Fixed-dose combination (FDC) drugs availability and use as a global public health necessity : intellectual property and other legal issues

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Executive summary

Patented medicines are priced far above marginal cost and patent holders are rewarded for research and development (R&D) with grants of exclusive commercial rights (primarily patents, copyrights and trademarks) so that intellectual property laws allow the "investor" to regain some of the benefits of their research and innovation. Fixed-dose combination drugs have the potential to involve multiple patents held by different parties. The transaction costs associated with bargaining over property rights for components of the FDC can arguably lead to both blocking of commercial development and, if already manufactured, to lack of access "on the ground" .

There are various ways to overcome or ameliorate the negative effects of IPRs on access to FDCs. Some unilateral mechanisms include:

- Put the 'invention' (e.g., fixed-dosage combinations) into the public domain and avoid IP/patent rights entirely or try to "design around" existing IP for FDCs.
- Make patents harder to get so that only real advances in medicines will be patented.
- Create exceptions to patent infringement so that various entities are spared the transaction costs of licensing or, more particularly, patent litigation.
- Use voluntary and, if needed, compulsory licensing between patent owners.

Other mechanisms include the creation of multilateral, collective business models for R&D and transacting IPRs. These might include the creation of voluntary or government-mandated patent pools. Another possibility, not yet well thought-out, would be to develop various IP information and transactional

"clearinghouses" specifically for IP related to fixed-dose combination drugs. Such a clearinghouse should be able to identify all relevant IPRs over a given (i.e., FDC) technology and, indicate which are and which are not available to be negotiated, and if they are, how they can be accessed. It should create a pricing scheme and terms of contract and a royalty disbursement accounting system.

Multiple components of FDCs can lead to complex issues of IPR access and implicates other factors such as R&D funding mechanisms and global IP rules. Creative approaches to the problem are required. For developing countries, IP-resource poor inventors, NGOs, and patients, ways are needed to reduce IPR transaction costs with regard to fixed-dose combination drugs.

Introduction

Intellectual property rights (IPRs) are legal and institutional devices to protect creations of the mind such as inventions, works of art and literature, and designs. A patent for an invention is the grant of a property right to the inventor, issued by a national, patent-issuing authority of a particular country. The term of a new patent is 20 years from the date on which the application for the patent was filed in the particular patent office or, in special cases, 20 years from the date an earlier related application was filed. Patent grants are creature of national, NOT international law and are effective only within the granting country and its territory and possessions. Recent global frameworks for intellectual property under the auspices of the World Trade Organization (WTO) (see Section 5) offer guidance as to minimal levels of IP protection that countries must have. There is a forum for resolving IP disputes between countries within the WTO but, unless individual countries' provide subsequent legislation or influence subsequent policy, such resolutions have no direct force of law in terms of dictating domestic IP policies.

A patent grant is NOT a positive right to make, use, offer for sale, sell or import, but it is a negative right to exclude others from making, using, offering for sale, selling or importing the patented invention. This is an important distinction and is often difficult to grasp. Obtaining an issued patent does not provide the patentee with the right to practice her own patented invention. Thus, "freedom to operate" (the ability to practice your own invention without having to obtain needed patented technology from third parties) and having an exclusive position in the market in which your invention is the only one practiced, are independent concepts. A patented drug can enjoy market exclusivity, but still have no complete "freedom to operate" because making the drug requires one or more third party manufacturing patents or patents to active pharmaceutical ingredients.

By pricing medicines far above marginal cost, patent holders are rewarded for *ex ante* research efforts with *ex post* grants of exclusive commercial rights[1] so that intellectual property laws allow the "investor" to regain some of the benefits of their research and innovation. However, the net effect of IPRs on innovation,

creativity and economic development are uncertain and it is probably not possible, on the basis of present knowledge, to be sure that a given patent system confers a net benefit or a net loss upon society. For developing countries the situation continues to be extremely unclear. IPRs create their own problems[1].

For the present discussion of FDCs, there are two related IPR issues:

a) IPRs can be a barrier to research and development into new FDCs,
b) IPRs can bar access to existing FDCs by the healthcare system.

That is, strong property rights arguably stifle research by creating a climate where researchers face legal action for using patented materials, processes or research tools (See Section 2). Fixed-dose combination drugs have the potential to involve multiple patents held by different parties. The transaction costs associated with bargaining over rights can arguably lead to both blocking of commercial development and, if already manufactured, to lack of access "on the ground" (See Section 3). High prices of patented medicines are but one important barrier to access. There are various ways to overcome or ameliorate the negative effects of IPRs on access to FDCs, some of which implicate other legal issues, notably antitrust and competition law (Section 4). Recently, the global community has, more or less (See Section 5), agreed that IPRs should be subservient to public health needs.

IPRs and Fixed-dose Combinations: Introduction to the "Anticommons Problem"

Garrett Hardin's "tragedy of the commons" [2] conceptualized resource overutilization topics such as overgrazing on renewable crops, species extinction, and market behavior. In each case, an under assignment or inability to enforce property rights leads to a set of incentives that cause overuse of a commonly-held property resource. In Hardin's view, too many owners of a common resource, each having the right to use, leads to overuse. Heller and Eisenberg[3] have developed the mirror image "tragedy of the anticommons" in which an over assignment of property rights for a privately-held resource leads to under utilization of the resource. In the "anticommons", multiple owners each have the right to exclude others from a resource and this leads to underuse since no one person can use the whole. One example occurs when patents for gene fragments in biomedical research lead to lack of freedom to operate since users of whole genes in downstream applications are required to license numerous already-patented gene fragments. The "cost of doing business" in this environment can be disruptive. Many IP stakeholders drive up the cost of establishing value for the IP and incompatible ownerships require individual negotiations. Within the communities of scientists, university technology transfer professionals, and private firms in the pharmaceutical and biotechnology industries, "there seems to be a widely shared perception that negotiations over the transfer of proprietary research tools present a considerable and growing obstacle to progress in biomedical research[3]."

IPRs and Fixed-dose Combinations: The "Anticommons Problem" (II)

Multiple/conflicting IP ownership will lead to multiple access requirements and this, in turn, can create significal technology access problems. An extreme example is that of agricultural biotechnology and vitamin A golden rice which is made using recombinant DNA technology. Each plant contains several exogenous DNA fragments that allow the plant to synthesize large amounts of Vitamin A[4]. Depending upon the country, between zero and 40 (!) separate patents need to be accessed in order to create a "golden rice" plant[i].

The "anticommons" barrier to improved availability of FDCs revolves around IPRs of the individual FDC components, exemplified by the antiretroviral FDCs. Trizivir ®, approved by the FDA in November 2000 for the treatment of HIV in adults and adolescents, is an FDC of Ziagen® (abacavir sulfate 300mg/ABC), Retrovir® (zidovudine 300mg/AZT), and Epivir® (lamivudine 150mg/3TC). Ziagen® was discovered and is being developed by GlaxoSmithKline and all rights to technology, including intermediates used in its were licensed to Glaxo Wellcome by the University of Minnesota in 1992. Lamivudine was discovered by BioChem Pharma of Laval, Quebec, Canada and licensed to Glaxo Wellcome in 1990. GlaxoSmithKline therefore has outright intellectual property ownership or exclusive rights to all components of Trizivir®. CIPLA, Ltd, the Indian drug company, makes an FDC ("Triomune") which contains nevirapine, stavudine (d4T) and lamivudine (3TC). Each component is owned by a different party; Yale (stavudine), BioPharma/Glaxo (lamivudine) and Boehringer Ingelheim (nevirapine)[5,ii]. Thus, even if components of FDCs may be patented separately and owned by different parties or all components may be owned by the same party, requiring a license to even one component of an FDC is enough to block access to the whole.

Table 1 lists the components of these FDCs (column 3: Triomune; column 4: Trizivir®). Data from Attaran and Gillespie White[6] allows us to list those countries that have patent protection for all three components of the particular FDC ("+++") or just individual components. We note that Combivir® is an FDC of lamivudine and zidovudine. Thus, the presence of patent protection for a Combivir® product might also effectively block production, sale, or use of Trizivir®®, since Trizivir® contains within it the components of Combivir®. Even if the healthcare systems in the countries of Table 1 were entirely efficient in delivering medicines (which they are clearly not), the blockage of these FDCs by IPRs affects tens of millions of people. Table 1 lists the prevalence of HIV+ adults affected by this lack of FDC access[7]. In this regard, Aspen has received a voluntary license for the components of Trizivir® and recently received a

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[i] Kryder, RD. Kowalski, SP. & Krattinger, AF. (2000), *The intellectual and property components of pro-vitamin A rice (Golden Rice): A preliminary freedom to operate review,* ISAAA Briefs No. 20. ISAAA, USA. (http://www.agbiotechnet.com).

[ii] India can manufacture these antiretrovirals domestically because its patent system, albeit only until 2005, only allows pharmaceutical method of manufacture patents. India can "design around" method patents by making them using a different method than that described in the patent.

voluntary license (terms unknown) apparently allowing it access to nevirapine and and stavudine. The terms of the license are such that FDCs can be made from these two components (Richard Laing, personal communication, 10 November 2003).

Table 1: Components of various FDCs that are patented in selected African countries

	HIV prevalence	Triomune components under patent protection	Trizivir® components under patent protection
Country	**Adult (%)**	**Stavudine/Lamivudine/ Nevirapine**	**Lamivudine/Zidovudine/ Abacavir**
Botswana	38.80	Nevirapine, lamivudine	+++
Zimbabwe	33.73	Nevirapine, lamivudine	+++
Swaziland	33.44	Nevirapine, lamivudine	+++
Lesotho	31.00	Nevirapine, lamivudine	+++
Namibia	22.50	Nil	Nil
Zambia	21.52	Nevirapine, lamivudine	+++
South Africa	20.10	?	+++
Kenya	15.01	Nevirapine, lamivudine	+++
Malawi	15.00	Nevirapine, lamivudine	Combivir®, lamivudine
Mozambique	13.00	Nil	Nil
Central African Republic	12.90	Nevirapine, lamivudine	Combivir®, lamivudine
Cameroon	11.83	Nevirapine, lamivudine	Combivir®, lamivudine
Djibouti	11.75	Nil	Nil
Cote d'Ivoire	9.65	Nevirapine, lamivudine	Combivir®, lamivudine
Rwanda	8.88	Nil	Combivir®
Burundi	8.30	Nil	Combivir®, zidovudine
United Republic of Tanzania	7.83	Nevirapine, lamivudine	+++
Congo	7.15	Nevirapine, lamivudine	Combivir®, lamivudine
Sierra Leone	7.00		Combivir®, abacavir
Burkina Faso	6.50	Nevirapine, lamivudine	Combivir®, lamivudine
Ethiopia	6.41	Nil	Nil
Togo	6.00	Nevirapine	Combivir®, lamivudine
Nigeria	5.80	Nevirapine	Combivir®, lamivudine
Angola	5.50	Nil	Nil
Uganda	5.00	Nevirapine, lamivudine	+++
Democratic Republic of Congo	4.90	Nil	Combivir®
Gabon	4.16	Nevirapine, lamivudine	Combivir®, lamivudine
Ghana	3.00	Lamivudine	+++
Sudan	2.60	Nevirapine, lamivudine	+++
Gambia	1.60	Nevirapine, lamivudine	+++
Seychelles		Lamivudine	+++

+++ signifies that all three components are under patent (as of 2001)
Data in column 2 are as of the end of 1999 (Source[vii])

Fortunately, the major components of FDCs for tuberculosis are off patent but the problem will resurface as new TB drugs become available and anti-mycobacterial resistance to existing drugs increases[i]. With regard to patented malaria FDCs, one example is Coartem®, marketed by Novartis. This patented FDC (artemether/lumefantrine) is being provided at cost by Novartis and distributed through the WHO as part of the worldwide 'Roll Back Malaria' initiative. Coartem® contains the same ingredients as far more expensive Riamet, a Novartis medication approved in Europe for travellers visiting malaria-endemic regions. The incentives for a third party (i.e., a generics manufacturer in India) to make Coartem® at a profit are necessarily undercut since Novartis is selling the drug at zero margin.

Overcoming IP/Legal barriers

Mechanisms exist for overcoming these IP "access" barriers to using FDCs. Some relate to collective ways of innovation and management of IPR issues Some are not specific to FDCs inasmuch as they deal with novel methods of funding R&D and many are radical enough not to be considered part of the mainstream ideas about IPRs. Some are unilateral, others are multilateral. All, however, are worth thinking about.

Put the 'invention' (e.g., fixed-dosage combinations) into the public domain and avoid IP/patent rights entirely

The genomes of major parasites are being sequenced and the data released into the public domain (see[8,9, 10,11]). There are numerous discussions at the present time regarding open source research systems, inspired by open source software development. Advocates of open-source innovation want research results to be a freely available commodity, with drug companies competing to market generic versions of drugs[12]. The common availability of information would help to overcome two serious barriers to fair trade in patented technologies: 'imperfect information' and 'information asymmetry', situations where one or both parties in a transaction lack some of the information on which their decisions to buy or to sell rest. Moreover, according to principles of patent rights "exhaustion", once a patented product is sold for the first time, then the patent rights attached to it

[i] In the US at least, there exist multiple incentives to stimulate the development of antimicrobial agents. They include orphan drug exclusivity (James Love *Comments on the Orphan Drug Act and Government Sponsored Monopolies for Marketing Pharmaceutical Drugs*. United States Senate, Committee on the Judiciary, Subcommittee on Antitrust, Monopolies and Business Rights, Anticompetitive Abuse of the Orphan Drug Act: Invitation to High Prices, January 21, 1992, Serial Number J-102-48, pages 259-283), the Waxman-Hatch initiative (Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, codified at 15 U.S.C. §§ 68b-68c, 70b, 1994), pediatric exclusivity (see, for example, the FDA's report (htpp://www.fda.gov/cder/pediatric/reportcong01.pdf), a certain prioritization for expedited review of agents effective for certain resistant organisms, higher consideration for expedited review of drugs in new classes with novel mechanisms of action, and federally funded clinical study groups. Most pharmaceutical companies are aware of these incentives and utilize them although for some of these intiatives, the public health consequences are far from clear. However, the real problem is that there is significantly diminishing FDA submissions and diminishing approvals of newer antimicrobials.

disappear. Unless the sales contract stipulates something different, patented medicines sold to a third party can be made with impunity into FDCs or blister packs.

"Design around" existing IP for FDCs

This is being done in India (see above, section 3) and at least is theoretically possible provided there are sufficient resources for IP review and product development. It is not clear that relevant FDC users (i.e., NGOs, developing countries) have the means to do this.

Make patents harder to get so that only real advances in medicines will be patented

This involves legislative/legal changes to the patent system. Stimulated by the proliferation of patents to DNA sequences of dubious usefullness, the United States has raised the standards for the requirement that inventions have practical "utility"[13]. It is too early to tell what the effect of this will be on innovation and development/access of new FDCs.

Create exceptions to patent infringement so that various entities are spared the transaction costs of licensing FDCs and components or, more particularly, spared the costs of patent litigation

Such exceptions do exist such as the so-called "Bolar safe harbor" in the U.S. which generally allows entities, such as generic drug makers, to legally infringe a patent if the allegedly infringing activities are performed pursuant to filing for FDA approval of a drug. Other countries have similar exceptions. Many people believe that universities are allowed a "research" exemption from patent infringement but, if this ever was true, this exemption is rapidly being eroded[14].

Manage the risk of poor FDC access by voluntary licensing

In the case of FDCs, this would involve negotiating a series of voluntary licenses so that an FDC manufacturer could have freedom to produce the combination. Cross licensing (i.e., where two or more entities license IP to each other) is very common in the biotechnology industry, although probably less common between pharmaceutical companies. "Set off" clauses in license contracts are often the subject of much voluntary negotiation, but provide language to deal with this "anticommons" problem. These clauses are primarily for the licensees' benefit. In their simplest form, they essentially state that " … if I need any patent from a third party that is not part of this negotiated IP package from company X, I will still pay 'rent' to access patents of company X but decrease them by the amount owed for the company Y patent". Notwithstanding cross licensing, the pharmaceutical industry has not consolidated its potentially conflicting IPRs to assist companies like CIPLA (although the voluntary license(s) to Aspen offer some hope that this will happen). The spectre of dealing with multiple IP owners in those countries that do recognize pharmaceutical product patents (see Table 1) is a difficult task for any governmental agency wishing to procure FDCs. With regard to Trizivir®, GlaxoSmithKline has the "dominating" patent position. Voluntary license IP transaction costs to access this FDC in the countries listed in Table 1 may be daunting, although this in part depends on the terms of the license(s).

Create new business/R&D models

There is certainly ample precedent for the ownership of intellectual property generated by collective business/R&D models such as research consortia to develop new FDCs that include universities as well as operating companies. These collective organizations are best suited to dealing with ambitious scientific plans that are too large in scope to be carried out by any individual organization. IPRs can become the common property of all the members involved in the project. Alternatively, ownership of the intellectual property can be retained by the consortium which then licensed it back to the members on a variety of schedules. The SNP Consortium was an important undertaking that testifies to the success of this R&D strategy[15]. The mission of the SNP Consortium was to create a high-quality, dense, genome-wide single nucleotide polymorphism (SNP) map that would be available to the public. The SEMATECH consortium, for example, was instrumental in recapturing the semiconductor market from the Japanese[16].

Manage the risk of poor FDC access by compulsory licensing

One way to have use of the potential for FDCs is to make full use of compulsory licensing provisions in the world trading system (i.e., TRIPS) frameworks. Compulsory licenses can be used to force availability of an FDC whose components are owned by different entities. Compulsory licenses can be issued for a variety of reasons, including use by the government. [i] Under compulsory licensing, a national authority gives a local producer the right to produce a patented product without explicit permission from the patent holder. The United States and Canada have much experience with compulsory licensing[17]. In Canada, between 1969 and 1992, there were 1,030 applications to import or manufacture medicines under such licenses, of which 613 licenses were granted[18]. European countries have fairly broad authority to issue compulsory licenses on public interest grounds. Threats of compulsory licensing influence the issuance of voluntary licenses[19]. Many developing countries have laws allowing for compulsory licensing but, aside from the aggressive threats and use of this remedy by Brazil (see http://www.cptech.org/ip/health/c/brazil), most developing countries still have little experience with compulsory licensing but this may change quickly. In October 2003, the South African Competition Commission ruled that the government should override patents to allow lower priced medicines and in particular fixed-dose combinations[ii]. In November 2003, Canada proposed to amend its Patent Act in order to add a new section authorizing third party use of patented inventions to address public health

[i] Globalization and Access to Drugs, Health, Economics and Drugs, DAP No. 7, World Health Organization, DAP 98.9, Geneva , Switzerland.

[ii] Moreover, in the same month, the Clinton Foundation announced that they would be able to broker deals for generic AIDS drugs in some developing countries at dramatically reduced prices – the new price of $0.36 per day nearly halves the lowest price to date. The generic companies involved in this agreement (Ranbaxy Laboratories Ltd., Cipla Ltd. and Matrix Laboratories Ltd., all of India, and the South African company Aspen Pharmacare Holdings Ltd.) could easily produce fixed-dose combinations. As noted above in Table 1, unauthorized production, or use or sale of certain FDCs in many countries in Africa would in principle be blocked by existing IP rights.

problems afflicting developing and least-developed. The new section in question will allow for the issuance of royalty-bearing compulsory licences to Canadian firms, typically generic drug companies, authorizing them to manufacture in Canada specific patented pharmaceutical products for the sole purpose of exporting them to least-developed and developing countries that are unable to produce domestically the needed pharmaceuticals.

Create patent pools

Another way to disentangle multiple ownership issues of FDC would be to encourage patent pooling[20]. A "patent pool" is an agreement between one or more patent owners who agree to license one or more of the patents to one or more third parties. Patent pools have played an important role in shaping the industry and the law in the United States[xx]. The U.S. government considers that a patent pool is procompetitive (and therefore legally acceptable on first principles) when the pool integrates complementary technologies, reduces transaction costs, clears patent "blocking" positions, avoids costly litigation and promotes the dissemination of technology[xx]. These would seem to be just those goals that would allow wider use of FDCs[i]. Patent pools currently in existence primarily involve industry standards in telecommunications and computer technology (i.e., MPEG-2 compression technology standards; DVD-Video and DVD-ROM standard specifications). As long as the blocking patent/technology could be reasonably defined, and the terms of the patent pool were fair, a patent pool including biotechnology/FDC patents is possible in principle. It is worth further study into these arrangements to see if they can improve access to FDCs (indeed to drugs in poorer countries generally).

Back to the Future: TRIPS, Public Health, Access to Medicines

The World Trade Organization meetings in Doha, Quatar[21] confirmed what was clear to many, that TRIPs allows compulsory licensing to provide patented medicines, including FDCs, to low income countries[22]. Therefore, one short-term way out of the multiple ownership problem exemplified by "Triomune" would be, under TRIPS imprimateur, forcing availability of FDCs when IPR issues become too complex. Compulsory licensing is only obviously useful for that

[i] Features common to most US patent pools include: 1. A technology standard that is definite and well defined; 2. An evaluator/independent expert to determine which patents are essential to the implementation of the standard, thereby defining a group of essential patent holders; 3. A license drafted and approved by the essential patent holders that allows the technology to be licensed on a reasonable and nondiscriminatory basis; 4. A patent pool administrator appointed by the essential patent holders to handle administrative tasks such as signing up licensees, collecting royalties from the licensees, and distributing the royalties to the essential patent holders; and, 5. The essential patent holders retaining the right to license the patents outside of the patent pool. Patent pools that conform to the above criteria should be approved and promoted by the government, industry, and the public, as they provide a win-win situation for all involved. If one of the above factors is not included in the patent pool, it does not necessarily mean that the patent pool is anticompetitive or in violation of the antitrust laws. It merely means that the patent pool will need to be more carefully scrutinized.

group of "rich" poor countries that have both domestic expertise and domestic pharmaceutical manufacturing capacity (Brazil, India, South Africa). However, there is nothing in the TRIPs agreement to prevent a country without significant local manufacturing capacity from importing the or its ingredients from a country where no patent protection exists on that drug . Until recently, it was not settled if TRIPs will be interpreted to cover the same situation if the drug or ingredient was under a valid patent in the exporting country[i]. It has, however, become clear since the August 2003 WTO meeting in Cancun, Mexico that TRIPS compulsory license provisions will be interpreted broadly enough to cover the situation where a country lacking domestic production capacity can import a drug from a producer in a third country. The Cancun agreement does not limit the scope of diseases for compulsory licensing, and it also does not require high standards such as epidemics or emergencies. Routine public health problems can be addressed. New proposed amendments to domestic Canadian law (Section 4) make export of patented medicines a possibility for Canadian generic drug manufacturers.

Those middle and lower income countries capable of producing FDCs (Brazil, India, Eastern Europe, probably Thailand, South Africa, Egypt, Jordan and a few others) are required by TRIPS to ensure full product patent protection by 2005. Thus, countries like India must provide patent protection for FDC components and can no longer "design around" method patents. Thus is likely to fundamentally change the nature of the pharmaceutical industries in those countries that have previously relied on weak domestic patent protection to make cheap copies of important drugs that are patented elsewhere. Now, these medicines will have to be patented in-country. There are, at least, three consequences of the post-2005 IP world for FDC manufacture, use and sale:

a) Voluntary licensing and the threat of, if not actual use of, compulsory licensing will become more important;

b) Prices of patented FDCs in these "post-2005" countries are likely to remain high or increase, as pharmaceutical companies continue to try and recover their sunk costs of R&D;

c) Combinations of off-patent drugs or combinations containing at least one off-patent drug will become of interest;

d) More creative ways to incentivize development of new FDCs and provide R&D funding (open sourcing, R&D consortia and so on) without exacerbating IP and market failures will be needed.

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[i] This was true notwithstanding the 14 November 2001 Doha Declaration on TRIPS and Public Health, which said: "We agree that the TRIPS Agreement does not and should not prevent members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health and, in particular, to promote access to medicines for all." The Doha Declaration also said: " Each member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted."

Recommendations

Make IP information more freely available

- Make available, at minimal or no cost to all users, a readily searchable database of US, European, and international (PCT) patents augmented by advisory and educational services so that end users can decide upon appropriate IP management tactics, such as whether to invent around or to negotiate with a patent owner.

Integrate IP/legal issues regarding FDCs of both HIV and TB

- The epidemics of HIV/AIDS and tuberculosis have converged in much of the world. To combat the seemingly inexorable march of antimicrobial resistance, new anti-TB FDCs as well as new ARVs are needed, with an integrated approach to treating both diseases. An integrated approach, involving collective R&D and IP ownership (See Section 5), that can manage R&D and the resulting IP for both TB and HIV would complement this;
- To assist in this, there already exist dedicated groups of IP specialists who provide advice on IPR "access" issues to NGOs, developing countries. Specialists in agricultural biotechnology have developed interesting views on this topic[23];
- Contractually or legislatively require non-exclusive licenses for critically needed IP such as FDC components;
- Create voluntary or compulsory patent pools;
- Create an FDC IP clearinghouse to reduce costs of transacting for IP rights, stimulate private sector incentives, education in practical policy/legal IP issues, conduct objective "due diligence", coordinate IP policies. Again, we can look to agricultural biotechnology for models[24].

Incentivize private sector FDC development

Previously suggested private sector incentives might be modified for FDCs to include:

1) The development of federal consortia to expedite and partially fund the development of a new selected FDCs, thereby reducing costs of development to a given pharmaceutical company;

2) "Wild Card Exclusivity" where the patent life of an agent, such as a lipid lowering agent, would be extended for a short time, if a valuable FDC were developed;

3) A "Modified Wild Card Exclusivity" where a short-term patent extension would be given to another drug in the same class (such as an anti-malarial) as a newer FDC;

4) Possible tax credits for the development of antimicrobials;

5) The adjustment of business loan rates for companies pursuing FDCs.

More controversial suggestions might include requiring regulatory agencies (i.e., the FDA) to make sure that FDCs are created as a vehicle for certain anti-infective agents or to treat certain diseases. Since it is always in the best long-term business interests of the private sector to extend their market share, this can be accomplished by combining a new drug with an off-patent generic into an FDC, as has been done with Malarone®[25]. For less developed countries, mechanisms of price differentiation[26] should be developed so that the private sector will get to extend market share and recoup R&D expenses (which are likely to be small for old drug combinations) in the developed countries, and the less developed nations will receive a low-cost FDC drug.

Even more radical proposals would include new forms of public support for FDC R&D and new types of collaborative partnerships, fueled by public funds. With regard to FDCs, one can imagine a consortium of private and public actors creating a clearinghouse for creating FDC drugs whose components are from different owners. The organization will sponsor clinical trials and/or provide quality assurance/quality control expertise and/or contract out manufacturing capacity. Initial support might come from pharmaceutical companies and international donors or NGOs. The respective governments would create tax incentives for the pharmaceutical companies. Some portion of the profits realized from IP licensing fees and drug sales would be placed into a global fund to be used to provide grants to developing countries to improve efforts to combat antimicrobial resistance.

Conclusions

The "anticommons" problem for FDCs is one of ACCESS and this implicates other factors such as R&D funding mechanisms and global IP rules. Multidisciplinary approaches to the problem are required. The perceptions of the different IPR stakeholders have lead to the evolution of different kinds of transactions. For developing countries, IP- resource poor inventors, NGOs, and patients, creative ways are needed to reduce IPR transaction costs with regard to fixed-dose combination drugs.

References

1 Love,J. *Paying for Healthcare R&D: Carrots and Sticks , h*ttp://www.cptech.org/ip/health/rnd/index.html) accessed 10 October 2003.

2 Hardin, G. 1968 *The Tragedy of the Commons* Science, 162:1243-1248.

3 Heller, MA. & Eisenberg, RS. 1998 *Can Patents Deter Innovation? The Anticommons in Biomedical Research* Science, 280: 698-701

4 Ye, X. Al-Babili, S. Klöti, A. Zhang, J. Lucca, P. Beyer, P. Potrykus, 2000, I, *Engineering the provitamin A (ß-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm* Science, 287:303-305.

5 Love, J. *A 3-drug fixed-dose ARV combination for USD 250?* e-drug, May 9, 2001, available at pharm-policy@lists.essential.org

6 Attaran, A. and Gillespie-White, L. 2001 Do patents for antiretroviral drugs constrain access to AIDS treatment in Africa? J. Am. Med. Assn., 286:1886-92.

7 UNAIDS 2000 Report on the global HIV/AIDS epidemic (http://www.unaids.org/epidemic_update/report/index.html#table) accessed 11 November 2002.

8 Blackwell, JM and Melville, SE. 1999 *Status of protozoan genome analysis: trypanosomatids* Parasitology, 118 (Suppl): S11-4.

9 Degrave, WM. Melville, S. Ivens, A. Aslett, M. 2001 *Parasite genome initiatives* Int J Parasitol. 31:532-6.

10 Gardner, MJ. et al. 2002 Genome sequence of the human malaria parasite Plasmodium falciparum,Nature, 419:498-511.

11 Holt, RA. et al. 2002 The genome sequence of the malaria mosquito Anopheles gambiae Science, 298:129-49.

12 Butler, D. *Drive for patent-free innovation gathers pace* 10 July 2003, 118 Nature vol. 424 (http://www.nature.com/nature).

13 Kaplan, WA. and Krimsky, S. 2001 Patentability of Biotechnology Inventions Under The PTO Utility Guidelines: Still Uncertain After All These Years? J. Biolaw & Business Supplement, 2001: 34-48.

14 Madey v. Duke University, Fed. Cir. 2001 (Research exception to patent infringement liability does not apply to research performed in universities) (http//www.ll.georgetown.edu/federal/judicial/fed/opinions/01opinions/01-1567.html) accessed 5 October 2001. This case is being appealed to the US Supreme Court.

15 SNP consortium website, *Single Nucleotide Polymorphisms for Biomedical Research* (http://snp.cshl.org) accessed 4 October 2003.

16 SEMATECH website (http://www.sematech.org) accessed 4 September 2003.

17 *Consumer Project on Technology: Compulsory Licensing* (http://www.cptech.org/ip/health/cl/cptech) accessed 6 October 2003.

18 Reichman, JH. and Hasenzahl, C. 2002 *Non-voluntary Licensing of Patented Inventions: The Canadian Experience* UNCTAD/ICTSD Capacity Building Project on Intellectual Property Rights and Sustainable Development.

19 Blood Screening HIV Probe License Agreement Between Chiron Corporation F. Hoffmann-La Roche Ltd. and Roche Molecular Systems, Inc. Article 5 (http://lists.essential.org/pipermail/ip-health/2002-February/002709.html).

20 Clark, J. Piccolo, J. Stanton, B. Tyson, K. 2000 *Patent Pools: A Solution to the Problem of access in Biotechnology Patents?* (http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf) U.S. Patent and Trademark Office, Accessed October 10, 2003.

21 The Fourth Ministerial Conference, Doha, Qatar Meeting, World Trade Organization, November 2001 (http://www.wto.org/english/thewto_e/minist_e/min01_e/min01_e.htm) accessed 3 September 2002.

22 The dispute over setting aside patents that limit cheap drug supplies became the key issue. Particularly in light of Canada's overriding the Bayer patent on ciprofloxacin with regard to the anthrax bioterrorism scare in late 2001 and the U.S. refusing to override the patent, certain developing countries were asking if there was a double standard at work. In the United States, federal statutes under the U.S Clean Air Act and the Atomic Energy Act, mandate compulsory licensing under certain circumstances.

23 CAMBIA (http://www.cambia.org.au/main/ipwhy_inv.htm) access 12 November 2003.

24 February 2001 *IP Clearinghouse Mechanisms for Agriculture* (http://www.farmfoundation.org/pubs2/berkeleyagbioworkshop.pdf) accessed 12 November 2003.

25 Looasreesuwon, S. Chuylay, JD. Canfield, CH. Hutchinson, DB. 1999 *Malarone® (atovaquone and proguanil (HCL): a review of its clinical development for treatment of malaria* Am. J. Trop. Med. Hyg. 60: 533-54.

26 *Report of the Workshop on Differential Pricing & Financing of Essential Drugs* April 2001, Hosbjor, Norway, WHO/WTO Secretariat Workshop, Høbsjør, Norway, (http://www.who.int/medicines/docs/par/equitable_pricing.doc) Background papers to this conference (http://www.wto.org/english/tratop_e/trips_e/wto_background_e.doc) Accesssed 15 November 2001.