Challenges and Opportunities in the International Protection of Biosimilars and Other Biologics

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1. The Challenge of Biosimilars

1.1. The protection of so-called "large molecule" drugs, biologics and biosimilars has become increasingly important in recent years given the rapid technological development of medical treatments using biologics and the rapidly approaching expiration of patent protection for various blockbuster "small molecule" drugs.

1.2. Medical research and marketing of "biosimilars" has steadily increased over the past ten years. This increase in research has created greater abilities to create and deliver efficacious biosimilars. The number of biosimilars that have been patented and/or approved for marketing has steadily increased. But the unique nature of biologics poses significant challenges for their originators and marketers.

1.3 Because of the biological nature of these new medical "treatments", both their protection under patent laws and the pathways for marketing approval remain problematic. Nevertheless, there is increasing pressure on the international patent system to create viable regimes for securing patent protection for biologics. There is also increasing pressure to create clearer paths for marketing approval of biologics. As discussed in greater detail below, this pressure has had variable success in changing current practices.

1.4 While there is pressure to accommodate the patent requests to protect biologics, there is also conflicting pressures that seek to reduce patentability for such innovations in order to assure greater access to medical treatments generally. Similar conflicts exist in the desire to improve marketing approval processes for biosimilars while simultaneously assuring that such biosimilars are efficacious and safe.

2. **Some Critical Definitions**

2.1. The term "biologics" refers generally to medical products made from a variety of biogenetic materials (human, animal, etc.). Some biologics treat diseases and medical conditions, others are used to prevent or diagnose diseases. Examples of biologics, include, but are not limited to:

- Vaccines
- Blood and blood products for transfuctio and/or manufacturing other products
- Gene therapies
- Cellular therapies

Biologics are created by biological processes, as opposed to being chemically synthesized (like "drugs"). Although the term "biologics" is often used to refer to cellular to tissue based products, it is also used in a broader sense to refer to "large molecule" products like protein based and nucleic based drugs.

2.2. "Biosimilar" refers to a biomedical product ("biologic") that is highly similar to an approved biologic and has no clinically meaningful differences in terms of safety, purity and potency. A biosimilar can be potentially less expensive than the originator and provide potentially increased access to biologic therapies. Because of the large and complex nature of biological molecules (as opposed to the smaller molecules of traditional drugs), biosimilars cannot be guaranteed to be identical to innovator biologics. Consequently various regulatory concerns arise from this "similar" but not "identical" nature of biosimilars. These concerns include undetected differences that may result in reduced efficacy or different adverse reactions. Quality assurance issues may also arise from manufacturing or delivery processes.

2.3. "Generics" are broadly defined as a drug product that comparable to an approved drug in dosage form, strength, route of administration, quality and performance characteristics. Because they are usually created using "small molecule," regulatory concerns regarding bio-equivalence are reduced. Under US law (Hatch Waxman Act) an abbreviated mechanism for approval of generic copies of approved drugs has been established that does not require pre-clinical or clinical testing be repeated for approval. Similar treatment has not been applied to biosimilars for the reasons listed above, among others.

3. **Current Legal Regimes Governing Biologics**

3.1. Various legal regimes have been put in place internationally to deal with the protection of biosimilars. Biologics raise many of the same issues regarding the patentability of medical "treatments" that have been debated for the past twenty years since the enacted of TRIPS. Thus, the historic background to protection for biologics under international and domestic patent regimes, and the policy regarding the scope of any such protection, remain largely the same as for traditional small molecule drugs. The major international instruments governing these issues include:

- Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS)
- The Convention on Biological Diversity (CBD)
- The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity
- Convention on Biological Diversity (CBD)
- European Union Directive on the Legal Protection of Biotechnological Inventions
- Andean Community Decisions 344, 486, 622

3.2. Various domestic regimes exist governing the marketing approval of biologics and biosimilars. They demonstrate various approaches related to the issues required to be examined, the degree of "similarity" required and the need for clinical test data to demonstrate the necessary quality assurance to receive approval. They include:

- European Medicines Agency (EMA) Guidelines on Similar Biological Products
- Brazil ANVISA Guidelines on Biological Products
- US Biologics Price Competition and Innovation Act

4. **Patent Protection Issues**

4.1. Some biologics may qualify for patent protection despite its biogenetic basis. Patent protection must be granted under TRIPS Article 27(1) to inventions "in all fields of technology" that are "new, involve an inventive step and are capable of industrial application." According to the World Trade Organization (WTO) responsible for administering TRIPS

compliance, this requires patent protection for pharmaceuticals that meet the three-step test for patentability.

4.2. Although pharmaceuticals are generally protected under international patent law, Article 27(3)(a) of TRIPS specifically allows member nations to *exclude* from patentability " diagnostic, therapeutic and surgical methods for the treatment of humans or animals." For biologics that do not act as pharmaco-equivalents of drugs, countries may therefore decide to deny patentability on the grounds of their nature as a diagnostic or therapeutic treatment without violating international law.

4.3. Even if biologics otherwise qualify for patent protection on the grounds of their novelty, inventiveness and industrial application, they may face additional challenges to patentability as a result of their origins in biological materials. These challenges include concerns over either subject matter eligibility (US, "natural phenomenon exception"; Australia, "artificial state" requirement) and the role of patent protection on biologic research incentives.

4.4. **Patents and Biologics: The "Natural Phenomenon" Problem**

4.4.1. Regardless of whether exceptions to patent eligibility are worded in terms of "natural phenomenon" (US) or "manufacture" (Australia), countries are presently divided over what activities are necessary to secure patent protection for biological. One excellent example of this differing treatment is the dispute over whether isolation of naturally occurring DNA qualifies for patent protection. This issue arose in both the United States and Australia with regard to the patent protection available for the BRCA gene, used for tests to diagnose breast cancer. The holder of the patent in both instances was Myriad Genetics.

4.4.2. In both cases, plaintiffs challenged the validity of various claims relating to the patentability of "isolated" DNA and RNA genes a valid patent may be granted for a claim that covers naturally occurring nucleic acid – either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) – that has been "isolated." Briefly, an isolated gene is one that has been removed from the cellular environment in which it naturally exists and separated from other cellular components also found there. At issue was the BRCA 1 and 2

genes which related to human breast cancer susceptibility and was used by the patentee in various tests to diagnose breast cancer susceptibility.

4.4.3. **US: Association For Molecular Pathology v. Myriad Genetics, Inc. (Supreme Court 2013)**

4.4.3.1 At issue in the United States was whether the simple act of isolating the BRCA genes qualified as potentially patentable act or was the isolated gene instead merely an unpatentable natural phenomenon. Ultimately, the Supreme Court held that isolated DNA and isolated RNA did not qualify as patentable subject matter. Even though the isolated gene might not necessarily occur in nature, the Court did not believe that the act of isolation itself was a sufficiently inventive act to alter the fact that patent protection would serve only to protect the information contained with the DNA strand. This information occurred in nature and was not altered by the simple act of removing chemical elements that did not affect such information: "Nor are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a non-naturally occurring molecule. Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes."

4.4.3.2. Although the isolated DNA and RNA were *not* patent eligible, the Court nevertheless found that complementary DNA (cDNA) did qualify as patent eligible subject matter because it was created with the input of a lab technician and was distinct from naturally occurring DNA: "cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it was derived. As a result, cDNA is not a "product of nature" and is patent eligible under §101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA."

4.4.3.3. The Court specifically did not address any method claims related to the isolation of the gene at issue: "Had Myriad created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method patent. But the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents..." The Court also did not consider to what extent

an alteration of genetic code might create patentable subject matter since that issue was similarly not before the Court: "Scientific alteration of the genetic code presents a different inquiry, and we express no opinion about the application of §101 to such endeavors. We merely hold that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material."

4.4.4. **Australia: Cancer Voices Australia v. Myriad Genetics, Inc (Federal Court 2013)**

4.4.4.1. Under Australian law an invention must be a "manner of manufacture" to qualify as patent eligible subject. The term has been broadly interpreted to require the invention demonstrate an "artificial state" to distinguish it from an unpatentable discovery: "It is trite law that you cannot patent a discovery, but if on the basis of that discovery you can tell people how it can be usefully employed, then a patentable invention may result." More precisely, the Court in *Cancer Voices* stressed: "A composition of matter may constitute patentable subject matter if it consists of an artificial state of affairs, that has some discernible effect, and that is of utility in a field of economic endeavor... It goes without saying that the relevant state of affairs must be the result of some human intervention. …The real problem lies in knowing, or rather not knowing, what degree of human intervention is necessary before it can be concluded that the requisite artificial state of affairs exists."

4.4.5.2 Applying the "artificial state" test, the Court found that the isolated genes qualified as patent eligible subject matter: "In the context of biological material, an artificial state of affairs may manifest itself in different ways. The physical properties of the naturally occurring material may have changed as a result of it having been isolated. But even if the physical properties of the material have not changed, the removal of the material from its natural environment and its separation from other cellular components may still give rise to what might reasonably be described as an artificial state of affairs." It went to explain that it did not matter what types of chemical bonds were broken or remained in the isolated gene for it to qualify: "[I]n the absence of human intervention, naturally occurring nucleic acid does not exist outside the cell, and 'isolated' nucleic acid does not exist inside the cell. Isolated nucleic acid is the product of human intervention involving the extraction and purification of the nucleic acid found in the cell.

Extraction of nucleic acid requires human intervention that necessarily results in the rupture of the cell membrane and the physical destruction of the cell itself. And purification of the extracted nucleic acid requires human intervention that results in the removal of other materials which were also originally present in the cell. It is only after both these steps are performed that the extracted and purified product may be properly described as 'isolated' in the sense that word is used in the disputed claims."

4.4.5. **Incentivizing Research and Innovation**

4.4.6.1. Even if a biologic qualifies as patentable subject matter, the invention may still lack sufficient "inventiveness" to be protected. As demonstrated below, this lack of "inventiveness" is described in various ways. However, at the heart of any such consideration is the ongoing concern that an overly broad scope of patent protection for biologics may increase research costs to such an extent that access to medicines is severely circumscribed.

4.4.5.2 In *Cancer Voices Australia v. Myriad Genetics, Inc* (Federal Court 2013), the Australian Court cited the great effort required to support its determination that the isolated BRCA gene was patentable: "The isolation of a particular micro-organism may require immense research and intellectual effort. … It would lead to very odd results if a person whose skill and effort culminated in the isolation of a micro-organism (a fortiori, an isolated DNA sequence) could not be independently rewarded by the grant of a patent because the isolated micro-organism, no matter how practically useful or economically significant, was held to be inherently non-patentable. In my view it would be a mistake..."

4.4.5.3. By contrast in *Association For Molecular Pathology v. Myriad Genetics, Inc.* (Supreme Court 2013), the US Court found that effort and cost alone were not sufficient to tip the balance in favor of patentability even though it recognized that "the study of genetics can lead to valuable medical breakthroughs." To the contrary, "[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the §101 inquiry."

4.4.5.4. Similarly, in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), demonstrates the issues of specificity that can arise when new biological tools and treatments are involved. In this case the Court ultimately upheld the applicant's patent on a composition that was claimed to have "antitumor

properties." Fortunately for the patentee the Court found sufficient specificity of the diseases against which the compound was useful, even though the application only defined by a rather oblique reference. But Brana underscores the difficulty of securing patent protection for early biologics where the precise utility is not clear. It also underscores that at every step where protection is sought, patent administrators and judges continually balance the need for patent protection with a concern to avoid unwarranted rights that might unduly restrict public access to new discoveries and new treatments by granting protection at too early a stage in the research and development process.

4.4.6. **New Uses**

4.4.6.1. Because the bio-genetic materials from which biologics and biosimilars are created pre-dates such creation, absent some genetic alteration to such pre-existing materials, there is a strong reluctance in some countries to grant patent protection for new uses. This may be one of the most contentious issues biologics may face. Various short-hand terms are used to refer to the issue – "new use," "second use," "evergreen." These "new use" patents may include new dosage regimes, new methods for securing efficacy or even new uses for known substances.

4.4.6.2. Under US law, new uses are subject to patent protection so long as such uses meet remaining patentability requirements – novelty, non-obviousness, utility, etc.

4.4.6.3. Article 18:8 of the recent Free Trade Agreement between the Republic of South Korea and the United States similarly requires patent protection be available for new uses: "[E]ach party confirms that patents shall be available for any new uses or methods of using a known product."

4.4.6.4. Canada similarly provides that a new use of a "known compound" qualified as a potentially patentable "because it involved the application of new knowledge to effect a desired result which had undisputed commercial value. (Shell Co. v. Commissioner of Patents (Canadian Supreme Court 1982).

4.4.6.5. By contrast, in Article 16 of Andean Community Decision 344, such new use patents are expressly excluded from patentability: "Products or processes already patented and included in the state of the art ...may not be

the subject of new patents on the sole ground of having been put to a use different from that originally contemplated by the initial patent."

4.4.6.6. Similarly Section 3(d) of the Indian Patent Act provides: "The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance" is not an invention under the Act. This provision has been recently applied to the issue of patent protection for the drug Glivec (or Gleevec) used to treat certain cancers.

4.4.6.7 In *Novartis AG v. Union of India* (Indian Supreme Court 2013), the Court rejected Novartis' attempt to patent Gleevec (Glivec), a salt form of Imatinib. The Court found that Imatinib was a "known substance" under Article 3(d), making Gleevec, a new form: "To satisfy the requirement of being publicly known...it is not necessary that it should be widely used to the knowledge of the consumer public. It is sufficient if it is known to the persons who are engaged in the pursuit of knowledge of the patented product or process either as men of science or men of commerce or consumers." It went on to assert that tests for "efficacy" will depend upon the function, utility or purpose of the product" and held that for medicines "designed to cure a disease" the only test was "therapeutic efficacy." Determinations of enhanced therapeutic efficacy "must be strictly applied." Increased bioavailability alone may not necessarily lead to an enhancement of therapeutic effect.

5. **Access Restrictions on Biologics**

5.1. Similar to issues raised for traditional pharmaceutical drugs, patent protection may be restricted by issues arising from concerns regarding its accessibility in the domestic market. There is an emerging trend toward granting compulsory licenses to third parties or allowing the importation of grey market drugs when patented medicines are found to lack "reasonable accessibility" in the domestic market.

5.2. **Natco Pharma Ltd. v. Bayer Corp. (Indian Comptroller of Patents 2012) Nexavar**

5.2.1. Ultimately, the Comptroller granted a local pharmaceutical company in India (Natco) a compulsory license to produce Bayer's patented drug Nexavar on the basis of its domestic unavailability. This determination that Nexavar was not "reasonably access" was based on an analysis that focused

largely on the pricing structure for the drug and unmet local need: "It stands to common logic that a patented article … was not bought by the public due to only one reason, i.e., its price was not reasonably affordable to them."

5.3. **Petition to Challenge 2008 Anti-Counterfeiting Act (Kenya High Court 2012)**

5.3.1 In a challenge to the Constitutionality of legislation designed to combat counterfeiting, the High Court limited the Act's effect to avoid any adverse impact on the ability to import and distribute grey market goods to meet local demand. The decision was supported by reference to the fundamental right of consumers to affordable, essential medicines: "Fundamental right to life, human dignity and health...encompasses access to affordable and essential drugs and medicines including generic drugs and medicines. Insofar as the Anti-Counterfeiting Act severely limits [such]access, including generic medicines for HIV and AIDS, it infringes on the petitioners' rights to life, human dignity and health..."

6. **Prior Informed Consent and Traditional Knowledge Issues**

6.1. Because biologics are based on biogenetic materials, care is required to assure that prior informed consent is acquired for both human-based biogenetic materials and for knowledge about the utility of other biogenetic materials that may be used that is acquired from indigenous peoples..

6.2. Article 15(5) of the Convention on Biological Diversity (CBD) provides that "access to genetic resources shall be subject to prior informed consent of the Contracting Party providing such resources, unless otherwise determined by that Party." Article 15(7) requires countries to take appropriate measures "with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources." It further requires that any such equitable benefit sharing "shall be upon mutually agreed terms."

6.3. Originally derived from field of medical ethics in which a patient has the right to decide whether or not to undergo a particular medical treatment after being fully informed about the risks and benefits of that particular treatment, the obligation to secure prior informed consent in connection with the use and commercialization (commodification) of biogenetic materials appears in diverse international instruments. This obligation has been

extended to include an obligation to secure prior informed consent for the use of indigenous knowledge and practices ("traditional knowledge") related to such biogenetic materials. regarding

6.4. Various international treaties and conventions, including the Convention on Biological Diversity and the Nagoya Protocol, also expressly require that uses of traditional knowledge be subject to equitable benefit sharing with the indigenous peoples whose knowledge is being utilized. Non-monetary benefits are often considered as valuable as monetary benefits since they ultimately contribute to the tribe's ability to secure greater self-governance over future activities.

7. **Disclosure of Origins of Traditional-Knowledge Based Biologics**

7.1. Under TRIPS, there is no obligation under Article 29, governing disclosure in patent applications, to require non-indigenous-community-member-applicants to disclosure inventions that have been created using indigenous knowledge. There is also no obligation for such disclosures under governing international law standards for patent applications, including the Patent Law Cooperation Treaty.

7.2. Globally, efforts to impose a disclosure obligation have been tabled during various treaty negotiations, including the Patent Law Treaty. Some countries, such as Switzerland, Brazil, India, the Andean Communities and South Africa, however, do impose such a disclosure obligation.

8. The Future

8.1. With the increased focus on biologics internationally, we will continue to see evolving legal standards regarding the protection and marketing of biologics, including biosimilars. The battles will be hard fought and may well alter the landscape for pharmaceutical protection and access.