

EXPERT REPORT BB

ESSENTIAL FACILITIES FOR FIXED-DOSE COMBINATION ARVs

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LEGAL BASIS OF ANALYSIS – REFUSAL OF ACCESS TO ESSENTIAL FACILITIES

Under Section 8 of the South African Competition Act “[i]t is prohibited for a dominant firm to – refuse to give a competitor access to an essential facility when it is economically feasible to do so.” Under the Act, an “‘essential facility’ means an infrastructure or resources that cannot reasonably be duplicated, and without access to which competitors cannot reasonably provide goods or services to their customers.” One possible interpretation of the essential facility doctrine, read against the background of the constitutional duty to interpret legislation to “promote the spirit, purport and objects of the Bill of Rights” (sec. 39), including the right of everyone to access to health services (sec. 27), is that the Competition Act imposes an obligation on the respondents to license their patented products on reasonable terms when doing so serves public health priorities. Specifically, it is the conclusion of this report that the essential facility doctrine should be used as a basis for compulsory licensing of the products subject to the complaint to enable consumer access to fixed-dose combination drugs (FDCs) that provide multiple ARVs in a single pill.

IMPORTANCE OF FDCs FOR LONG-TERM PATIENT COMPLIANCE WITH ARV TREATMENT REGIMES

There are two central and interrelated benefits that arise from the use of FDCs in the administration of Highly Active Antiretroviral Therapy (HAART) in developing countries. The first is a lower overall pill count that predictably increases adherence to treatment regimes. The second is that FDCs have been shown to increase compliance because patients can take all their required medicines on a regular and fixed schedule rather than having to cope with a more complicated schedule of multiple pills on differing time schedules. The impact of reduced pill count and of simplified dosing schedules is to decrease the incidence of resistance of the AIDS virus to ARV treatment.

Adherence is aided by decreased pill count and simplified dosing frequencies

The World Health Organization has emphasized the importance of developing innovative strategies for enhancing adherence to antiretroviral therapy because it is a life-long

therapy.¹ It is widely accepted, including by surveys by pharmaceutical manufacturers, that a main obstacle to patient compliance with Highly Active Antiretroviral Therapy (HAART) is too many pills and complicated dosing schedules.² For several years, combinations of medicines within a single pill have been available that can both decrease overall pill counts and simplify dosing schedules. The WHO has recommended that medical providers utilize strategies to increase adherence to treatment regimes “include minimizing pill counts and dosage frequencies by preferentially using combination pills on a once-daily or twice-daily basis.”³ According to the WHO, “[w]hen available, fixed-dose combinations are advantageous with respect to the simplification of regimens and consequent improved adherence.”⁴

In addition to referencing the benefits of fixed-dose combinations produced by major pharmaceutical manufacturers,⁵ the WHO acknowledges that fixed-dose formulations have been produced by generic manufacturers, “which [formulations] may facilitate simplified regimens, decrease cost and promote adherence if they can be legally used and their quality and bioequivalence has been demonstrated.”⁶

The theoretical importance of FDCs has been confirmed by recent research on twice-daily regimens. “[R]ecent work on simplification of HAART regimens, reported at the latest Glasgow conference on HIV treatment, could have a major impact on compliance-related treatment failure in both resource-rich and resource-poor countries. ... It is well documented that adherence rises as the complexity of a HAART regimen declines, a point emphasized by a recent comparison of the fixed-dose combination of zidovudine and 3TC (Combivir) with the 2 drugs given separately.”⁸ Of course, the long-term

¹ World Health Organization, *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach*, 16 (June 2002) [*WHO Scaling Up*]; World Health Organization, *Adherence for Long-Term Therapies: Evidence for Action*, 95-106 (2003) [*WHO Adherence for Long-Term Therapies*] (noting that the large number of medications, complicated dosing requirement, and suboptimal tolerability make adherence difficult).

² See, e.g., *HIV-Positive Patients Find Medications Hard to Take, GlaxoSmithKline Survey Finds*, Kaiser Daily HIV/AIDS Report (March 19, 2001) http://www.kaisernetwork.org/daily_reports/print_report.cfm?DR_ID=3495&dr_cat=1; *Protease Inhibitors: Drug Companies Seek Treatments to Reduce Pill Intake*, Kaiser Daily Reports (February 3, 2000) (reporting a small study by Bristol-Myers Squibb and multiple quotes from medical experts about the desirability of reducing the pill burden) <http://www.kaisernetwork.org/aids/2000/02/kh000203.3.htm>.

³ *WHO Scaling Up* at 16. The WHO notes that, “[a] number of fixed-dose combination products containing two or three ARV drugs, current on the market, can be used twice a day.” *Id.* “There is evidence that simplified regimens that require fewer pills and lower dose frequencies improve adherence.” *WHO Adherence for Long-Term Therapies* at 97. See, Panel on Clinical Practices for Treatment of HIV, *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents* (NIH 2002) (recommending, if possible, to reduce dose frequency and number of pills).

⁴ *WHO Scaling Up* at 31.

⁵ *WHO Scaling Up* at 31 (including GlaxoSmithKline’s Combivir and Trizivir).

⁶ *WHO Scaling Up* at 31 (referring presumably to fixed-dose combinations like Triomune from Cipla Ltd.).

⁷ Médecins Sans Frontières, *Equitable access: Scaling up HIV/AIDS treatment in developing countries* (World AIDS Day 2002 Briefing Paper, November 27, 2002).

⁸ Jeffrey Laurence, M.D., *Simplifying HIV Therapeutics, and the Global Treatment of AIDS*, AIDS Read 13(1): 5-6 (2003)(citing J. Jordan, T. Delea, B. Sherrill, et al., *Impact of fixed-dose combination zidovudine/lamivudines on adherence to antiretroviral therapy: a retrospective claims-based cohort study*, in: Program and abstracts of the 6th International Congress on Drug therapy in HIV Infection; November

goal is to reach a goal of a once-daily regimen that “provides patients with a regimen that can fit more easily into their established routines, thereby increasing treatment adherence.”⁹

The medical experts have emphasized that patient compliance is dependent on a reduced pill burden and simplified dosing schedules, but fixed-dose combinations have other advantages in terms of ensuring that patients take triple as opposed to mono or dual therapy. Triple therapy is essential to counteract HIV’s extraordinary mutation rate, which leads to an accelerated incidence of drug-resistance in mono or dual therapy regimens.¹¹ Providing HAART through three-drug FDCs reduces the possibility that patients will be treated with mono or dual therapy, which is still unfortunately common in African countries.¹²

Administering HAART through fixed-dose combination pills might also reduce, though not eliminate, the risk that the patient would split therapies with others. Although there has been little research on pill splitting in resource poor settings, especially since there has so little ARV therapy provided, there is reason to believe that patients are sometimes coerced to share pills or do so out of concern for others, especially within family settings.¹³ This is one reason why treatment providers have begun to encourage voluntary counseling and testing with both partners and why mother-to-child-prevention-plus programs¹⁴ extend ARV therapy to an entire family group, since HIV infection is likely to be intra-familial.

17-21, 2002; Glasgow, U.K., Abstract P97) (accessed July 1, 2003
www.medscape.com/viewarticle/449706_print).

⁹ Richard B. Pollard, M.D., *Management Trends: Can HIV Infection Be Treated Successfully With a Once-Daily Regimen?*, *AIDS read* 12(11): 489-500 (2002) (accessed July 1, 2003

www.medscape.com/viewarticle/444894_print). “HAART typically involves a complex intermingling of medications, dosing schedules, and side effects that often place a heavy burden on patients. Once-daily dosing is the least confusing schedule and is the one preferred by patients, as is a regimen with fewer pills that can be taken without dietary restrictions. Although drug research has not quite met all of these conditions, achievement of this objective is coming closer. . . . The potential advantages of once-daily dosing include better understanding of the regimen by the patient and, hence, increased adherence.” *Id.*

¹⁰ See, e.g., *HIV-Positive Patients Find Medications Hard to Take, GlaxoSmithKline Survey Finds*, Kaiser Daily HIV/AIDS Report (March 19, 2001)

http://www.kaisernetwork.org/daily_reports/print_report.cfm?DR_ID=3495&dr_cat=1; *Protease Inhibitors: Drug Companies Seek Treatments to Reduce Pill Intake*, Kaiser Daily Reports (February 3, 2000) (reporting a small study by Bristol-Myers Squibb and multiple quotes from medical experts about the desirability of reducing the pill burden) <http://www.kaisernetwork.org/aids/2000/02/kh000203.3.htm>.

¹¹ *Scaling Up* at 24.

¹² *Scaling Up* at 29 (noting that “it is recognized that many HIV-infected individuals in the developing world are being treated with dual [nucleoside analogue reverse transcriptase inhibitor] combinations because potent three-drug and four-drug combinations are not affordable”).

¹³ Julian Meldrum, *Success and failure in HIV treatment: contrasting lessons from South Africa*, AIDS MAP (August 25, 2003) <http://www.aidsmap.com/news/newsdisplay2.asp?newsId=2264>.

¹⁴ “The MTCT-Plus Initiative is a new HIV/AIDS treatment program coordinated by the Mailman School of Public Health at Columbia University in response to the UN Secretary General’s Call to Action. The MTCT-Plus Initiative will support the provision of HIV-specific care, including access to a number of standardized antiretroviral options when clinically indicated, to HIV-infected women and children identified in pMTCT programs, and to their HIV-infected family members as appropriate. The MTCT-Plus Initiative aims to decrease morbidity and mortality, further reduce mother-to-child transmission of HIV, lessen

orphanage, promote VCT, and strengthen local health care capacity. It is hoped that this Initiative can provide an important first step towards greater access to HIV care in resource-limited settings.”
<http://www.mtctplus.org/index.html>.

Increased adherence leads to decreased resistance

The clinical benefit of increased adherence resulting from the use of fixed dose combinations is the decreased incidence of resistance of the AIDS virus to individual medicines and to entire classes of medicines. According to the WHO, adherence to HAART must be at a very high level to achieve lasting viral suppression because of the rapid replication and mutation rates of HIV.¹⁵ The advantage of triple-therapy is that it attacks HIV in three ways at the same time, meaning that a mutation that is resistant to one medicine is unlikely to be simultaneously resistant to the other two. Richard Laing, Associate Professor of International Health at the Boston University School of Public Health, has explained the special importance of FDCs in preventing resistance:

Learning from the experience of Fixed Dose Combination FDC's in TB management, we can see that these drugs can prevent the development of resistance. If formulated correctly, the dose can be adjusted for weight and compliance can be improved. The logistic advantages of such a system are obvious.

For this to happen drugs which are complementary in action, have similar half lives and different side effects should be combined. Learning again from TB, we should recognize that combining drugs may affect bio-availability (sic), but this is a technological problem that can be solved if detected early in the production process. However, drug manufacturers will need to demonstrate bio equivalence as part of their production process.

As nearly all of the AIDS patients in Africa have never been exposed to ARV's, and if only FDC's are used the problems of resistance developing can be reduced or hopefully avoided!¹⁶

Although fixed-dose combinations are believed to be an important adjunct to increased patient compliance and thus to reduced resistance, there are some practical barriers to the availability of fixed-dose combinations, other than patent issues discuss further below. The main barriers deal with problems of drug registration in multiple nations and with WHO pre-qualification.²⁰ In this regard, the most immediate barrier is to produce

¹⁵ WHO *Adherence for Long-Term Therapies* at 96.

¹⁶ Email from Richard Laing to Pharm-policy list, Aug 13, 2001, <http://lists.essential.org/pipermail/pharm-policy/2001-August/001356.html>.

¹⁷ Email from Richard Laing to Pharm-policy list, Aug 13, 2001, <http://lists.essential.org/pipermail/pharm-policy/2001-August/001356.html>.

¹⁸ Email from Richard Laing to IP-Health list, March 16, 2002, <http://lists.essential.org/pipermail/ip-health/2002-March/002781.html>. In essence, the Competition Commission is poised to start a patent pool involving GlaxoSmithKline and Boehringer Ingelheim. In the future, on an essential facilities theory, other patent holders of ARVs such as Merck, Abbott, Roche, and Bristol-Myers Squibb might be added.

¹⁹ For a recent comparison of generic versus patent-branded fixed-dose combination ARVs, see *Médicins Sans Frontières, Untangling the web of price reductions: a pricing guide for purchase of ARVs for developing countries* 13 (May 5, 2003) [*MSF Untangling the web*].

²⁰ WHO has instituted a process of pre-qualifying ARVs that meet internationally recognized standards for good manufacturing processes and, in the case of generics, bio-equivalence. See *WHO list of Pilot*

evidence of bio-equivalence as well as proof of good manufacturing practices in manufacturing facilities. Although none of the generic three-drug fixed-dose combinations have yet been pre-qualified by WHO, it is expected that such pre-qualification will occur in the near future.²¹

WHY GENERIC COMPANIES PRODUCE MIXED-BRAND FIXED-DOSE COMBINATIONS AND PATENT HOLDERS DO NOT

Cipla stirred the imagination and hopes of treatment activists and people living with HIV/AIDS worldwide on August 7, 2001, by formulating a new three-in-one antiretroviral tablet combining stavudine, lamivudine, and nevirapine.²² The public announcement of this breakthrough emphasized the cost advantage of the new combination, only slightly more than a \$1 a day – a fifth or sixth of the cost of treatment with brand-name drugs. Since Cipla's historic announcement, multiple other Indian companies have begun to produce fixed-dose combination ARVs,²³ as have companies in Thailand,²⁴ and China,²⁵ and prices of these treatments have decreased over time.²⁶

Given the therapeutic importance of FDCs, it is important to understand why so few proprietary pharmaceutical manufacturers have produced combination ARVs and, more to the point, why none of them have done so with a competitor's product. In this context, it is important to remember that HIV medicines are individually patented and that patent-holders have a perverse economic interest in avoiding the creation of FDCs and in delaying product improvements.²⁷ Let's take the Cipla example. Britain's

Procurement, Quality and Sourcing: Access to HIV/AIDS drugs and diagnostics of acceptable quality (Sixth edition, May 5, 2003).

²¹ “[T]he Indian pharmaceutical company Cipla announced that a fixed-dose combination ... known as Triomune, produced pharmacokinetics similar to those produced by the 3 drugs when they were given individually.” Jeffrey Laurence, M.D., *Simplifying HIV Therapeutics, and the Global Treatment of AIDS*, AIDS Read 13(1): 5-6 (2003)(citing J. A. Gogtay, V. Manek, V. G. Nayak, et al., *A pharmacokinetic evaluation of lamivudine, stavudine, and nevirapine given as a fixed dose combination pill versus the same drugs given separately in health human volunteers*, in: Program and abstracts of the 6th International Congress on Drug therapy in HIV Infection; November 17-21, 2002; Glasgow, U.K., Abstract PL8.4).

²² *Cipla Releases Three-in-One Drug Combination of Stavudine, Lamivudine and Nevirapine*, Kaisernetwork.org: daily reports (August 7, 2001).

²³ See *MSF Untangling the web* at 13.

²⁴ *Thai Government to Sell AIDS Drug Combination Pill for Less Than \$1 Per Day*, Kaisernetwork.org: daily reports (March 25, 2002).

²⁵ *Chinese Pharmaceutical Firm Begins Distribution of Generic Antiretroviral Drugs*, Kaisernetwork.org: daily reports (January 30, 2003).

²⁶ *MSF Untangling the web*.

²⁷ In the search for simpler treatment regimes, it is also important to emphasize the goal of developing once-a-day, time-released pills and medicine formulations that reduce the side effects of ARVs, such as nausea. Once again, the perverse financial interests of patent-holders stand in the way of truly effective treatment protocols. Why? Because patent-holders like to hold reformulations of their already patented medicines in reserve so that they can extend their patents through a process called evergreening. For example, Bristol Myers Squibbs waited until 2000 to file a patent application on a once a day enteric-coated ddI, the third generation of this drug. ddI is the second oldest AIDS drug and one developed at public expense to the degree that the U.S. Department of Health and Human Services holds the first patent. Why did Bristol-Myers wait over ten years to announce an enteric-coating? Did it lack such “technology”

GlaxoSmithKline holds the patent for lamivudine, Germany's Boehringer Ingelheim the patent on nevirapine and the US's Bristol-Myers Squibb the patent on stavudine. Nothing in principle prohibits these three companies from entering into voluntary cross-licensing agreements to produce a three-in-one fixed-dose ARV tablet, especially since this combination is both efficacious and inexpensive; indeed, the WHO recommends it as a first-line combination for resource poor settings.²⁸ However, in practice, the proprietary manufacturers do not want to dilute individual brand recognition, nor do they want to indirectly promote the products of a competitor. Although GlaxoSmithKline will combine its own HIV products, e.g. Combivir (AZT+3TC) and Trizivir (AZT+3TC+ABC), neither it nor its competitors will combine medicines with other manufacturers. In fact, none of the major manufacturers currently cross-license their ARVs. As a consequence, in countries where generics are excluded because of patent status, doctors and patients are left with the unwieldy task of prescribing and taking multiple tablets, multiple times a day, and then monitoring compliance with overly complicated treatment regimes.

The logic of single-medicine pills makes sense in the twisted world of global pharmaceuticals, where maximizing profit, maintaining competitive advantage, and promoting brand recognition prevail, but it does not make sense in the actual lives of AIDS patients in developing countries where simpler regimes are crucially important to survival. FDC medicines can be distributed more easily and reliably; they can ease patient compliance; and they can even reduce risks of resale of drugs by desperately poor patients who might otherwise be tempted to resell part of their treatment regime in the hope that one out of three medicines might be enough. One three-in-one pill twice a day will also be easier for health aids to monitor if directly observed therapy is instituted on a broad scale.

It is bad for consumers when patent holders refuse to cooperate among themselves to cross-license their medicines to create rational FDCs, but worse when these same manufacturers refuse to license their patented medicines, as an essential facility, for development of FDCs by generic competitors. For example, Cipla requested voluntary licenses in 2001 from both GlaxoSmithKline and Boehringer Ingelheim, offering a standard 5% royalty on annual sales in South Africa to each company. In what should be interpreted as an effort to avoid competition with a better fixed-dose combination product, neither company granted the request. Although the response of the respondents to the license requests was to request voluminous amounts of proprietary and irrelevant information from the requesting company, this response is best interpreted as a refusal to deal with Cipla on reasonable terms. This refusal in turn may, and should, be interpreted as a denial of access to an essential facility where the reasonable royalty offered for the license would have made it economically feasible for the respondents to grant such access.

in 1990? Of course not, it delayed an improved formulation so that it could "evergreen" and extend its pricing monopoly with a "new" patent on this minor but important reformulation.

²⁸ *WHO Scaling Up* at 30, Table 3.

SUGGESTED REMEDY

Assuming that a violation of Section 8 is found, the most appropriate remedy is a compulsory license that allows all qualified firms, domestic and international, to supply the South African market. As Dr. Laing has commented, “[t]he use of compulsory or voluntary licenses may be an essential tool in ensuring that the most rational combination of ARV's are produced and used.”²⁹

The issuance of non-exclusive compulsory licenses for the respondents' products will, in essence, be the beginning of the creation of a patent pool of essential ARVs that can thereafter be combined into rational fixed dose combinations and registered for use at significant cost savings and public health benefits to South African consumers. Writing on the FDC-benefits of creating a patent pool for ARVs, Professor Laing wrote:

One major attraction of patent pools for ARV's would be to promote the creation of Fixed Dose Combination (FDC) products without regard to the patent status of the individual component products. One way to avoid the development of Multiple Drug Resistance (MDR) is to combine complementary products into a single tablet or formulation. MDR is a serious problem and has been demonstrated in AIDS, bacterial infections particularly TB, malaria and in other diseases. If AMR progresses as it has, we may be left without effective antimicrobial agents and the world will be back to the days before 1950 when we did not have such drugs.

It is my belief that ARV's are too valuable to be sold as single products. By combining them, the rate of resistance developing is reduced. At the moment the few FDC products are coming from companies which hold multiple patents and can produce them. But these may not be the most logical FDCs. Ideally, you want the component drugs to have synergistic effects, different side effects and have similar pharmacological properties (half life etc). Producing such logical combination products can only occur if all of the available drugs are available to be included. This could most easily be done by such a patent pooling activity. From a public health standpoint requiring such a product pool makes sense because once resistance develops to a specific drug that drug becomes useless in that environment.³⁰

²⁹ Email from Richard Laing to Pharm-policy list, Aug 13, 2001, <http://lists.essential.org/pipermail/pharm-policy/2001-August/001356.html>.

³⁰ Email from Richard Laing to IP-Health list, March 16, 2002, <http://lists.essential.org/pipermail/ip-health/2002-March/002781.html>. In essence, the Competition Commission is poised to start a patent pool involving GlaxoSmithKline and Boehringer Ingelheim. In the future, on an essential facilities theory, other patent holders of ARVs such as Merck, Abbott, Roche, and Bristol-Myers Squibb might be added.

CONCLUSION

To permit the therapeutically appropriate FDC option, South Africa should grant non-exclusive compulsory licenses so that generic competitors can manufacture locally or import (and then register) three-in-one ARVs. Obviously, the desirable combinations will change over time in response to new discoveries and to assessment of emerging drug resistance, if any. However, the significant cost advantage of high quality generic medicines will be matched by an equally important fixed-dose therapeutic benefit if the Competition Commission vigorously pursues a compulsory license on an essential facilities theory.