FOLLOW-ON INNOVATION AND INTELLECTUAL PROPERTY

This working paper has been prepared by the Secretariat of the World Intellectual Property Organization (WIPO) as part of an ongoing process of technical input to the World Health Organization Commission on Intellectual Property Innovation and Public Health (CIPIH) as its commissioners work to "review the interfaces and linkages between intellectual property rights, innovation and public health . . . and examine in depth how to stimulate the creation of new medicines and other products for diseases that mainly affect developing countries".[1] It is also a response to the December 2004 invitation by the CIPIH for comments on the topic of "me too" or "follow-on" innovation.[2] The issues addressed are guided by comments made to the CIPIH and concerns raised in other policy forums relating to intellectual property protection in health technologies.

In that regard, this paper aims to contribute examples and information that prompt further discussion and consideration on three broad topics pertaining to follow-on innovation: (1) the role of current intellectual property tools (patents in this instance) in collaborations on adaptive technologies to address neglected disease problems; (2) the nature and value of advances and technologies other than therapeutic substances that may appear small or incremental; and (3) distinctions between assessments of patentability of an invention, and other regulatory assessments, namely: evaluation of a product's therapeutic contribution and concerning anti-competitive behavior. As a working paper, this document is provided to contribute to ongoing discussion, and is open to further development.

I. Clarification of Issues and Terms

The issues associated with follow-on drugs have given rise to considerable debate and analysis. They also provide a valuable platform from which to address a number of the broad issues confronting the CIPIH: for instance in considering what forms of innovation are required to address the neglected disease burden, what policy and legal mechanisms and collaborative structures would promote these forms of innovation, and how these mechanisms and structures can be used most effectively to yield desired public health outcomes. The three broader topics mentioned above are addressed in Sections II – IV respectively of this paper.

Section II of the paper "Patents and Partnerships to Develop Health Products" explores the role of present IP tools (patents) in promoting efforts to address the public health needs of the poor. This topic is addressed with two examples. The first describes secondary uses and the role patents covering secondary uses play in forming partnerships useful in achieving public health objectives. The second example illustrates the role patents can play in the implementation of global partnerships in the context of antibiotic health technology.

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[1] January 25, 2004 Note by the Director General of the World Health Organization establishing the CIPIH (EB113/INF.doc/1) paragraph 3.

[2] Two papers were circulated to initiate discussion, one authored by Joseph DiMai and Cherie Paquette and the other authored by Aidan Hollis. Both papers focus on therapeutic drug produts (chemical entities) and discuss "me-too" or "follow-on" drug products in terms of their therapeutic characteristics.

Section III "Follow-on Innovation in Diagnostics, Dosage Formulations and Mechanical Devices" explores innovations other than drugs that are useful in addressing neglected disease burdens. Examples are given of advances in diagnostic tools, material science and mechanical devices in improving health products in developing and developed countries. In debate over incentives and innovation in the public health domain, innovations are often characterized in general terms as either 'breakthrough' or 'fundamental' innovations, on the one hand, and incremental, cumulative or 'follow-on' innovation on the other. These examples revisit this broad distinction, and contribute to discussion of the relevance of fundamental and adaptive innovation in addressing neglected health needs, and the question of whether the patent system should focus on fundamental innovations, or innovations characterized as incremental, cumulative, or adaptive.

Section IV "Assessing Patentability, Product Merit and Anti Competitive Behavior" explores policy and evidentiary differences between assessment of an innovation's patentability based on grant criteria, and two distinct assessments that arise in discussions of the regulatory environment for follow-on innovation: criteria for assessing the value to society of health related products embodying an innovation; and criteria for assessing assertions of IP rights to challenge generic market entry, and the misuse of patent rights contrary to laws relating to competition. This section uses examples that illustrate the accumulation of patents on salt forms and isomers of known antimicrobial substances and on derivatives of a natural substance with anti-malarial properties.

In this paper, the term "follow-on" is used in connection with research and development innovations of all types because it encompasses technological advances; large and small, pioneering and incremental. It also captures the way one technological advance follows from prior technological advances and prior knowledge. An individual advance can be defined and discussed but each advance is also part of a larger innovation process in which one development follows from previous developments. Not all follow-on innovations are or should be patentable. Patentability criteria are expressions of policy choices made in the public interest that circumscribe which innovations will be granted patent protection.

The phrases "patentability criteria" or "grant criteria" are used interchangeably in this paper to refer to the prerequisites of patent grant known as novelty, inventive step and utility that are applied to determine which technological advances will be eligible for exclusive rights.[3] These criteria are not mere technicalities. They have been developed by policy makers to achieve important public interest objectives. One of these objectives is preventing unwarranted incursions on the public domain, including the appropriation of publicly known technology and obvious or non-inventive adaptations of it. Rigorous application of grant criteria is needed to prevent such incursions through grant of property rights to technology that is already available to the public, and to obvious applications of that technology. In addition, because the patentability criteria require comparison of defined innovations with existing technology rather than other factors, adherence to them also serves the function of preventing discrimination and decisions based on transient conditions that can change as easily as patent ownership. In applying patentability criteria, advantageous effects of the technology for which a patent is applied are also considered in comparison with those of the existing technology. The criteria do not require commercial success to be proven and they do

[3] The term "inventive step" is treated here as being interchangeable with "non-obviousness" and the term "industrial application" is treated here as being interchangeable with "utility". These criteria do not characterize advances as small or large, incremental or pioneering breakthroughs, but do establish a framework for assessing the inventive quality of an innovation or claimed invention against what is already known.

not hinge on subjective concepts of "minor" or "significant" because at the time of applying for a patent, the technology has not been converted into products or put on the market. Apart from patentability criteria, legislators may also choose to pursue public policy objectives by excluding from patentability certain subject matter such as diagnostic methods, therapeutic methods, surgical methods and things offensive to ordre public. These exclusions may be termed exceptions to patentable subject matter, and would typically be considered by a patent examiner prior to applying grant criteria to a claimed invention.

The subject of a patent is an invention, which is an abstract conception of a specific technological advance, so that patentability criteria do not apply to a new product as such: for example, one specific pharmaceutical product may also embody several patented technologies, while several different products may fall within the scope of one patent. Regulatory approval relating to safety and efficacy typically applies to a specific new drug, rather than an invention as such.

II. Patents and Partnerships to Develop Health Products

A. Secondary Use Patents and Research Collaborations on Neglected Disease

The formation of public-private partnerships has gained recognition as a mechanism that can increase and accelerate innovation and product development needed to address neglected public health problems. These partnerships marshal the strengths of the private and public sectors to increase research and development for diseases that have not drawn sufficient resources, and to draw new pharmaceutical products through the development pipeline that would not otherwise be available. Public-private partnerships such as the Medicines for Malaria Venture (MMV) are interested in supporting or engaging in drug discovery efforts. There is no one template for such arrangements, and drug development may entail partnering between public and private players even without a specific, formalized partnership. They may seek to enable fundamental breakthroughs (the identification or synthesis of a new active compound), or they may seek to adapt known technologies for neglected disease needs.

The present case study does not address the full range of issues and practical lessons that have arisen from such partnerships,[4] but considers one specific development scenario, which would entail access to a compound library to screen it for neglected disease applications. A basic step in conventional drug discovery is screening existing stores (libraries) of chemical agents for therapeutic effect on target diseases. Pursuing this approach in a sustained, broad-based manner for neglected disease applications can benefit from access to the compound libraries of pharmaceutical companies, which are not generally available to outside researchers. While many factors would affect the feasibility or desirability of such collaborations, the incentive or disincentive effects of IP policies can be separately considered in the specific context where a compound has two or more potential therapeutic applications, for different disease burdens, thus raising the implication of patents for 'secondary uses.' [5]

[4] See for example Jon F. Merz, 'Intellectual Property and Product Development Public/Private Partnerships,' a CIPIH study, and the series of studies by the Initiative on Public-Private Partnerships for Health (IPPPH), at www.ippph.org.

[5] The term 'secondary use' can itself raise definitional issues. It is not identical in meaning, for instance, to the phrase 'secondary indication.' In drug regulatory approval contexts, a secondary use for a known therapeutic

Many of the compounds (perhaps most) in the possession of pharmaceutical companies have no known use. If researchers first identify a possible therapeutic use against a neglected disease (such as malaria, schistosomiasis, sleeping sickness, or leishmaniasis) for one of these substances with no known use, some IP policies leave open the possibility of the pharmaceutical company securing patent protection for later-identified secondary uses of that same or similar compounds or class of compounds. This is only a possibility, because patentability criteria and expansions to the public domain created by disclosure of the first use will bar many patentability options for subsequent uses (for example, secondary uses that are obvious or non-inventive in the light of the first use would be excluded). However, the possibility of developing even a limited patent estate in the future relating to a commercially viable secondary use is an incentive to pharmaceutical companies, to allow access to their compound libraries for external researchers to screen for neglected disease applications, or to develop and produce a drug based on a substance newly identified as efficient against a neglected disease in partnership with a public interest entity. Alternatively, neglected disease initiatives or partnerships may identify secondary uses or adaptations after a primary use has earlier been identified; this may have implications for patenting practice, to the extent that such initiatives or partnerships elect to make use of the patent system to manage the development of new treatments.

In considering the necessary incentive structures and technology management mechanisms that would enhance research, development and dissemination of new treatments for neglected diseases, it may be helpful to consider such scenarios. As noted, some secondary uses may be assessed as being obvious or lacking an inventive step, and patents on such uses would be contrary to the core public interest considerations at the center of the patent system. But in other cases, the same public interest considerations and incentive effects may need to be considered. Here, a specific incentive issue would arise in considering how to promote external or collaborative access to company-owned chemical libraries, to promote screening for neglected disease applications. The prospects for patents on secondary uses of compounds after a first use is identified could affect the mix of incentives that would promote broader access to compound libraries the first place. More generally, where neglected disease initiatives use the patent system in structuring their activities and in inducing research and development outcomes,[6] availability of patent protection for some non-obvious secondary uses may possibly contribute to an incentive and technology management structure for research and development collaborations on neglected diseases.

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substance is usually referred to as a secondary indication. It occurs when a therapeutically active component is found to be effective in treating a condition or disease distinct from the condition or disease for which it was originally used. In the broader context of innovation, the first use of a substance or class of substances may not be therapeutic at all. Coumarin compounds, for instance, were first used as rat poison. About ten years later, Coumarin compounds were used therapeutically as blood thinners for heart patients. (http://www.emedicine.com/emerg/topic443.htm) The second use is a therapeutic one but would not be called a secondary therapeutic indication. Should this impact patentability decisions? In this, as in all secondary use situations, the scope of patent protection available for the follow-on innovations will be different than that available for the initial innovations, for the very reason that the claimed new use would be assessed for novelty and inventive step against the first known use (together with any other relevant knowledge).

[6] See the cases discussed in Merz, note 4 above.

B. Forming Global Partnerships in Health Technology: Lessons from Antibiotics

Developing additional antibiotics is important to achieving health goals of all countries, particularly as strains of infectious organisms acquire resistance to antibiotics in current use. The innovation history of Erythromycin illustrates the role incremental innovation and IP can play in developing improved antibiotics and fostering the capabilities of enterprises in developing economies to address health needs.

Erythromycin, a well-known macrolide antibiotic, was described and patented in the late 1940s and early 1950s as a class of antibiotics produced by fermentation.[7] In the years following discovery and commercialization of Erythromycin, many derivatives within the class were experimented with a view to create incrementally different chemicals with modified biological or pharmacodynamic properties.[8]

One of the successful derivatives of that follow-on research is known today as Azithromycin, a broad-spectrum antimicrobial compound. It was patented in the mid-1980's by Gabrijela Kobrehel and Slobodan Fjokic, two scientists who were then living in Yugoslavia and working for Pliva Pharmaceutical, Chemical, Food and Cosmetic Industry (Pliva). [9]

The grant of patent protection in this instance enabled a small entity in a country with a transitional economy to occupy a place in the global value chain for this product. Pliva was not the only enterprise competing to make derivatives of Erythromycin fifty years ago. Pfizer completed successful experimentation on this antibiotic at about the same time as Pliva and obtained patents on compounds quite similar to those patented by Pliva's inventors.[10] Discussions between the companies occurred largely because of Pliva's patent estate.[11] Pliva licensed its patent exclusively to Pfizer for sales and marketing in major countries and Pfizer purchases the compound in bulk crude form Pliva and Pfizer marketed the drug under the name Zythromax®.[12]

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[7] U.S. Patent No. 2,653,899 (Issued September 29, 1953).

[8] There are many categories of antibiotic drugs: cephalosporins, macrolides, nitroimidazoles penicillins, quinolones sulfonamides, and tetracyclines, to name a few. Each class contains more than one variant resulting from follow-on research and incremental innovation. Penicillins for instance include Crystapen (penicillin G), Floxapen (flucloxacillin), Penbritin (ampicillin), Amoxil (amoxicillin) and Augmentin (amoxicillin + clavulanic acid. Quinolones include Negram (nalidixic acid), Cioproxin (ciprofloxacin), Tavaric (levofloxacin) Avelox (moxofloxacin), and Tarivid (ofloxacin). A question for policy makers to consider is whether development of these alternative advances is to be discouraged because they can be labeled "me-too" drugs or whether their development is to be encouraged and rewarded.

[9] Pliva's U.S. Patent 4,517,359, issued May 14, 1985. It remains in force at least until late 2005. The seventeen-year statutory term of the patent was extended, apparently in view of regulatory delays in marketing approval that occurred after the patent was granted.

[10] Compare U.S. Patent 4,474,768 assigned to Pfizer to U.S. Patent 4,517,359 assigned to Pliva.

[11] The patents were valuable assets, which helped lead to a mutually beneficial relationship between a small enterprise (Pliva), and a large enterprise in a developed country (Pfizer). The flow of economic and technical credibilities to Pliva is useful in closing the technology gap (cite).

[12] Pfizer 2004 SEC 10K for fiscal year ending Dec. 31, 2003, page 9; filed March 10, 2004.

The incremental development by Pliva and the patent estate acquired for that innovation formed the core of a development partnership between enterprises in a developed country (United States) and a country in transition (Yugoslavia).[13] Through this partnership worldwide distribution of the improved derivative was accomplished and a scientific institution received income, bolstered its scientific reputation and acquired manufacturing expertise.

In addition to ongoing commercial sale of the drug, Zythromax is today the subject of drug donation program run by The International Trachoma Initiative (ITI).[14] Established in 1998, this program tackles trachoma which the World Health Organization (WHO) identified as the worlds leading cause of preventable blindness (15 million people with trachoma, 6 million blind or at immediate risk of blindness and is prevalent in areas of poor hygiene and poverty. Pfizer provides grants and donates medicine while the Foundation contributes funding and experience in the field of treating trachoma. Agreements are made with partners in eleven countries in Africa and Asia. As a result of this program, Zithromax, the WHO-preferred treatment, has contributed to sustained reduction of the disease in Morocco, Tanzania and Vietnam. This may be a productive way forward for innovative enterprises in developing countries.[15].

III. Follow-On Innovation in Diagnostics, Drug Delivery and Mechanical Devices

Discussion of health care research and development can emphasize the need for "major breakthroughs" or "pioneering advances" such as new classes of chemicals that open entirely new therapeutic options. Some incremental or adaptive innovations, such as new dosage forms of existing products, alternative salt forms or isomers of known substances, or minor changes to existing medical devices, can be characterized as "minor" or "small" by contrast with pioneering innovation. The question arises as to whether such developments are appropriate subject matter for the patent system, and whether the patent system has a role in inducing investment in research and development for such innovations. Concern is expressed that patents granted on small innovations misdirect investments towards minor changes that do not contribute to new public health outcomes, and only serve to form thickets that discourage further innovation and impede legitimate generic entry to the market. At the same time, useful and valuable innovation is far more diverse in nature than major breakthroughs. Advances in science and technology most frequently occur in small steps referred to here as

[13] In all countries, whether they are countries with economies in transition, developing countries or developed countries, the business model for successful innovation in the health field may often be based on incremental innovations. Familiar IP tools (patents, trade secrets and trademarks) and strategies support that business model. This means that from the viewpoint of improving public health in developing countries, incremental or adaptive innovations generated in developing countries merit IP protection as much as they do when they originate in developed countries. Business models focused on adaptive follow-on innovation are practical for and accessible to enterprises in developing countries. Recognizing and capturing the value in adaptive innovation through intellectual property systems may thus assist developing countries address their own health priorities.

[14] It is a public-private partnership between Pfizer and the Edna McConnell Clark Foundation that incorporates a multi-faceted public health strategy (SAFE – surgery, antibiotics, face washing and environmental control).

[15] The Report of the Millennium Development Project Task Force on Science, Technology and Innovations is supportive of the formation of such partnerships in an increasingly globalized economy as a way forward for development. See, 2005 Report entitled "Innovation: Applying Knowledge in Development" pages 128-129 and 134-136.

"follow-on" or "incremental" or "adaptive" innovations. Such advances may also warrant appropriate recognition[16] accorded by intellectual property protection and the investment incentives such protection provides for both the original research and its development into viable, clinically proven products.[17] Since necessary public health innovation may range between the poles of basic research outcomes and precise adaptation of known technologies to address neglected health needs, the task for the policymaker is to consider how to promote appropriate forms of research and development while avoiding negative or perverse incentives. Meeting neglected disease burdens may entail many other forms of innovation other than breakthroughs in biochemistry, and may entail developing forms of known technologies that are more appropriate for distribution, storage and clinical administration to neglected patient needs.

Pioneering breakthroughs resulting from basic research are, of course, important and should be pursued. But as the examples in this section suggest, health benefits can often result from follow-on innovations in technologies other than therapeutic substances. Transforming basic, breakthrough or pioneering innovations into practical products normally requires further development-focused innovation that is follow-on, adaptive and incremental. While product development and basic research are closely reliant on each other they are also distinct from each other, particularly in the context of innovations needed to make available products with an impact on health.[18] It may be easier for researchers in resource-poor settings to realize follow-on innovations than pioneering large breakthroughs, and this may provide a more rapid and economic path to positive public health outcomes to complement ongoing basic research. Moreover, actual cases of adaptive innovation can illustrate that some necessary adaptations of existing technology can be difficult and time-consuming.

A. Diagnostic Tools

Diagnostic technologies provide examples where breakthroughs have occurred but follow-on, incremental or adaptive innovations are needed to achieve use in poor regions. Most cervical cancers, for instance, are preventable if detected and treated early. Digene Corporation of Bethesda, Maryland (Digene) is one of the companies responsible for recent technological breakthroughs in cervical cancer screening technology. Products embodying those breakthroughs have been given marketing approval and have contributed to reduced mortality in Western countries.[19] Worldwide, however, cervical cancer remains a leading

[16] Recognition by grant of a patent does not by itself constitute an economic reward. Economic reward flows from products placed in use that embody the patented innovation. This is particularly important in pharmaceutical technologies because patentability is determined long before any product exists from which one could calculate economic value with certainty.

[17] Bale, Harvey and Azais, Boris "Pharmaceutical Innovation is Evolutionary and Incentive – Driven", Id. At 788 – 789; Attaran, Amir "Patents do not Strangle Innovation, but Their Quality Must be Improved", Id at 788. Recognition by grant of a patent is not an economic reward. Economic reward flow only through products placed in use.

[18] They are distinct from each other in several ways. Research innovations often precede product development innovations by many years in the health field. The investments required to transform a research innovation into a useful form through product development innovations exceed investments in research by a large ratio. In addition, product development innovation often requires different expertise and skills that research innovation.

[19] See press release and article at: http://www.path.org/resources/press-release.php?id=3 and http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/02-18-2004/0002111586&EDATE=

cause of cancer deaths among women in some poorer regions. One of the causes of this imbalance is that detection technology is not available in a form that is appropriate for the social and infrastructure context of poor regions where doctors and trained medical staff are not readily accessible.

Work to diminish the imbalance in availability of cervical cancer diagnostic tools was initiated recently by a partnership between Digene and the Program for Appropriate Technologies in Health (PATH). That work would build on the existing basic technology now used in developed countries with strong medical infrastructure. This joint effort could yield low-cost, easy-to-use, culturally acceptable tests for cervical cancer screening, suitable for regions with minimal resources and medical infrastructure. The task is not trivial: research and development may take at least five years. Changes required to adapt existing technology may be incremental, but that is not cause for criticism or assuming it is of low value to society. Adapting the existing diagnostic technology to developing country conditions could have significant benefits to women's health in poor regions.

Digene's collaboration with PATH is too recent to provide a patent example but the possible existence of pull demand in developing countries with substantial domestic markets for creating and patenting innovations needed to adapt this technology would be understandable. These countries may contain sufficient commercial markets to make such follow-on development work attractive with the protection to investments afforded by patents.

B. New Drug Delivery Products for Existing Therapeutics

Advances in medicine result from a wide range of technologies that are not necessarily classified as new chemical entities. In the example described here, material science was the basis for a patentable new drug delivery mechanism. New drug delivery products and dosage formulations (including slow release formulations of existing products) are follow-on innovations often characterized as minor or unimportant. The active substance remains unchanged by the advance and the basic therapeutic function of the active substance also remains unchanged by the technological advance. The concern is expressed that merely creating different dosage forms of existing products may divert research resources from more important goals, and can result in minor developments that do not merit the recognition of patent protection.

Policy makers may need to consider carefully, however, whether broad value judgments about importance of such innovations can be reliably formed at the early stages of innovation when IP protection is sought. As the example described below suggests a technically minor difference can provide the promise of significant public health improvements later in time, assuming products embodying the advance come into existence.

A new drug delivery innovation is the subject of U.S patent 6,623,762 granted in 2004. That patent discloses and claims a composition and method for the controlled release of drugs or vaccines encased in soluble glass-like microspheres made of sugars. The claimed microspheres are formed from sugars suspended in liquids that do not contain water (i.e. oils, fluid silicone or perfluorocarbons). A slow, controlled dissolution of the microspheres and release of product occurs over a considerable period of time after injection. The invention is

therefor a delivery vehicle for existing substances; it does not create a new therapeutic substance or effect.[20]

Although the function of the therapeutic substance is unchanged by this advance, its potential impact on public health has been met with enthusiasm and acclaim. The patented microspheres can survive temperatures as high as 55 ˚C for months, conditions that destroy normal vaccines. Even though some vaccines may be transported as dry powder rather than in solution, they still need to be dissolved in water before injection. That dissolution step can lead to bacterial contamination. The new microspheres, however, can be injected directly into the body, potentially eliminating those problems and with them the need for preservatives found in ordinary vaccines. In addition, several different vaccines might be embedded in the microspheres making possible injection of several vaccines in a single jab. Destructive chemical reactions that would otherwise occur between different vaccines in solution are prevented by the physical separation created by the microspheres.

Articles written about this innovation emphasize its possible use as a vehicle for delivering vaccines in mass immunization campaigns. By eliminating the need for refrigeration, the technology could save up to $300 million a year in global vaccine costs, which means another ten million children could be protected.[21] Currently 50 percent of all vaccines may be wasted in part due to temperature damage. Such stable vaccine delivery system could enable children in remote areas to be reached and allow emergency response teams to store vaccines in readiness for outbreaks of disease and business travelers and the military to carry vaccines with them.

The new technology also offers the potential of slow release vaccines, which may overcome the need for boosters.[22] Typically, vaccinations require multiple injections over time in order to generate a protective memory immune response. Immunity is an adaptive or learned process in which each subsequent exposure to antigen elicits a stronger antibody response both in quantity of antibody produced and binding affinity.[23] Use of the patented invention could reduce the need for repeated injections and avoid other problems associated with vaccine forms that work well in some clinical contexts, but are poorly adapted to the realities of those regions that lack refrigeration or sufficient medical personnel.

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[20] The inventors took inspiration from plants that are able to survive hundreds of years in suspended animation through a process called anhydrobiosis. During drought conditions, their tissues produce sugars which turn into a syrup as they start to dry out, eventually forming a sort of glass which preserves them. To package an existing drug or vaccine, the inventors coat clusters of drug or vaccine molecules with a sugar spray. Then they dry them in such a way that they form tiny glassy beads called microspheres. These are suspended in a liquid containing no water, which keeps them intact until they are injected into the body. There, the sugar dissolves in the blood and the drug or vaccine is released.

[21] The Economist, Oct. 23rd 2004 at 77 – 78.

[22] Cambridge Network web site <http://www.cambridgenetwork.co.uk>. The vaccine is to be manufactured by Panacea Biotech, based in New Delhi.

[23] Childhood vaccinations for diphtheria, tetanus and pertussis, for instance requires a priming dose of vaccine at 2 months of age, a first booster injection at 4 months of age, a second booster at 6 months of age another dose at 16 – 18 months and a recommended final dose at 4 – 6 years of age. Compliance with this regimen is too frequently lacking, causing the World Health Organization to identify the compliance failures as a widespread occurrence resulting in jeopardizing mass immunization campaigns. Jodar L., Aguado T., Lloyd J. and Lambert P-H (1998) Revolutionizing Immunizations" Gen. Eng. News 18 p. 6.

C. Simple Modifications of Mechanical Devices

In addition to advances in material science illustrated in the previous example, follow-on innovations can make changes to mechanical devices so as to improve delivery of health outcomes in resource-poor regions. These innovations are not new therapeutic treatments but their potential impact can be significant, particularly in regions where health care workers are in short supply. Here again policy makers may want to consider whether the clinical impact can be reliably measured at the time IP protection is sought, whether technical criteria should be adhered to when IP protection is sought with different societal evaluations being left to a later time.

Once a vaccine or medicine is developed, it must still be administered to patients as a tablet, capsule or liquid form, or by injection. Some therapeutic substance and vaccines can not be formed into forms suitable for oral delivery, making administration by injection necessary. But the use of standard syringes and needles for injection requires expertise that is not consistently available in poor regions. In addition, unsafe injection practices can lead to unwanted infections. This is a significant problem in the developing world where unsafe injections are believed to increase the prevalence of AIDS, Hepatitis B and Hepatitis C .[24] One estimate is that 6 – 8 million cases of Hepatitis B, 2.3 – 4.7 million cases of Hepatitis C and 80,000 HIV infections occur each year as a direct result of unsafe injections.[25]

Efforts have been made to address these concerns with adaptive innovations such as the single-use, pre-filled device known as the Uniject® made be Becton Dickinson Company.[26] Other alternatives to standard syringes and needles are described in U.S. Pat. 6,102,896 and indeed, the patented variations of the conventional syringe are numerous enough to make this a very crowded field, which makes pioneering advances quite unlikely.

An additional recent incremental innovation by a small British company[27] may provide yet another alternative for addressing problems associated with conventional syringes. It is described by the inventors as a "*surprisingly simple and cheap modification*" to a standard syringe and needle.[28] The modifications are shown in the following drawing in which Figure 1A is a conventional syringe and Figures 1B and 1C illustrate the innovations relative to the conventional syringes represented in Figure 1A.

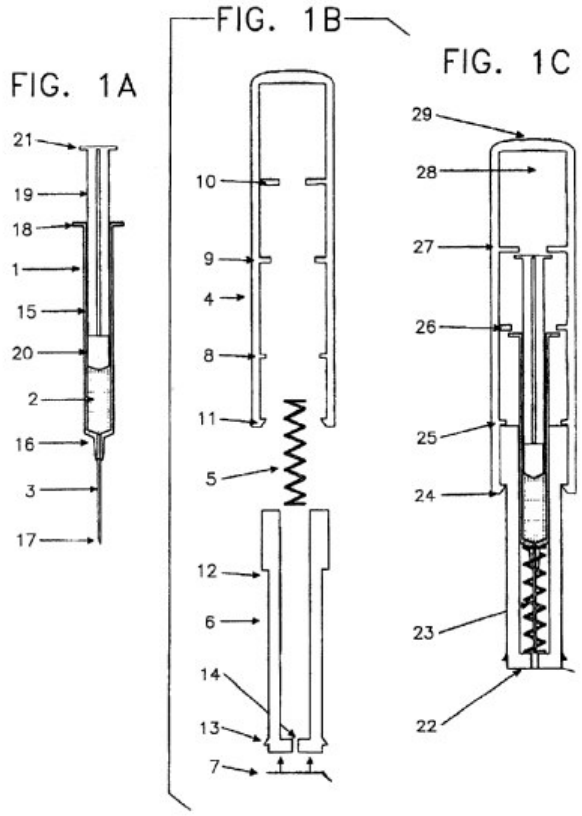
[24] (US Patent 6,808,507 col. 1, lines 22 – 32).

[25] (Bull. World Health Org. 77, 801 – 807 (1999).

[26] US Patent 6,808,507.

[27] Cambridge Biostability, Ltd.

[28] U.S. Patent 6,808,507 issued October 26, 2004. Col. 3, lines 15 – 20.

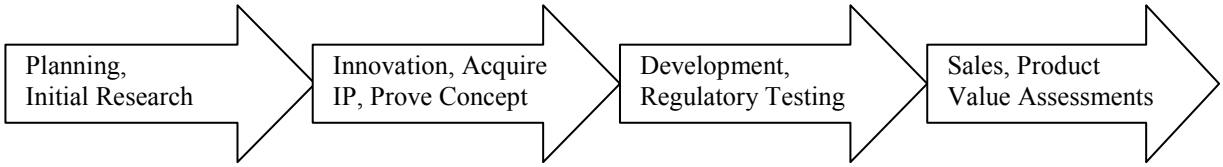


Although the physical modifications (shells 4 and 6 and spring 5 illustrated in Figures 1 B and C) that makes up this innovation are "small" according to the inventors, the possible benefits may be significant to addressing health needs in regions where health workers are in short supply. By automating injections skilled medical workers are not needed to administer injections as is required by conventional syringe and needle. By sheathing the needle and providing a structure that ensures only a single use is possible, it may reduce the proliferation of dangerous diseases through unsafe injection practices. The same company that developed microspheres for vaccines discussed above makes this innovation. The possible advantages from using this mechanical device with vaccines in dosage forms developed by the same company are apparent.

IV. Assessing Patentability, Product Merit and Anti-Competitive Behavior

Discussions of the innovation process and intellectual property implications involve a wide range of different activities that occur at different times. The discussions span initial research or early discovery activity and behavior in markets relative to proven pharmaceutical products. The different events that occur during these separate stages of innovation raise policy issues that are often quite distinct from policies embodied in patentability criteria. It is

useful to recognize that the innovation process proceeds through different phases over time and to distinguish the different policy issues implicated at different stages.[29]



The intellectual property system in a broad sense is made up of many components applicable at different times during the full research and development process. Public policies embodied in patent grant criteria are applied at the initial two stages illustrated by the arrows above. After patent grant, different public policies are used to modulate enforcement of patent rights and their impact on third parties, such as competition rules, patent interpretation rules, and jurisprudence fashioned by courts against infringers or owners of IP who wrongfully assert IP rights.

Patent offices have the focused job within this broader policy context of applying grant criteria objectively. Their primary responsibility is to grant only valid patent rights based on criteria articulated by policy makers. As noted above, the criteria for granting patents need to consider the technical relationship between defined innovations and pre-existing technology to serve the public interest in preventing incursions on the public domain that occur if property rights are granted on publicly available technology or obvious uses or adaptations of such technology. In addition, transient factors that change as readily as patent ownership are not considered patent grant criteria (apart from consideration of an applicant's entitlement to apply for and to receive a patent).

A. Assessment of Patent Grant Implicate Different Policies and Evidence than Assessment of Product Value

The two papers circulated by the CIPIH secretariat (see footnote 1) to initiate discussion of "me-too" or "follow-on" innovation focus on therapeutic drug products (chemical entities). Both papers appropriately discuss assessment of therapeutic drug products in terms of their therapeutic characteristics and describe three options for assessing them: 1) product comparisons used to create a registration hurdle, 2) product comparisons used to formulate reimbursement criteria, and 3) product analyses after market introduction of disease management programs. All three of the options appropriately require data from products that are available for testing and clinical comparison.

Assessments of product value to society can occur after the events required to transform innovations into actual products have already taken place. Assessments of innovations to determine patentability occur at the earliest stages of innovation when products are not ordinarily available. This difference has substantial policy and evidentiary implications. Clinical testing and comparison of products, for instance, are not required for patentability decisions. In fact, product data will not be available for most innovations because products embodying them do not come into existence. Patentability decisions on

[29] This point was also made in WIPO's earlier submission to the CIPIH.

drug innovations (chemical entities) are instead based on comparisons of chemical structure and function using research stage *in-vitro* data that may or may not be accompanied by early *in-vivo* examples, usually done in animals. The patentability comparison is also made relative to technology existing prior to the date the invention was made or the application for patent protection was filed; not relative to later technology developments or characteristics, or the objectives of applicants. That approach promotes transparent and objective decision making free from reliance on transient circumstances. It also recognizes the fundamental need for distinct and thorough assessment and regulation of matters other than patentability before new products are made available to the public, in particular the need for full assessment of safety and efficacy in the health domain.

1. Assessing Patentability of New Salt Forms and Isomers of Existing Substances Is Distinct from Assessing the Value of such Innovations to Society

The premise that patents functions to reward, to broaden the base of and to hasten innovation is generally accepted, although alternative approaches are also pursued in practice and are extensively discussed in the literature on innovation. Developing countries are increasingly becoming sources of innovation. Policy makers may consider in this context whether innovative health-related enterprises in developing countries will focus their efforts on incremental and adaptive innovation or aim primarily for breakthrough and pioneering developments. This will in turn affect how the IP incentive systems are structured and used in those countries.

Developing a new salt form or isomer of an existing substance does not create a new therapeutic agent and is thus another type of follow-on innovation that has been criticized as minor. Research on and development of new salt forms and isomers of existing therapeutics or substances and patenting of those innovations is some contexts attributed to the motivation to create intellectual property thickets or evergreening (see page 17 below). In some contexts, such innovations may be essential to providing new products in commerce or alleviating side effects or enhancing efficacy of existing products. Moreover, altered physical characteristics created by different salt forms (stability in varying conditions of humidity or heat and solubility) can be useful in adapting therapeutic substances to local conditions.

Research efforts focused on development of new salt forms and isomers of existing substances with known therapeutic potential are illustrated by a growing patent estate on antimicrobials being accumulated by Wockhardt Limited (Wockhardt Research Institute) of India. Wockhardt owns six United States patents issued to Indian inventors. Five of the six issued patents concern alternative salt forms of a known class of antibacterial agents known as pyroloquinolines and benzoquinolizines.[30]

Long before Wockhardt began its work, the subject classes of compounds were patented by Otsuka Pharmaceutical Company, Ltd. of Japan.[31] They were described as potential antimicrobial agents against bacteria that were resistant to conventional antibiotics such as penicillin, ampicillin, and streptomycin. The new salt innovations disclosed and claimed by the Indian enterprise are: arginine salt forms (6,514,986; 6,753,333); specific isomers of

[30] The sixth issued patent claims a new once-a-day dosage formulation for diltiazem, a well-known heart medication.

[31] U. S. patent 4,399,134 issued in 1983 and expired in 2000.

arginine salts referred to as L-arginine salts (6,664,276); and optically pure carboxylic acid salt forms (6,750,224; 6,608,078). The Indian inventors explain that the active substances original patented in the 1980s have undesirable solubility characteristics in aqueous solution has crated problems in formulating the drug as a tablet or capsule or in making injectable formulations. The claimed arginine salts for instance are focused on resistant Staphylococcus duress and respiratory pathogens[32] are said to possess "very desirable properties in processing . . ." more favorable solubility characteristics and a "low propensity to cause phlebitis, and favorable acute toxicity values." The improved characteristics also include greater stability in the presence of high humidity climates.[33]

These researchers are devoting resources in this instance to incremental innovations that provide improvements relevant to them (i.e. stability in high humidity climates). Increased investment in research and development by the Indian pharmaceutical sector is projected to increase from its current 1.9% of turn over as patent protection is extended to pharmaceutical products in 2005.[34] The Wockhardt salt and isomer examples described above suggest portions of those efforts will be directed to incremental and adaptive innovation.

The development of humidity resistant salt forms and isomers of known antimicrobial substances an objective may potentially be viewed as a form of innovation that addresses hitherto unmet public health needs. This raises the question of what incentive structures apply to recognize and support research and development efforts focused on incrementally different isomers and new salt forms. It also underscores the practical difficulty of making broader value judgments at the time a patent application is assessed, which can occur long before comparative data in humans is available. Policymakers may need to weigh the choices for appropriate incentives to local innovative enterprises of IP protection for this type of innovation as potentially useful in developing technologies tailored to meet neglected health needs.

2. Assessing Patentability of Advances in Anti-malarial Products from Natural Substances

The example in this section illustrates an effort to accumulate patents covering closely related follow-on innovation. Conclusively assessing the full value of the innovations to society can not be done at this early stage because no product exists. The patentability assessments, however, can be and are being made now on the basis of patent grant criteria.

Artemesinin (qinghaosu), a naturally occurring substance used as a traditional Chinese medicine for centuries, has provided a unique molecular model for malarial treatment and

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[32] U.S. Patent No. 6, 514, 986 (col. 6, lines 55 – 67).

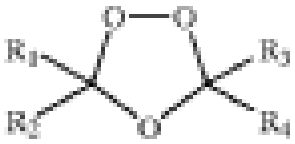
[33] U.S. Patent No. 6, 514, 986 (col. 2, lines 13 – 28; lines 48 – 60; col. 4, lines 31 – 35).

[34] "The R & D expenditure by the Indian pharmaceutical industry is around 1.9% of the industry's turnover. This obviously, is very low when compared to the investment on R & D by foreign research-based pharma companies. They spend 10 - 16% of the turnover on R & D. However, now that India is entering into the Patent protection area, many companies are spending relatively more on R & D." From Indian Pharmaceutical Manufacturers web site on November 29, 2004. http://www.pharmaceutical-drug-manufacturers.com/pharmaceutical-industry/research-development.html.

research.[35] Many synthetic versions of the active compound have been prepared and tested with the same core molecule containing three linked oxygen atoms (oxygen is symbolized in chemical drawings by the letter O) referred to here as trioxolane.[36] The synthetic variations result from incremental changes to the core molecule. [37]

One recent incremental innovation based on the natural substance resulted from collaboration among medical researchers in Omaha, Nebraska in the United States and Basel, Switzerland. It was described and claimed as a generic group of compounds and many specific substances, in U.S. patent 6,486,199 issued November 26, 2002.[38] That same research group filed another patent application, published in February 2004, on innovations based directly on the previously patented innovations. Key attributes of these stepwise innovations are described below.

The claims issued in 2002 cover generic classes of compounds (spiro and dispiro trioxolanes) useful in preventing and treating malaria. The discovery was "that trioxolanes that are relatively *sterically hindered* on at least one side of the trioxolane heterocycle provide metabolic and chemical stability to the trioxolane ring, thereby providing better in vivo activity, especially with respect to oral administration."[39] In other words, efficacy was improved by hindering (blocking) access to parts of the molecules through addition of certain chemical structures. In the following formula taken from the 2002 patent, the letters $R_1 - R_4$ represent chemical ring structures and a wide range of other chemical structures that could optionally be used in accordance with the invention to hinder (block) access to adjacent parts of the core molecule.



[35] The active chemical substance contains a pharmacophorific peroxide bond in a unique 1,2,4 – trioxane heterocycle. Klayman, D.L. Qinghaosu (Artemesinin) an anti-malarial drug from China, Science 228, 1049 – 1055 (1985); Venneerstrom J.L. et al. Identification of an Anti-malarial Synthetic Trioxolane Drug Development Candidate, Nature 430, 900 – 904 (2004).

[36] US Pat. Appl. 2004/0039008 at Paragraphs 0028-0031.

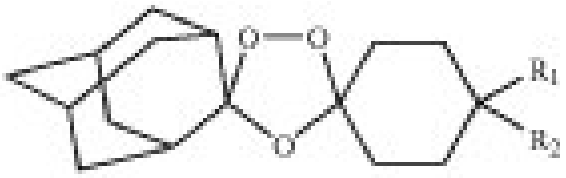
[37] As with antibiotics, there are many other "me-too" anti-malarial products. Examples include Avloclor (chloroquine), Daraprim (pyrimethamine), Fansidar (suphadoxine/pyrimethamine), Paludrine (proguanil), Malarone (atovaquone/proguanil), Lariam (mephloquine), and Riamet (artemer/lumfantrine).

[38] It was assigned to Medicines for Malaria Venture MMV.

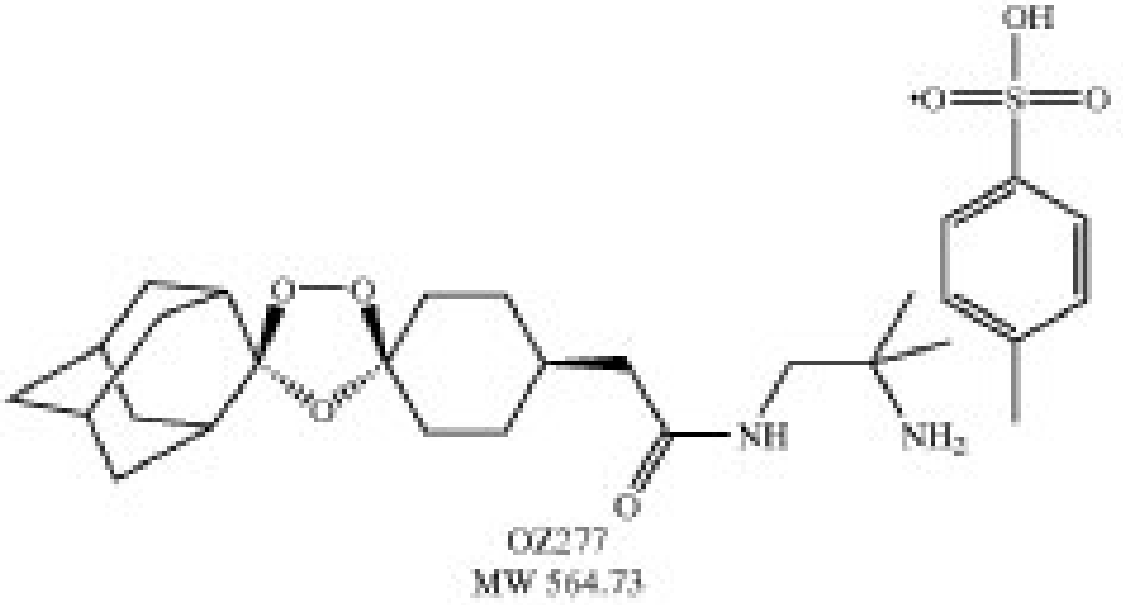
[39] 6,486,199 patent at col. 3, lines 15 – 23.

The new patent application published in February 2004 discloses and claims many additional specific compounds closely related to those disclosed in the earlier 2002 patent. In the newer 2004 application molecular access is always hindered on one side with fixed ring structures shown on the left side of the molecule in the following depiction.

1. A Spiro or dispiro 1,2,4-trioxolane having the following structure:



One of the compounds in this group became the subject of preclinical tests. It is represented by the following formula and was given the designation of OZ277 in the patent application:



The incremental change resulting in the inventions shown in the previous two figures was combining the fixed structure shown on the left with the structures shown on the right side of the molecule. The inventors explained that this provided efficacy against malarial parasites (in-vitro tests) and a low degree of neurotoxisity.[40] The compounds are also said to be easy to prepare synthetically. Thus, by hindering the accessibility of parts of the molecular structure in a particular way, improved potency was achieved, a problematic side effect (neurotoxisity) was reduced and synthesis was made easier.

[40] U.S. Application 2004/0039008, page 2, paragraphs 0023 and 0024 and page 21 – 22 paragraph 0070; Vennerstrom et.al. *Identification of an Anti-malarial Synthetic Trioxolane Drug Development Candidate* Nature, vol. 430, 900 – 904, 19 August 2004. This application reflects ongoing work on the basic discovery patented in 2002. MMV is again the assignee of the patent application.

The innovation in the pending application published in 2004 is derived directly from the work patented in 2002. Both the pending patent application and the issued patent disclose hundreds of structures which means OZ277 is not first in class or even second in class. No product has yet been approved containing OZ277 but the inventors identified it as one of the lead compounds for additional testing aimed at regulatory approval. One might speculate whether easier synthesis reported by the inventors could be a key to making a new anti-malarial product available.[41] Policy makers may also question whether the fact that both the innovation published in 2004 and the innovation disclosed in the 2002 patent are modifications of previously known substances should be relevant to the importance of these subsequent generations of modifications. Should this kind of question (and the difficulties confronted in seeking answers) be pertinent to patentability of a claimed innovation, or to an assessment of an innovation's importance well before product development and regulatory testing takes place? If a product results from these patented innovations, will the patents be useful to a potential development partner in finding a suitable technology management structure and commercial arrangement than can help sustain product testing development and manufactures?

Malaria is a key example of a disease that disproportionately affects people in developing countries. Resistance to established therapies has increased the need for innovation. As the example of this section suggests, therapies being developed for the future may result from incremental advances, and not solely from major or pioneering discoveries. This raises the question of the appropriate role of IP in this context. Because malaria predominantly impacts regions with less attractive markets (or in many cases with no effective markets) for health products, there are continuing questions about whether, and if so how, IP tools, like patents which are associated with wealthy market economies, can contribute to meeting this need for increased innovation. Indeed large companies concentrated on developed country markets have not, overall, been drawn to focus on malaria, presumably because of undesirable market circumstances. The fact of unattractive market circumstances for large corporations may not necessarily mean, however, that markets do not exist that can provide an economically sustainable basis for ongoing development and manufacture in this area, including for enterprises located in developing countries which may focus on adaptive innovations aimed at health needs overlooked by the business models of large enterprises based in developed countries. If economically viable markets exist in some developing countries and can be combined with the traveler and military markets of developed countries, there may be a role for patents to assist enterprises (public-private partnerships and small entities) in finding a margin that can help sustain innovation and manufacture economically, with a focus on adaptive or follow-on technologies such as those discussed here.

B. Policy and Evidential Considerations in Patent Grant and in Assessment of Competitive Behavior

The previous sections of this paper illustrated the accumulation of multiple patents by the Wockhardt Institute on various salt forms and isomers of previously known antimicrobial

[41] As an outsider to this technology it is impossible at this time to know from reading the patents whether the innovations claimed in MMV's new patent application will be incorporated into a commercial product. The hope, of course, is that the innovation will be successful but that hope can not be confused with the fact of product availability. This is, of course, typical of most innovations where patentability is assessed at the time when limited information is available and long before product data can be obtained.

substances and efforts by MMV to accumulate patents on closely related advances based on a known natural substance with therapeutic value in treating malaria. The patentability of those innovations is assessed on patent grant criteria, not product data. As those examples illustrate, clinical information is ordinarily not available at the patentability assessment stage.

After patents are granted, however, strategies for using those rights can be put in place by whoever owns the patents at that later stage. As mentioned above, that use of granted patents is moderated by public policies articulated in contract law, competition law, rules of procedure and legal remedies against illegitimate acts. The enforcement of intellectual property rights is usually accommodated as one part of competitive commercial activity. These assertions of patent rights, however, are sometimes criticized as part of a strategy referred to as "evergreening". Those assertions raise policy and legal concerns that are sometimes distinct from patent grant policy concerns. One approach to those concerns is to implement policies and rules focused on competitive behavior entailing the assertion of rights based on granted patents.

Concerns about 'evergreening' arise in policy debate about follow-on innovation. The term 'evergreening' is attached to a range of different practices or events, which include acquisition of patents claiming different embodiments of innovations (such as dosages), to wrongful assertions of IP rights beyond their legitimate scope. Concerns regarding the accumulation of claims or patents can be addressed by rigorous application of grant criteria and effective mechanisms for challenging patent validity. The use of patent rights, however, have at times presented challenging issues of fair competition and the balance between innovators' need for market exclusivity afforded by patents, the need for market entry by generic producers after patent expiration, and the desire to avoid deterring non-infringing acts.

Policies associated with patent enforcement in the context of health care products have justifiably drawn significant attention. In the United States of America, for instance, the Drug Price Competition and Patent Term Restoration Act of 1984[42], commonly known as the Hatch-Waxman Amendments, altered patent enforcement procedures to facilitate generic drug approvals. That legislation made use of a so-called "Orange Book" where patents that cover approved products are listed and created a legal mechanism enabling generic applicants to challenge validity of listed patents before their competitive product is finally approved for manufacture and marketing. Over the years following enactment of those laws, small and large pharmaceutical companies through the patent listing and litigation process have tested the legal boundaries of the policy and regulatory framework. The United States Federal Trade Commission, competitors, Congress, and courts monitored and challenged practices that appeared to violate Hatch-Waxman laws and other laws governing competition.[43] Recently, the United States Congress modified the policy and regulatory regime to improve the balance between practices involving use of patents and the regulatory drug approval process.[44]

[42] Pub. L. 98-417.

[43] Penalties were imposed for wrongful listing, for instance, on Biovail (a Canadian generic drug manufacturer) C-4060 (consent order issued October 2, 2002) and Bristol-Myers Squibb (a large pharmaceutical company) C-4076 (Consent order issued April 14, 2003).

[44] Pub. L. 108-173, signed into law by President Bush on December 8, 2003 amended 21 U.S.C. Section 355 (b), (c) and (j). See also the FDA's "Guidance for Industry Listed Drugs, 30-Month Stays, and Approval of ANDA's . . . .".

Competition rules and regulatory regimes that modulate use of intellectual property may warrant further discussion and analysis. Those issues lie beyond the scope of this paper. Even so, it should be noted that patentability criteria are conceptually distinct from those laws that restrain the illegitimate or anti-competitive assertion of patent rights beyond the legitimate scope of a granted patent. The issues differ in terms of when they arise, the mechanisms used to effect regulation, the substantive criteria that apply, and the information that is available and required to evaluate them. To the extent that 'evergreening' is used to refer to illegitimate outcomes, they may be addressed firstly in terms of ensuring that patent grant applies to genuinely patentable inventions, and subsequently in terms of ensuring that legitimate patent rights are used legitimately in the marketplace.

V. Conclusion

The discussion of follow-on innovation spurred by the CIPIH is a useful avenue for considering the linkages between intellectual property rights and public health related innovation. By focusing on specific innovations that have occurred and that are emerging, this working paper seeks to illustrate the incremental nature of most innovation and promote consideration of its value. Some follow-on innovations are patentable and others are not. Examples included in this paper suggest, however, that many follow-on and patented innovations might contribute in a positive way to the improvement of public health and also to economic development, and that some forms of adaptive innovation may be especially relevant to meeting neglected health needs. It also illustrates the different considerations that need to be made at different stages of the innovation process required to transform an innovation into a product. Finally, the incentives provided by IP policies, such as those pertaining to secondary uses need to be understood in the context of efforts being made to find new advances that help reduce neglected disease burdens. By understanding and accommodating the legitimate interests of the public and private sectors, and focusing on those mechanisms which harness the full resources needed to address neglected health needs, the agreed upon objectives of accelerating product development and expanding the pipeline of future developments in the public interest can be achieved.