
EXECUTIVE SUMMARY

The Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH) is being asked by the World Health Assembly (WHA) to devise workable solutions to deal with the high disease burden in the developing world.

There is no single formula for success. The vital importance of public health, the essential need for biomedical innovation, the enormous costs of research and development, and the right to intellectual property protections are all key variables that will impact how effectively and efficiently available therapies as well as improved future therapies can be delivered to patients in developing countries.

Understanding and discussing these complex, global issues are important first steps toward finding solutions. As a service to all who seek to grasp their complexities, the CIPRH requested engagement of the biomedical industry around these issues. In this light, we offer a completely new and updated CD-ROM on the research and development process (R&D Guide) and 10 articles in four major areas:

- Addressing the Landscape
- Value of Innovation
- Intellectual Property Rights
- Research and Development Incentive Proposals

ADDRESSING THE LANDSCAPE

Three articles (#1 through #3) offer a foundation for understanding the global health care environment.

Article 1: Addressing the Burden of Disease in the Developing World: Root Causes, Perceptions and Some Key Elements of a Solution

Failure to adequately treat diseases of the developing world (DDW) results from multiple factors. While effective therapeutics—typically off-patent products—exist today for almost all DDW, less than a third of the people afflicted receive effective treatment. Most of the DDW either have effective therapies that are not reaching patients in need and/or there are multiple therapies in active R&D. However, the truly neglected diseases from an R&D perspective are:

- 1) Human African Trypanosomiasis
- 2) Chagas Disease
- 3) Dengue Fever

There are many reasons for poor access and weak pipelines for new therapeutics in the “truly neglected” diseases: inadequate medical infrastructures; R&D challenges that keep new therapies from being adequately studied in patients in the developing world where the diseases exist; developing world markets that lack the means to provide adequate incentives; and insufficiencies in both political will and sustained funding.

The process is also financially risky, because due to the limits of our knowledge of disease processes, researchers never know if their candidate drug will pass each successive R&D stage. One other way to determine the true R&D cost is to compare the number of new product launches in the late 1990s (246 products) with the \$230 billion US spent on all R&D by the top 25 biopharmaceutical companies during that same time interval. The result: \$900 million US per drug. If the basic science of a disease is well understood, R&D costs for a drug treating that disease can be much lower (such as those in the ~\$200 million US range), but when the disease is not well understood, costs are significantly higher.

What's more, it is becoming more difficult to bring new drugs to market: In the late 1990s, one of five new drug candidates entering development won regulatory approval; in 2004, the success ratio has plummeted to one approval for every 11 candidates. Studies using these different attrition rates vary widely in their cost estimates. But what is clear is that the cost of R&D is tremendous and growing as attrition rates increase. Therefore, it is critical to support industry innovation in this environment to make sure there is sustained R&D investment targeted to reversing the burden of DDW.

VALUE OF INNOVATION

Three articles (#4 through #6) illustrate how patient health benefits from the innovation process and the importance of the current intellectual property protection system.

Article 4: Pharmaco-evolution: The Advantages of Incremental Innovation

Technology advances in the healthcare industry, as with most major fields of study, tend to occur one step at a time. While some critics charge that there are too many similar drugs, the truth is that drugs based on incremental improvements almost always bring significant advances in safety, efficacy, and/or dosing refinements that improve patient compliance with proper use. The result: reduced hospital stays, fewer physician visits and increased worker (patient) productivity. Moreover, because people respond differently to different versions of a particular class of medicine in ways that are not predictable—and virtually no medicine is effective in all patients—multiple versions benefit more people than a single product. Newer versions also assure supply of needed medications if, for safety reasons, the lead drug in a certain class is removed from the market or in the case of anti-infectives, resistance to the therapy develops. And expanding drugs within a class spark price competition, with new drugs entering existing classes typically priced at a discount from the first-in-class product. Drugs resulting from incremental innovation even help fund research and development in higher risk diseases with few effective therapies, such that disincentivizing incremental innovation would ultimately inhibit biomedical companies from creating breakthrough medications.

Article 5: Patents are Not Trivial: The Case for Innovation in Research and Development within the Biomedical Industry

Opponents of Intellectual Property Rights (IPR) claim that biomedical research companies care more about extending the commercial life of current products than they do about benefiting patients with true medical advances. However:

- Patent law lays down exacting requirements for approval. A patented drug must be proven to have a chemical structure sufficiently different from others in its class, or it must provide new or unexpected therapeutic effects. Patent holders must prove that their inventions are both novel and “non-obvious,” which means a competitor skilled in the art could not derive a similar product from prior efforts. Patented innovations may also include manufacturing improvements or modifications or changes in the drug's ingredients that have a defined therapeutic and/or compliance benefit.

- A single drug may warrant multiple patents if developers overcame significant hurdles that might have prevented its manufacture or safe or effective use. In the long journey from laboratory to patient, biomedical companies must prove that the new medicine is stable, that medicinal content doesn't degrade in the human system, that it can be safely stored on the shelf, and that it can be uniformly manufactured in acceptable quantities.
- At the same time, a patent covering an improvement to an existing patented product does not prohibit generic competition against this existing or previous product once the patents protecting the original product have expired. For example, if a company develops a once-a-day dose for the original product and patents the new formulation, generic forms of the original formulation can still be marketed so long as the patent on that drug has expired.

With this system of protections, products must prove that they are legitimately innovative, yet allow generic competitors to enter the market once patents expire.

Article 6: The Economics of Follow-on Drug Research and Development

There are potentially damaging misconceptions about “follow-on” or “me-too” drugs—new drug entities with chemical structures similar to medicines already on the market. Some view follow-on drugs as wasteful, a perception that short-changes the drugs' potential benefits to large patient populations. In fact, evidence reveals that these drugs are needed therapeutic options offering improved clinical benefit and price competition. Over the past 30 years, for instance, market exclusivity for breakthrough drugs—the period in which there is no other competitor on the market and the company has the best opportunity to recoup R&D costs—has fallen dramatically: from an average of 10.2 years in the 1970s to only 1.2 years in the 1990s. The vast majority of follow-on drugs created in the last decade were already in clinical development before the class breakthrough drug was approved, suggesting that new drug development tends to be characterized by a race between candidates, rather than by *post hoc* imitation. Thus, the distinctions between breakthrough and so-called “me-too” drugs are not meaningful.

INTELLECTUAL PROPERTY RIGHTS

Two articles (# 7 and #8) help unravel the often confusing and controversial issues surrounding intellectual property rights, with specific focus on the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement.

Article 7: A Global Framework for Intellectual Property Rights: Trade Related Aspects of Intellectual Property Rights (TRIPS) Agreement

Many consumer activists and representatives of international organizations allege that provisions within national patent laws and bilateral free trade agreements impose so-called “TRIPS-Plus” obligations that extend beyond those expressly outlined in the TRIPS agreement. In fact, the TRIPS agreement provides a minimum standard of intellectual property protection—a general framework to which countries can adhere, allowing significant flexibility in meeting IPR protection requirements. National governments are within their sovereign rights to enhance intellectual property protections within this framework.

Characterizing provisions in national laws or bilateral free trade agreements as “TRIPS-Plus” is misleading and inaccurate, because these provisions are fully compliant within the framework established by TRIPS.

Article 8: Impact of India's Adoption of TRIPS: Access to Medicines in the Developing World

Under the TRIPS agreement, India is now obligated to extend product patent protection to biomedical products. This has prompted concerns about India's ability to supply generic products under patent protection to developing countries. But many of these concerns are spawned by assumptions based on commonly held—if dubious—beliefs and fears regarding the impact of TRIPS guidelines on India, and about drug patents and intellectual property in general. Five common misconceptions can be easily clarified by studying available evidence:

1. Myth: Access to medicines by the developing world depends on generic production of currently patented products.

Reality: As defined by the WHO, 95% of essential medicines worldwide are off-patent. Of those drugs that are patented, few of those patents extend to the developing world. In fact, in the developing world, of all essential medicines on the WHO list, only 1.4% are patented.

2. Myth: India is the main exporter of generic medicines worldwide and is the world's supplier of cheap AIDS drugs.

Reality: India's antiretrovirals account for only one-third of drugs administered to African patients by Medecins Sans Frontieres, or 6300 patients. A much larger number of patients with HIV in Africa are treated with the the original patent holders drugs at even lower cost.

3. Myth: India's TRIPS compliant law will prevent production and export of generic medicines.

Reality: 97% of medicines on the Indian market are not patented. Further, an amendment to the patent law allows Indian producers to manufacture generic drugs for export to countries that have insufficient internal production capacity.

4. Myth: Compulsory licenses create “burdensome” conditions for importing needed drugs.

Reality: The Doha Declaration sets a clear international mechanism for allowing compulsory licenses that are not burdensome in any way.

5. Myth: Importing countries lacking patents on needed products cannot use World Trade Organization (WTO) mechanisms.

Reality: Countries do not need patents to import needed products.

Accordingly, evidence shows that TRIPS reforms will not jeopardize production and export of existing generics from India to the developing world.

RESEARCH AND DEVELOPMENT INCENTIVE PROPOSALS

Two articles (#9 and #10) outline issues concerning incentives for R&D and their impact on treating diseases that impact the poorest populations.

Article 9: Industry Proposals to Increase Research & Development for “Neglected Diseases”

With international public health authorities advocating for increased disease management programs and new therapeutic tools, a number of incentives or initiatives could significantly improve the R&D environment for neglected diseases. As a crucial first step, political leaders must set a public health agenda to establish targeted policies. With these in place, biomedical companies R&D can help address the need for improved therapies through a series of initiatives:

- **Product Development Public Private Partnerships (PPPs):** These independent organizations can attract public and private funding to finance applied research and development for neglected diseases.

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- **Advanced Purchasing Commitments (APC):** APCs compensate for inadequate market size by specifying price and volume requirements for the development of a certain drug.
 - **Global Fund for Tropical Diseases:** Such a fund makes necessary finances available to countries and communities, so they can purchase new and existing drugs for neglected diseases.
 - **Tropical Diseases Drug Act:** Similar to the Orphan Drug Act, this legislative package would provide incentives to increase R&D for neglected diseases. Key features would include a combination of “push/pull” mechanisms, such as R&D tax credits, grants, reduced regulatory fees, and fast track regulatory approval.

Article 10: Patents and R&D Incentives: Comments on the Hubbard and Love Trade Framework for Financing Pharmaceutical R&D

Hubbard and Love have stated that without today’s patent system, current levels of pharmaceutical R&D can be maintained along with lower costs for discovering medicines. These proposals, however, have largely been rejected, both by academics and governments, because they fail to address many of the realities of therapeutic research and development. Hubbard and Love suggest two systems:

- In one, prizes would be awarded after innovation is complete with resulting intellectual property quickly entering the public domain. This prize system, however, does not provide enough incentive for researchers to bear the enormous risks associated with new drug discovery and development. The very high costs of R&D are outlined in article #3.
- The second system would finance R&D through a tax-like mechanism, with global R&D budgets disbursing funds as determined by a treaty. Yet this proposal is plagued with problems of misaligned incentives and asymmetric information. For example, setting a flat R&D tax will likely significantly increase some developing nations’ overall R&D spending, so chances are high they will not sign such a treaty; and R&D organizations are likely to have better information about scientific opportunities, whereas governments and agencies may pursue funding for reasons that have little to do with treating disease.

In fact, multiple examples demonstrate how both of these proposed systems produce inefficient outcomes, both practically and theoretically. Accordingly, the proposed compulsory termination of the patent system, given the strong role that patents have played in encouraging drug R&D and innovation, would have a decidedly negative impact on efforts to bring more effective disease treatments to poor populations around the world.