How Much Intellectual Property Protection Do the Newest (and Coolest) Biotechnologies Get Internationally?

Alix Weisfeld
How Much Intellectual Property Protection Do the Newest (and Coolest) Biotechnologies Get Internationally?

Alix Weisfeld*

Since the completion of the Human Genome Project in 2000, we are already seeing changes in health care. As we better understand the genetic basis of disease, we are able to target therapies to these root causes of disease. This paper will consider how two nascent areas of genetic medicine, pharmacogenetics and biologics, interact with international intellectual property ("IP") law. Neither of these areas fits comfortably in the traditional intellectual property model we use for pharmaceuticals. Due to their growing importance, however, the implications for international law concerning these advances are great.

The first section of the paper will give a background on what biologics and pharmacogenetics are. Section II will examine regulatory protections given to pharmaceuticals both nationally and abroad. Section III will consider what patent protections have been awarded to pharmaceuticals in the US and internationally. Section IV concludes.

I. WHAT ARE BIOLOGICS AND PHARMACOGENETICS, AND WHO CARES?

A. WHAT ARE BIOLOGICS?

Biologics are drugs manufactured through biological processes. They are some of the hottest drugs around today and are certainly among the most expensive. Unlike chemical drugs, which typically are comprised of several

* JD Candidate 2006, The University of Chicago and Academic Programs Director at the MacLean Center for Clinical Medical Ethics at the University of Chicago. The author expresses appreciation to Richard A. Epstein, Mark Siegler, and Neil Weisfeld, for their ongoing support (and editorial suggestions). The author would like to thank Lori Andrews and especially Jordan Paradise for their assistance, which went above and beyond any call of duty.
hundred atoms, biologics are complex proteins that contain thousands of atoms folded over onto themselves.¹ This structural complexity makes them much more difficult to create, and consequently to duplicate.

Some biologics act as catalysts for biologic processes that subsequently occur in the patient's body. A major example of this type of biologic is insulin. Diabetics either do not make insulin properly or are desensitized to it, but bacteria can be manipulated to produce human insulin when injected with the human gene for insulin. Likewise, many vaccines are created by the biologic process.

Other biologics, called monoclonal antibodies, interfere with the adhesion of certain compounds to cell receptors. For example, rituximab is the generic name for a monoclonal antibody that adheres to a particular molecule found on the surface of the cells of abnormal B-cell lymphocytes that often occur in non-Hodgkin's lymphoma. Rituximab binds to this molecule and causes the body to destroy the cancerous cell. In addition to treating cancer, monoclonal antibodies are useful for treating anemia, diabetes, hepatitis, and multiple sclerosis, and are an effective growth hormone (which is often prescribed to prevent AIDS-related wasting disease).

Because they are proteins and not chemicals, biologics must be manufactured through living organisms. This makes them expensive to produce, and consequently expensive for consumers.² In 2001, 25 percent of all increases in US hospital expenditures (which themselves account for 30 percent of all medical expenses) were attributable to four products, three of which were biologics (epoetin alfa, infliximab, and rituximab).³ Biologic sales in the US may top $56 billion in 2006.⁴

---

¹ For a good overview of biologics, see Michael Kleinberg and Kristen Wilkenson Mosdell, Current and Future Considerations for the New Classes of Biologicals, 61 Am J Health-Sys Pharmacy 695 (2004), on which I relied heavily in this discussion.


B. WHAT ARE PHARMACOGENETICS?

The term pharmacogenetics (commonly called “personalized medicine” in the lay press), describes the process of targeting drug therapies to individual patients’ genetic make-up. Unlike biologics and chemical compounds, it is not a drug product per se.

Pharmacogenetics aims to improve pharmaceutical safety and efficacy based on genetic variation. This variation can occur in two ways. The first way pharmacogenetics can be applied is to attack irregularities within the disease itself (for example, drug-resistant strains of HIV or differences in tumor type). A prominent example is Herceptin, which can effectively treat breast cancer, but only works in about 25 percent of all women with the disease. Patients need to be genetically screened before they are prescribed the medicine because there is no other way to distinguish responders from non-responders.

The second way pharmacogenetics can be effective is when a patient’s genetic make-up affects interaction with a drug. Patients with asthma are a prime example, since certain genetic haplotypes are more responsive to bronchospasm drugs than others. Other areas where research has already begun to suggest pharmacogenetic advances are Alzheimer’s disease, pain management, and depression.

Depending on how a drug works, genetic differences in either the disease or the patient can affect the safety and efficacy of the drug. These differences are not insignificant; some researchers estimate these effects are shockingly pervasive: as few as one-third of all drugs patients take may act as expected when they are prescribed. The bad effects of a wrong prescription can be severe. For example, there is wide variability in the reactions of patients to asthma medication, so the same medicine can be an efficacious treatment for one patient but result in dangerous side effects for another. Studies have found that patients’ genetic make-up is the source of much of this variation. A prophylactic determination of how a patient is likely to respond to a particular asthma drug can mean the difference between life and death. For some drugs, side effects may not be obvious despite their negative effects on patient’s health.

---


Pharmacogenetics' potential is limited by the fact that many diseases with a genetic component, such as obesity, diabetes, coronary artery disease, and depression, are complex. They are either multifactorial (the result of gene-environment interactions) or polygenetic (the product of the interaction of many genes). Although we currently have a solid understanding of how genetics affects diseases when just a single genetic mutation results in a disease (examples include Down's syndrome, cystic fibrosis, or Huntington's, all of which are relatively rare), comprehension is less complete when we are dealing with more complex (and prevalent) diseases that have a genetic component but are not completely genetically determined. Nevertheless, even today, pharmacogenetics can be a beneficial tool, particularly for diseases for which there is a lot of variability in patients' responses to drugs. In these cases, it is difficult to observe (without genetic tests) a patient's response to the drug, and there are not a lot of substitute treatment options available that work well for everyone. A prominent disease that fits these parameters is cancer.

The health policy and economic implications of pharmacogenetics are legion. At first blush, this technology appears to be bad for pharmaceutical companies that will lose profits when blockbuster drugs are demonstrated to be inefficacious or even harmful to certain populations. However, several opposing arguments have been put forward. First, increased information about drugs' usefulness may allow drugs that had been abandoned because they were too unsafe for the general population to be resurrected for select populations. An example might turn out to be the high-profile cases of Celebrex and Vioxx, which may still be the best treatments for people with osteo-arthritis and a history of gastrointestinal bleeding, for whom the increased risk of heart attack is acceptable, although they are not the best option for the general population given the other options available. If these subpopulations are not identified, the drugs will be taken off the market and abandoned. Second, more targeted and specific knowledge may make the process of development both faster and cheaper, since drugs can be tested based on signaling molecules that have been linked with the disease in humans. Third, marketing will also be more specific and therefore less costly than the blanket ads that are necessary for undifferentiated blockbusters.

Regulatory agencies, such as the Food and Drug Administration (“FDA”) in the US, require safety and efficacy data before they will approve a drug. As information about who can take a particular drug becomes more significant, these regulatory agencies will certainly require additional warnings on packaging. It is possible they will also require genetic tests to be bundled with the drugs, in

---

order to emphasize the specificity of the drug's regulatory approval. Some health economists maintain these genetic tests may be a useful way for governments and payers to ration expensive medications that will not benefit patients (and may even harm them), while others argue that the expense of the genetic tests will be to prohibit the making of any population-wide changes in how we prescribe most drugs. The loss of a segment of the American market may also spur pharmaceutical companies to be even more interested in overseas markets than they already are.

Whatever the long-term economic and health policy effects of these drugs are, pharmacogenetic-based medicines are expected to become more and more prevalent in the future. Pharmacogenetics almost certainly will result in the development of thousands of variations targeted to specific subpopulations that could never be developed under the traditional, “one size fits all” blockbuster model.

C. THE OVERLAPPING RELATIONSHIP BETWEEN BIOLOGICS AND PHARMACOGENETICS

Biologics are a subset of the broader category of pharmaceutical substances, whereas pharmacogenetics describes the process of prescribing the right drug to a particular patient. Sometimes, therefore, where a biologic drug only works in people who have a certain genetic make-up, it may be prescribed to a specific patient based on individual pharmacogenetic data. An example of such a drug is Gleevec, a successful biologic that can eliminate certain kinds of leukemia and stomach cancers. However, Gleevec only works in people whose leukemia is associated with a genetic abnormality that is not shared by everyone with the disease. Studies have found that people who do not have the particular gene mutation that Gleevec treats do not respond well to the drug, while people with the mutation had an 84 percent chance of a partial remission. A simple

---

9 Rebecca S. Eisenberg, Will Pharmacogenomics Alter the Role of Patents in Drug Development?, 3 Pharmacogenomics 571, 573 (2002).
11 There are, of course, many other economic implications for pharmaceuticals, including raised prices based on smaller demand and greater efficacy (quality), lower drug development costs as clinical trials become more targeted, faster approval time by the FDA (and the subsequent increased value of the patent), and potential application of the Orphan Drug Act (by which the US government provides incentives for pharmaceuticals developing drugs that only benefit a small population and that otherwise would not be viable). Although these topics are fascinating, I will not focus on them here.
genetic lab test of a patient’s bone marrow can be administered to determine if the drug is appropriate.

D. WHY SHOULD WE CARE?

By all accounts, both biologics and pharmacogenetics will quickly and steadily increase in importance during the coming decades. Both biologics and pharmacogenetics have thus far had their biggest successes in diseases like cancer and rheumatoid arthritis, which are primarily first world diseases. Although the largest killers in the developing world (Africa, Asia, South America) remain HIV/AIDS, tuberculosis, malaria, and respiratory infections, the potential demand for advances like pharmacogenetics and biologics in those regions may still be great. Pharmacogenetic advances have implications for some of these conditions, such as malaria, but this is still speculative. Biotechnologies may not have much impact on sub-Saharan Africa at any time in the foreseeable future, but other third world countries (including India and China) may have a large demand for these drugs because of their growing middle classes. In middle-income countries, including much of Europe, the demand for these drugs is large.

II. REGULATORY IP PROTECTIONS

A pharmaceutical company’s IP is protected in two ways: by data exclusivity provisions provided by the FDA and by patent laws. In the US, the FDA imposes two requirements on any drug it approves: 1) it must be safe; and 2) it must be efficacious. Pharmaceutical companies must prove drugs meet both these tests through the submission of data collected in clinical trials. The FDA examines the data and, if it determines the benefits of the drug outweigh the risk, the agency will allow the drug to be released to the public. In addition, the FDA must approve the labeling of the drug and determine that the drug’s

---

13 One reason for this is systemic—the current blockbuster drug model is simply untenable. The statistics are staggering: only one in ten compounds ever reaches the market; each one costs, on average, $897 million to develop; and more than 50 percent of compounds that are developed cannot provide adequate returns on investment. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs, 22 J Health Econ 151 (2003). Of course, not all pharmaceuticals have such poor return on investment. Even so, the potential for smaller-scale therapies (as are both pharmacogenetics and biologics) that may be cheaper to develop because they are more specific is attractive to pharmaceutical companies, and is a motivating factor behind the surge of research in both these areas.


manufacturing process sufficiently ensures purity. The FDA approval process is generally accepted as the most rigorous in the world. A drug that has been approved by the FDA will certainly meet the safety and efficacy standards in other nations, both developed and developing.

Data exclusivity, or the protection of proprietary information that pharmaceutical companies submit as part of the FDA approval process, is an important IP protection. It is explicitly provided by the regulatory agency and not through the patent process.

The key issue raised by harmonization of drug approval processes involves the exclusivity of information. The FDA requires a lot of data, data that are an important proprietary asset worth billions of dollars to pharmaceutical companies. Naturally, these companies are wary of passing this information on to drug approval institutions that do not offer strong IP protections. In 1997, the US and other developed nations—specifically, European Union members and Japan—entered into Mutual Recognition Agreements ("MRAs"), in which the countries agreed to work toward a system where reviews by one country would be recognized by the other countries. MRAs have less force than a treaty, but are more than letter agreements. A key requirement for the US in these agreements was that data the FDA would protect would likewise be shielded by the receiving nation.

A. HOW DO BIOLOGICS FIT UNDER THE REGULATORY SCHEME?

Biologics are complex molecules. Without access to proprietary information, process conditions, and clinical trial data, it is very difficult to replicate a biologic. Government regulatory agencies may also be concerned about the difficulty in evaluating generic biologics.

Even if a nation's government regulatory agencies are not concerned, developers face high purchase and maintenance costs for manufacturing and storage facilities, which must keep the drug at precise temperatures. Although it might be possible to manufacture and properly store a generic biologic, its characteristics explain why generic equivalents are thus far not a major issue.

16 See, for example, Linda Horton, Mutual Recognition Agreements and Harmonization, 29 Seton Hall L Rev 692, 706 (1998).
19 Id.
the US, the FDA requires full clinical trials for every biologic even though, with chemical compounds, an abbreviated new drug application (or approval process) might suffice. This is because, with biologics, it is the process of manufacturing that determines the end result.

Manufacturing generic biologics is not nearly as cost-advantageous as traditional chemical pharmaceuticals because so much is embedded in the process, and it is not clear that they could be offered at much lower prices than the original biologics. In addition, this area of medicine is still changing so fast that by the time a copycat biologic has come along, the developers of the original may have already come out with a better version.

B. HOW DO PHARMACOGENETICS FIT UNDER OUR REGULATORY SCHEME?

The exclusivity of information about drugs is particularly important to manufacturers of drugs whose marketability is based on pharmacogenetics. It is especially important when the patents on the drugs have already expired. Typically, once a drug's patent has expired, the company will let it languish because it is no longer valuable to invest in additional research. Generic manufacturers can legally manufacture the drugs, free ride off the data collected by the no longer protected initiating company, and sell the copycat drug on the cheap. To encourage additional investment in already existing drugs, the Hatch-Waxman Act includes a bioexclusivity provision to encourage investment in research of new active ingredients by allowing originators to recoup the considerable losses they incur in clinical trials. Under the Hatch-Waxman Act, competitors are prohibited from using the data submitted by the originator of a drug containing an active ingredient that had not previously been approved by the FDA. After five years, competitors can use the data if they can demonstrate bioequivalency with the originator's product. If these generic companies want approval sooner, they have to obtain the data independently through their own clinical trials. Data exclusivity may encourage drug companies to undertake additional research (relying on pharmacogenetic technology) on drugs that would otherwise fade into obscurity because they are no longer protected by a patent.

---

If, however, international regulatory bodies do not protect these data, the benefit of data exclusivity will be eroded. For these drugs, there are no other IP protections available.

III. PATENT PROTECTIONS

A. US IP LAWS

The US has a long history of strong patent protections. Article I, Section 8, clause 8 of the Constitution states that Congress shall have the power "to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." The statutory grant of patent protection holds, "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor." That is, patents can only be issued for inventions that are useful, new, and nonobvious. In addition, the invention must fall into an identified statutory category, such as processes, articles of manufacture and compositions of matter.

Traditional pharmaceuticals are chemical compounds, and fall under the compositions of matter heading. This category is the one most commonly recognized by foreign laws and by international treaties. Neither biologics nor pharmacogenetic products fit squarely within it.

B. BIOLOGICS AND PATENT PROTECTION IN THE US

Biologics that are exact replicas of naturally occurring substances are not themselves patentable. Any patent involving biologics can be contentious, because many people philosophically disagree with the notion that life can be patented. Companies will seek patents for biologics after they make minor modifications to a naturally occurring molecule, even though it is nearly identical to the natural substance. In addition, in the US, manufacturers patent the cell line used to develop the biologic. The US recognizes these patents (the landmark case was *Diamond v Chakrabarty*, in which the Supreme Court held man-made microorganisms were patentable). Other countries, including European Union

---

23 US Const, art I, § 8, cl 8.
members, who typically support strong patent protections, have moral objections to the idea of patenting natural substances.\(^2\)

In addition to cell line patents, manufacturers of biologics also obtain process patents, which are allowed for the production of a nonobvious or novel product. In 1995, Congress passed 35 USC § 103(b), which enables manufacturers of biologics to avoid a review to determine whether the process is nonobvious if it produces a nonobvious product.

C. PHARMACOGENETICS AND PATENT PROTECTION IN THE US

Before analyzing how pharmacogenetics will be covered by international intellectual property law, we must first ask what, exactly, would be covered. Many drugs associated with pharmacogenetics are traditional chemical or biologic compounds, and as such can be patented in the same way traditional pharmaceuticals are, based on their chemical compound or, if they are biologics, with process patents. In addition to these, drug manufacturers can also seek method-of-use patents in the US.\(^2\)\(^7\) Method patents are obtained under 35 USC § 101 in the same way that machine patents are. However, they are not universally accepted; more than eighty countries exempt medical method patents from patent protection.\(^2\)\(^8\)

But pharmacogenetic drugs, by definition, are bound up with genetic tests. The tests, however, are protected separately from the drugs because they are different things. The drug tests are patentable, even if the drugs that require them are not. Genetic tests are patentable under both the “methods-of-use” and “composition-of-matter” categories.\(^2\)\(^9\)

D. INTERNATIONAL IP LAWS

International intellectual property law as it relates to pharmaceuticals has been developed to balance: (1) efficacy; (2) safety; (3) quality; (4) access; and


\(^{27}\) 21 CFR § 314.53(b) (2004).

\(^{28}\) Robert M. Portman, Legislative Restriction on Medical and Surgical Procedure Patents Removes Impediment to Medical Progress, 4 U Balt Intell Prop L J 91, 98 (1996).

the incentive to invest in research. The first three of these five considerations are largely issues of national policy carried out through governmental regulatory agencies, which can (through their governments) be held responsible for any violations of international law. The tension between the last two, however, is evident in international law.

The application of international intellectual property law to traditional pharmaceuticals is well-studied. Although bilateral trade agreements may supersede multinational agreements, the most important source of intellectual property protection is the World Trade Organization’s Agreement on Trade-Related Aspects of Intellectual Property Rights (“TRIPS”), arts 27–34. In general, member countries must provide patent protection for twenty years from the date of filing the application, for both products and processes (but not methods).

This provision of TRIPS is supposed to enter into force completely in 2006. However, there are a number of “exceptions” to the basic rule that threaten to swallow it whole, and may cast the value of the ostensible patent protection into some doubt. Several exceptions have been justified by the prototypical example for overriding patent protection: the need to provide low-cost HIV drugs to poverty-stricken countries. However, only two have really been effectively applied: Article 31’s compulsory licensing and the parallel importation and exhaustion of Article 28. The following are all potentially relevant exceptions:

1. Article 31: Compulsory licensing, or use without authorization of the right holder, such as in cases of national emergency or other circumstance of extreme urgency.

Under Article 31, countries can manufacture a patented pharmaceutical without the permission of the patent holder. In 2001, the WTO held the Doha Round to clarify TRIPS. The Round produced the Doha Declaration, which provides that countries have the right to issue compulsory licenses (allowing the drugs to be manufactured in violation of the patent) and to determine “what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to

---

30 See, for example, Alan O. Sykes, TRIPS, Pharmaceuticals, Developing Countries, and the Doha "Solution," 3 Chi J Intl L 47 (2002), and 't Hoen, 3 Chi J Intl L at 27 (cited in note 14).
32 Sykes, 3 Chi J Intl L at 49 (cited in note 30).
33 Pharmaceutical companies can overcome this problem by offering low-cost sales of certain drugs to poor countries, of course, which in many cases they do.
HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency.\textsuperscript{34}

2. Articles 6 and 28(1)(a): TRIPS' silence on the issue of parallel importation, or the exhaustion of the rights of the patent-holder over products once they have entered another country.\textsuperscript{35}

Under Article 28, countries can "exhaust" or terminate the patent-holder's rights after the initial sale into a country. The Doha Declaration provides that "each Member [is] free to establish its own regime for such exhaustion without challenge, subject to [nondiscrimination limitations]."\textsuperscript{36} Exhaustion (which is often called parallel importation) means that the patent-holder's control over a product ends with the first sale of it into a country. In subsequent sales, he has no control over how the product is sold. The result is that a poor country that has negotiated to buy drugs at a low price can resell them to a richer country where the price of the pharmaceutical, when bought directly from the patent-holder, is higher. By declining to eliminate this practice, the Doha Declaration and TRIPS are permitting parallel importation. This undermines the incentive to pharmaceutical companies to provide low-cost drugs to poor countries, which in turn creates a market for the drugs to be made elsewhere and sold cheaply to the poor country, in violation of the patent-holder's intellectual property rights.

3. Article 27(2): Any inventions that negatively affect the ordre public or morality, including human life or health.

This is a possible exception, but it has been interpreted to apply only to "inventions dangerous to human, animal or plant life or health or seriously prejudicial to the environment."\textsuperscript{37}

4. Article 30: Limited exceptions to the rights conferred ... taking account of the legitimate interests of third parties.

Article 30, which allows nations to make limited exceptions to patents, has not been raised, since overriding patent rights even for a proscribed period of time would probably not constitute a "limited exception."\textsuperscript{38}


\textsuperscript{35} This category may be more of a trade issue than an intellectual property issue, but the World Trade Organization's materials on intellectual property discuss it because of its implications for the producer's ability to maintain control over its product.

\textsuperscript{36} WTO, \textit{Declaration on TRIPS}, WTO Doc WT/MIN(01)/DEC//2 at ¶ 5 (cited in note 34).


\textsuperscript{38} Sykes, 3 Chi J Ind L at 52 (cited in note 30).
E. BIOLOGICS UNDER TRIPS

Are biologics likely to be protected under the TRIPS framework? Before answering this, we must ask whether biologics qualify for patent protection at all. The functional similarity between biologics and traditional pharmaceuticals—both of which treat health conditions—makes this an easy question; biologics do qualify under TRIPS.

The next question is whether the popular Article 31 exception can be invoked to override the process patents held by manufacturers of biologics. The answer to that question is a resounding “no.” The emergency provisions that allow suspension of patent protection may be justified by the scourge of epidemics like HIV, but are much harder to defend when the “epidemic” is rheumatoid arthritis or cancer. Unlike HIV or other public health crises that spread from person to person, the biologics that have been developed so far are useful for diseases that are grounded at least partially in genetics. There is no public health danger here because the market can still work efficiently in this situation. Whether an affected individual takes the drug or not does not affect the health and well-being of his neighbor, and therefore there is no public health crisis, as the term was traditionally used. This is very different from, say, tuberculosis, where if one person goes untreated, an entire community may be infected. If, however, a biologic were discovered that dealt with a public health crisis (say, for example, a vaccine for HIV), it would certainly fall under the Article 31 exception. Thus far, however, biologics have not been developed for pandemic conditions.

What about the issue of exhaustion under Article 28? Although parallel importation has been all over the news in the US lately, the issue may be less relevant for biologics than for traditional pharmaceuticals. Like vaccines, which are notorious for having to be thrown away because they have not been stored properly, biologics are complex three-dimensional molecules, and their properties must be carefully maintained not only at the time of manufacture but also through proper storage. Biologics are therefore less viable candidates for shipping back and forth, especially since any potential safety hazards will be pounced upon by pharmaceutical companies’ public relations teams as further evidence that parallel importation leads to breakdowns in safety. In addition,

40 At this time, biologics are exempt from reimportation proposals in the US.
42 See, for example, Joel B. Finkelstein, Drug Import Crackdown Shows Hazards, American Med News 5 (Oct 25, 2004).
many biologics have a limited shelf life, which means extensive shipping becomes riskier.

Another reason parallel importation is less salient for biologics relates to their patent type. In the US, biologics are covered by the Process Patents Amendment Act of 1988. Under the US Process Patent Amendments Act, it is a violation to import, sell, or use within the US a product manufactured abroad in violation of a US process patent. US courts have said in dicta that exhaustion does not apply to process patents, perhaps on the theory that processes do not involve discrete steps in the same way that a sale does. The law on this question is not entirely settled, however, and since the adoption of the Process Patents Amendment Act in 1988, no buyer or seller has been held directly liable under this provision. They have, however, been held liable for indirect patent infringements. Although this Act only applies in the US, this country is one of the largest markets for imported drugs. TRIPS, of course, makes no universal policy regarding exhaustion, and therefore individual countries’ laws apply.

Another possible exception particularly relevant to biologics is Article 27(3)(b), which exempts “biological processes for the production of plants or animals other than non-biological and microbiological processes.” Although the wording might be somewhat ambiguous with regard to genetic material, it seems clear that microbiological processes are not included in this exception, so they remain protected. Moreover, reviews of the 27(3)(b) provisions did not mention pharmaceuticals once.

---

43 Pub L No 100-418, 102 Stat 1563, codified at 35 USC § 295 (1988). This Act has been construed to apply only to process patents that result in actual products (such as biologics), not the production of data. See Bayer AG v Housley Pharmaceuticals, Inc, 340 F3d 1367 (Fed Cir 2003).
44 35 USC § 271(g) (2004). The purpose of this statute is to prohibit the manufacture abroad of products with a patented processes that can then be brought back to the US without violating the patent.
45 Bandag Inc v Al Bolster's Tire Stores, Inc, 750 F2d 903, 924 (Fed Cir 1984) (“The doctrine that the first sale by a patentee of an article embodying his invention exhausts his patent rights in that article is inapplicable here, because the claims of the . . . patent are directed to a ‘method.’”).
47 Endress & Hauser, Inc v Hawk Measurement Systems, 32 USPQ 1768 (SD Ind 1994); Lucas Aerospace, Ltd v Unison Industries, 899 F Supp 1268 (D Del 1995).
48 WTO, TRIPS, (emphasis added) (cited in note 31). The full provision reads: “plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes.”
F. PHARMACOGENETICS UNDER TRIPS

TRIPS article 27(3)(a) allows countries to exclude “diagnostic [or] therapeutic... methods for the treatment of humans” from patent protection. This provision will cover any method patents for pharmacogenetics, because any such method patent will involve the diagnosis or treatment of people’s health care problems. Although genetic tests can be patented in the US, the European Patent Office recently limited a US company’s patent on all diagnostic testing for mutations in the BRCA1 and BRCA2 genes (which are associated with a higher risk for breast and ovarian cancer) to “a probe of a defined composition for the detection of a specific mutation in the breast and ovarian cancer susceptibility,” and disallowed the patent for diagnostic methods.

TRIPS is like the European law: diagnostic methods can be exempted from protection under Article 27(3)(a). Although the drugs themselves are not diagnostic, they are by definition implicitly, and at some point may be explicitly, bundled with genetic testing capabilities. The question is whether the presence of a bundled genetic test with the drug will overcome the protection granted to the pharmaceutical. This seems unlikely because the two products are very different; the test is given only once, whereas the drug may be taken for a lifetime.

If the test is not considered a diagnostic method exempt from patent protection, a question remains about whether pharmacogenetics can fall into the Article 31 public health emergency exception. At this point, unlike retroviral and similar HIV therapies, pharmacogenetic technologies do not treat acute conditions for which there are no adequate substitute therapies available. Instead, they tend to be for late-onset conditions, such as cancer and rheumatoid arthritis. Although these conditions are devastating, they hardly constitute an epidemic under Article 31.


50 WTO, TRIPS, (cited in note 31).
51 Lori B. Andrews, The Gene Patent Dilemma: Balancing Commercial Incentives with Health Needs, 2002 Hous J Health L & Pol'y 65, 91–92. Professor Andrews also contends pharmaceutical companies may patent genetic tests and then refuse to develop them, in order to keep patients from finding out they should not take a drug. However, the potential liability for such practices, in addition to all the other market forces that are encouraging the development of small-scale pharmacogenetics, may weaken this argument.

53 See Eisenberg, 3 Pharmacogenomics at 573 (cited in note 9).
Another locus for pharmacogenetic protection under TRIPS is data exclusivity. Even if the drug cannot be patented or its patent has expired, the manufacturer might still be able to control proprietary information. The data at issue are the data submitted by the pharmaceutical company to a country's regulatory approval organization (in the US, this is the FDA) regarding the drug's safety and efficacy. If these data are protected, even if there is no patent protection for a drug, the lack of data could conceivably function as a "partial substitute for patent protection." Article 1(2) of TRIPS provides that test data qualify for protection as its own category of intellectual property. Article 39(3) of TRIPS guarantees that countries whose regulatory agencies require data in order to approve a "pharmaceutical . . . which utilize[s] new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use." The major hurdle for manufacturers is that the data must be for a "new chemical entity." The pharmacogenetic products seeking this type of protection are not new at all; they are rehabilitated drugs that had been developed and discarded, but now can be used to treat new indications. It would not make sense to choose protection under Article 39(3) if the drug were still on patent and there were other patent protections available. As one scholar put it, this type of exclusivity is not "on the same footing as other intellectual property rights. In particular, it cannot be inferred that such protection requires exclusive rights." This means plaintiffs may be granted remuneration, for example, but not the right to prohibit the violation of their patents. The word "new" could be used here to mean brand new or else "novel," in the traditional patent sense.

---


55 Carlos Maria Correa, Unfair Competition Under the TRIPS Agreement: Protection of Data Submitted for the Registration of Pharmaceuticals, 3 Ch J Intl L 69, 70 (2002).

56 WTO, TRIPS, (cited in note 31).

57 It is possible, of course, that they could be drugs that are still on patent, but are not protected under some other provision of TRIPS (say, art 31). It is very unlikely that this would trump any other clause, especially since these data, while protected, are considered to deserve less intellectual property protection than the products.

58 Correa, 3 Ch J Intl L at 72 (cited in note 55).

59 Id at 72–73.
Commentators disagree about which interpretation is preferable. However, since WTO member nations have discretion to choose whichever meaning they prefer, it seems unlikely this avenue will be a profitable one for manufacturers.

Another exception under Article 39(3) is that manufacturers cannot keep secret data necessary to protect the public. That means they cannot simply rely on this provision to provide trade secret status (and give monopoly rents to themselves) to information regarding who can benefit and who can be harmed by the drug. And at any rate, this information is likely to be public anyway through publication in scientific journals, especially if it relates to which patients will benefit from the drug (and not its ingredients), and so it would already be ineligible on those grounds.

H. METHOD-OF-USE PATENTS

The US recognizes method-of-use patents. These are particularly relevant to drugs that have to be administered only to certain populations. However, TRIPS does not explicitly call for protection of these patents. Moreover, these patents are not infringed until someone actually uses the product (as when a doctor prescribes it or a patient actually takes the drug), which means governments cannot be held responsible for direct patent infringement. This will make prosecution of these violations much more difficult and fact-intensive and is not an optimal way for drug manufacturers to protect their property interest.

IV. CONCLUSION

TRIPS is not radical for developed countries, since it basically tracks (or may even be less protective than US) domestic intellectual property law. It is far more significant for developing countries that have not established strong internal intellectual property regimes. For these countries, the international intellectual property protections biologics and pharmacogenetics receive seem

---

60 Compare Skillington and Solovy, 24 Nw J Intl L & Bus at 26 (cited in note 22) ("TRIPS Article 39.3 protects data and products involved in the marketing approval systems, rather than as such data relate to the patent systems. Consequently, the word 'new' in this context refers to the status of a chemical entity within the marketing approval system, not with respect to the state of the art or 'novelty' in the patent sense.").

61 See, for example, Corn Products Refining Co v Eddy, 249 US 427 (1919).


63 Id.
inverted: biologics do not need them, but have them, while pharmacogenetics need them, but do not have them.

Biologics are largely protected under existing international intellectual property laws. But biologics are different from traditional chemical compounds in an important way: the complex molecules must be manufactured in living systems of one sort or another (mammalian, yeast, bacterial), and therefore they must be essentially grown from scratch with living material and with great precision each time they are made.® Generic manufacturers (especially in developing countries) may have difficulty acquiring the raw materials and obtaining the precise conditions necessary for the delicate processes to occur. The exceptions to this rule are Eastern European countries, China, and India, all of which are capable of mastering the requisite complexity.

Without intellectual property limitations, the only restrictions on the manufacture of generic biologics are safety, efficacy, quality, and economics. Living organisms are more difficult to standardize than traditional chemical compounds. For example, human growth hormone, one of the simplest biologics to manufacture, is made by six companies, and each version is different.® Another frequently cited example is an anemia drug that was manufactured by two different companies. One was fine, but the other had serious efficacy and safety problems. Nobody was able to explain the difference.® Economic issues are more complex. Even cheap biologics are more expensive than chemical drugs, and there may be limited markets because they treat conditions most prevalent in developed countries.®

Pharmacogenetic technologies, on the other hand, are afforded much less IP protection. This is problematic from a public policy perspective: it is both inefficient and inhumane not to invest in research designed to improve the way we prescribe drugs to patients. The field of pharmacogenetics has economic implications that differ greatly from traditional pharmaceutical products. It is difficult to tell whether pharmacogenetic products will prove profitable for manufacturers. It is even more difficult to assess the potential profitability of generics. The main difference between pharmacogenetics and traditional pharmaceuticals is that increased market segmentation may make the revenues insufficient to cover fixed costs, rendering the drug not viable in the long run (even with a price increase to reflect greater specificity). There is already a strong

---

® For this reason (the fact that there is no bioequivalence), Hatch-Waxman does not cover biologics.

® Aoki, Generics Face Roadblocks, Boston Globe at D1 (cited in note 20).


® A limited market is not a negligible market, however, especially in countries as large as China.
economic argument that the development of pharmacogenetics will erode the large profits companies can extract for blockbuster drugs. Also, as was the case in Vioxx, additional research into subpopulations can turn up disastrous data that results in crippling liability. These fears discourage additional research in the realm of pharmacogenetics. If pharmacogenetics are not provided with some sort of intellectual property protections internationally, there is even less of an incentive to invest in the field.