy to anticompetitive practices.

6.1.2. Right to manufacture and export world-wide

The open license should include the rights to use the patents to make, sell, use, import or export ritonavir as either a standalone product or as a component of a fixed dose combination. The license should include the right to export ritonavir to overseas markets. These rights are necessary to enable a US manufacturer to achieve the best economies of scale so that consumers can benefit from the lowest possible prices, and also to allow the manufacturer to meet global treatment needs.

6.1.3. Right to produce fixed dose combinations

There are substantial benefits from allowing other protease inhibitor manufacturers to produce fixed dose combinations that include ritonavir in a single pill format. Currently, Abbott's Kaletra is the only protease inhibitor on the market that combines a ritonavir booster with another protease inhibitor. This format has advantages for patients in terms of lowering pill counts and simplifying treatment. But for many patients, a different protease inhibitor combination may be more effective for treating their illness or may pose fewer side effects. An open license would allow other manufacturers to supply this important consumer need, increasing competition in the market for protease inhibitors to the benefit of consumers.

7. Proposed Terms of Open License

The Bayh-Dole requires that march-in licenses include "terms that are reasonable under the circumstances." We propose terms that include a royalty paid directly to the patent holder. We also propose a special requirement that each generic manufacturer of ritonavir contribute to research on HIV/AIDS, benefiting persons living with AIDS.

7.1. Royalty to the Patent Owner.

We propose that the Bayh-Dole open license provide to the owners of the ritonavir patents a combined royalty of 5 percent of the net sales of the generic ritonavir. The five percent royalty is roughly equal to the average US pharmaceutical royalty payment, as reported by the pharmaceutical manufacturing sector to the US Internal Revenue Service (IRS). This is more than adequate given that each of the patents in question were invented through a government funding agreement, and that Abbott earned more than sixty times its initial investment (over $1 billion) in ritonavir sales in its first five years on the market.

Normally, the base for calculating the royalty will be the net sales price of the generic product. However, when ritonavir is included as a component in a fixed does combination, the royalty should be five percent of the average price of generic ritonavir when sold on a standalone basis, adjusted for the dose used in the fixed dose combination.

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product. If more than one patent is practiced in a product, the maximum rate is five percent of the selling price of that product."

7.2. Special obligation to finance R&D for new treatments for AIDS.

We anticipate and share concerns that efforts to reduce prices for this government-funded invention will reduce profits to Abbott and consequently may reduce somewhat private sector incentives to invest in research and development. We also recognize that large research and development investments in advanced industrialized countries, and in the United States in particular, are needed to ensure access to new and better medicines for the entire world.

Therefore, in addition to a royalty payment to the patent holder, there should also be a requirement that producers of ritonavir under the open license contribute to research and development for new treatments for HIV/AIDS.

7.3. Cisplatin case as a model for funding AIDS R&D

The proposal that the open license contain a provision that requires every manufacturer of generic ritonavir to make an investment to a special fund for research for HIV/AIDS is modeled after an earlier case involving cisplantin, a cancer drug invented at Michigan State University and marketed by Bristol-Myers.[19] After Bristol-Myers enjoyed five years of exclusive rights to market cisplatin, the federal government was asked to permit competition. Bristol-Myers said that competition would result in lower profits and less R&D. One generic manufacturer proposed that every generic manufacturer contribute to an R&D fund, either managed by NIH or a private non-profit party. While the ultimate resolution of the cisplatin case was a negotiated reduction in the price of cisplatin and an agreement that Bristol-Myers transparently fund approximately $35 million in third party R&D on cancer, the proposal is revisited, as a logical mechanism to permit competition and lower prices while ensuring that R&D objectives are met.

The Secretary can decide if such an R&D requirement is appropriate, and if so, how large the R&D contributions would be, who would manage the fund, and how the intellectual property rights would be allocated. Here we offer suggestions for alternatives the Secretary may consider, which of course are subject to discussion and further negotiation.

7.4. Mission of the fund

The mission of the fund should be to support drug discovery based on novel scientific ideas that may not receive adequate investment but for the presence of the fund.

7.5. Required contribution to fund

We recommend that each manufacturer of ritonavir under the open license should contribute to the fund a minimum amount as follows:

1. For the US and other countries designated by the World Bank as High Income, $.004 per milligram.

[19] Prior to the merger with Squibb.

2. For countries designed by the World Bank as Low Income, the minimum contribution is zero.

3. For countries designed by the World Bank as middle income, the minimum contribution should be $.004, multiplied by the ratio of the country per capita income divided by the average per capita income of the countries designed by the World Bank as high income.

7.6. Management of the Fund

There are a variety of approaches that could be used to manage the Fund, including but not limited the following options:

1. The NIH could manage the R&D Fund

2. A private non-profit foundation could be identified or created to manage the R&D Fund.

3. A for-profit investment Fund could be created, with shares allocated on the basis of contributions to the fund.

7.7. Advisory board

Essential Inventions, Inc. recommends the Secretary create an Advisory Board that would review how the R&D funds were invested. This board should include representatives from the AIDS affected community and experts in medical research.

7.8. Ownership of intellectual property rights

The Secretary could choose different approaches to the allocation of intellectual property rights. Essential Inventions, Inc. recommends that commercial discoveries be treated in one of the following manners.

1. The inventions could be owned by the Federal Government. This approach might be particularly appropriate if the Fund is managed by the NIH.
2. The inventions could be owned by the investors in the fund.
3. The inventions could be owned by the original patent owners.
4. The commercial rights in the inventions could be split evenly between the original patent owners and the investors in the Fund.

Essential Inventions preferred approach is (4).

7.9. Reach Through March-In Clause

Essential Inventions, Inc. recommends that if options (2), (3) or (4) or used, there also be a reach-through clause that attaches the same rights the government now has under the Bayh-Dole Act for March-In rights.

7.10. Transparency of R&D

Essential Inventions, Inc. strongly recommends that all contributions to the fund and all distributions from the fund should be made transparent to the public through appropriate means.

8. Conclusion

The Bayh-Dole Act provides the government with the tools it needs to lower the prices of government funded medicines where the patent holder is abusing its rights, including through the kind of excessive and anticompetitive pricing practices demonstrated in this case. We request that use the March-In provisions of the Act to remedy the abuses of patent rights by Abbott in its marketing of ritonavir.

Essential Inventions, Inc.
January 29, 2004