

How to Control the United States Pharmaceutical API Market Using Patents on New Synthetic Intermediate Compounds

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The multinational pharmaceutical industry now out-sources a much higher volume of active pharmaceutical ingredients from manufacturers in non-regulated markets such as Brazil, India and China. This economic change presents an opportunity for API manufacturers to potentially control the market in the United States for certain APIs, by capitalizing on a particular provision of US patent law. This paper reviews this law, examines several actual case studies under this law, and provides a check list of characteristics useful to identify the most valuable Active Pharmaceutical Ingredients (API) manufacturing opportunities.

Keywords: ANDA, pharmaceutical patent, drug patent, pharmaceutical economics, synthetic intermediate

USA Manufacturing Intermediate Patents are Extra-Territorial

Patents are national rights. In general, patents are 'territorial': that a patent issued by a particular country has effect only in the issuing country. Thus, for example, if a company obtains an Indian patent, then the company can use that Indian patent to stop infringement which occurs in India; the Indian patent would not, however, be particularly effective in stopping infringement in Brazil or China.

In the United States, however, synthetic process patents have a unique extra-territorial reach. This reach can perhaps best be understood in the context of a bit of American legal history.

In the early 1930s, an American mining engineer found a way to separate a desirable mineral (apatite) from crude mined rock using floatation. He obtained a US patent on this process. A mine in northern Russia mined rock and used the patented separation process in Russia to isolate apatite. The Russian mine sold the resulting apatite to an American distributor. The US patent owner sued the American distributor for importing and infringing apatite. The patent owner

lost. The US Court commented that the process was performed in Russia, not in the United States. The Court recognized that a United States patent is legally effective only within the United States. The Court thus concluded that performing the patented floatation process in Russia did not infringe the United States process patent in the United States.

In response, the United States changed its law. The law now says that if an inventor obtains a US patent covering a synthetic process, then the patent owner can prevent importation of products made by that process, even if the process is done outside the United States:

- (a) Except as otherwise provided in this title, whoever without authority offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention, infringes the patent.
- (b) Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer * * * A product which is made by a patented process will, for purposes of this title, not be considered to be so made after -(1) it is materially changed by subsequent processes.

The general intent of the law is clear: If apatite is isolated by floatation in Russia, then the resulting apatite cannot be imported into the United States. If,

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however, the apatite is used in Russia to make, for example, mineral acid, then anything made with the mineral acid, and perhaps the mineral acid itself, could be freely imported into the United States.

The legal exception for synthetic process intermediates which are 'materially changed by subsequent processes,' however, is often misunderstood in the pharmaceutical context. For example, synthetic process intermediates are neither therapeutically active nor approved by the relevant medicinal regulatory agencies. Thus, a common assumption is that finished API compounds are so materially different from the precursor intermediates that the API compound is 'materially changed' from the intermediate.

This assumption is incorrect.

For example, most chemists would agree that a polypeptide is quite different from the DNA sequence coding for that polypeptide. Chemists would also likely agree that the polypeptide is more than a 'materially changed' modification of the precursor DNA sequence, but is an entirely new chemical entity altogether.

This difference appeared important in the early development of the biotechnology industry. By the mid-1990s, the first biological products had been approved for sale in the United States. One biological product manufacturer (Genetech Corporation) obtained a US patent on a plasmid coding for its human growth hormone product.

At that time, biotechnology patents were still disfavoured outside the United States. Competitors could thus legally use the same plasmid outside the United States. One competitor, an Israeli generic manufacturer¹ used the plasmid outside the USA to make the biological product, and then imported the finished biological product into the USA. Genetech and the Israeli generic company wound up in court.

The Israeli company noted (correctly) that the active ingredient itself (human growth hormone) is a generic compound. The Israeli company also noted that Genetech's patent merely claimed a plasmid, rather than the generic active ingredient. The Israeli company noted that while it used the plasmid, it used it in Israel, not in the United States. The Israeli company did not import the plasmid into the United States, and did not even import any 'materially changed' version of the plasmid. Rather, the Israeli company only imported a polypeptide produced using the plasmid. The Israeli company thus argued that its polypeptide was not covered by the plasmid patent.

The Court, however, noted that the plasmid was an 'essential part' of the process to make the polypeptide. The Court thus concluded that importing the polypeptide infringed the patent on the plasmid.²

Two aspects to this decision are monumental for the Indian API industry.

First, the Court recognized that the active ingredient itself (human growth hormone) is generic. The Court thus did not preclude the Israeli generics manufacturer from making generic human growth hormone. all competitive sales of human growth hormone. The Court only precluded sale of human growth hormone made using a plasmid. The Israeli company (indeed, anyone in the world) could thus use any other technology to make human growth hormone, for example, solid-phase polypeptide synthesis was available, albeit that technology was still in its infancy, and would prove cost-prohibitive commercially.

Alternatively, extraction from the pituitary glands of human cadavers had already long been employed to make the polypeptide. This approach, however, requires a supply of fresh human cadavers (and thus is less reliable commercially) and exposes patients to potential prion infections. This ruling is quite narrow from a legal standpoint. As a practical matter, however, it was broad enough to provide Genetech with a monopoly position.

This is because the alternative synthetic routes were prohibitively expensive, or unreliable due to supply constraints. Thus, the legally-narrow court ruling precluded the sale of any competitive generic product except those which by their nature were commercially unfeasible. Thus, the legally-narrow court ruling gave the plasmid patent owner an effective monopoly on a generic active ingredient. Second, this decision shows how the legal meaning of 'material change' is different from the scientific meaning. A chemist would undoubtedly say that a polypeptide is quite different from a poly-deoxyribonucleic acid sequence coding for that polypeptide. In contrast, however, the three-judge panel which ruled on the human growth hormone case did not find human growth hormone materially changed from a DNA plasmid.

This is important because the difference between a DNA plasmid and its polypeptide product is, chemically speaking, far greater than the difference between a small-molecule organic synthetic intermediate compound and its API product. If a

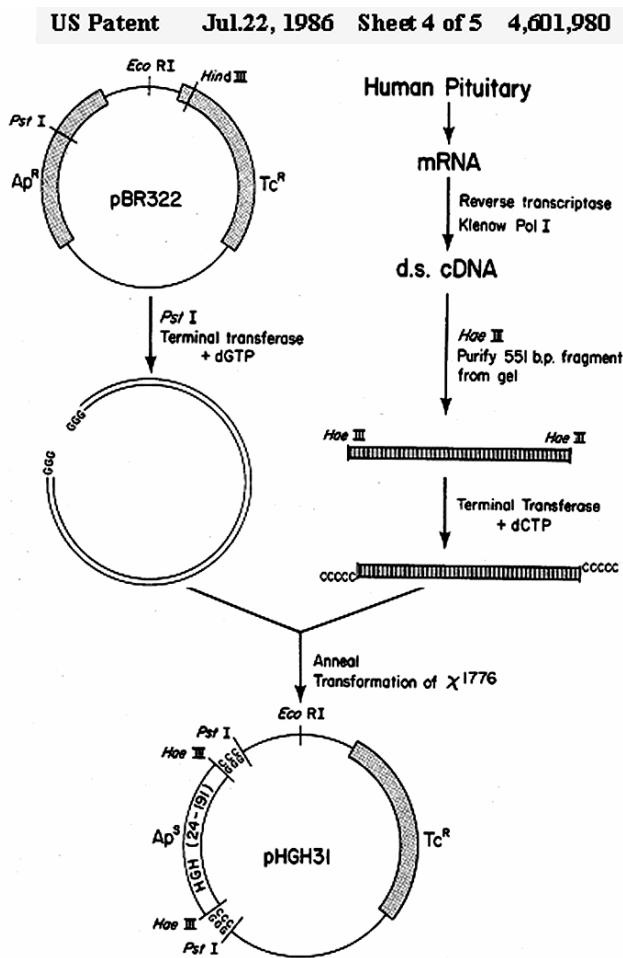


Fig. 1—Microbial expression of a gene for human growth hormone

polypeptide is not considered 'materially changed' from the poly-deoxyribonucleic acid plasmid coding for it, an API would seem by contrast to be even less 'changed' from its precursor intermediates - and thus entitled to greater protection using a synthetic intermediate patent.

How to Identify Valuable API Manufacturing Opportunities

The Most Valuable API Manufacturing Opportunities Share Three Characteristics

The most valuable generic API manufacturing opportunities share certain common characteristics. These common characteristics are found by examining the synthetic pathway used to make the API; where the synthetic pathway has these characteristics, the generic API manufacturing opportunity can be truly exceptional. For example, while human growth hormone is a generic active

ingredient, Genentech used that generic API opportunity to build one of the largest pharmaceutical companies in the world. The most profitable generic API manufacturing opportunities share the following characteristics:

- 1 The synthetic route used provides a material economic advantage over alternative methods.
- 2 At least part of the synthetic route is patentable.
- 3 The synthetic route used leaves on the resulting API a unique analytic 'fingerprint' which can be detected by analytical methods.

The Manufacturing Process Provides a Significant Economic Advantage versus Alternative Pathways

Most APIs can be synthesized using any of several alternative pathways. With human growth hormone, however, the various synthetic pathways are not always equal economically. One characteristic shared by the most attractive API manufacturing opportunities is that the synthetic pathway used is clearly superior from other pathways economically.

Economic superiority can come from any of a number of aspects. Certain synthetic routes require less expensive reagents, or may require less purification of the resulting crude API, or may use less toxic (and thus less expensive to dispose of) solvents. Any of these can provide an economic advantage.

It is critical, however, that the economic superiority be significant, not merely marginal. This means that the process used should reduce the cost of goods sold for the API so much that the API cost differential will impact the cost of the final finished dosage form.

This is not easy to accomplish because as a fraction of the cost of goods sold for the final finished dosage form, the cost of the API is generally not large. For example, in the human growth hormone case studied earlier, the cost of the recombinant human growth hormone accounted for only about five percent of the cost of the final finished dosage form. A minor improvement in its synthetic process would have produced only a minor change in the cost of the API: this would be a minor change in an accounting line item which accounts for only five percent of the total cost of the finished product. The human growth hormone plasmid patent was so successful in large part because the plasmid-based method produced a large economic improvement viz the other available alternatives.

The smaller the contribution of API cost to the total cost of the finished dosage form, the larger the cost savings which the API process must provide, to achieve a measurable, material economic advantage for the finished dosage form. For example, in the human growth hormone manufacturing the product using a plasmid provided a far more consistent and reliable commercial supply than the previously-used alternative - extraction from human cadaver pituitary glands. Thus, the recombinant plasmid-based synthetic scheme provided a clear economic advantage over the available alternative pathways.

The most commercially valuable generic API manufacturing opportunities employ a manufacturing pathway which provides a significant economic benefit compared to the available alternative synthetic pathways. Significantly, it is exactly this kind of invention - refining and improving synthetic process chemistry - for which Indian chemists are so well known.

Part of the Manufacturing Process is Patentable

Some part of the manufacturing process must be patentable.³ The entire process need not be patentable. Rather, only part of the process needs to be patentable. This part can be, for example, a unique intermediate compound, or the use of a new and different starting material.

The part which is patentable need not be the product itself, nor any particular quality or characteristic of the API product itself (This finding questions the current industry practice of patenting any new polymorphic form of an API). The part of the synthetic process which is patentable, however, should be the part which is responsible for the process' relative commercial or economic advantage. For example, in human growth hormone Genetech did not obtain a patent on the active ingredient itself, nor on the entire process of producing it. Rather, Genentech patented only one small – but critical – component of its more cost-effective manufacturing process.

The part must be patentable, rather than merely secret. Many drug products have used secrecy to maintain profitable long-term franchises. Wyeth's Premarin® conjugated estrogens, for example, have been manufactured under a secret process for perhaps sixty years. This secrecy has made it quite difficult for several generic manufacturers to launch true generic copies of Wyeth's product.

Secret manufacturing processes provide protection for innovator products. In contrast, a generic product must by definition copy the innovator product closely. Thus, in practice it is extremely rare for a secret manufacturing advantage to provide a long-lasting commercial advantage to a generic product. The manufacturing process must be at least partially patentable.

The Manufacturing Process should Leave an Analytic Fingerprint on the Resulting API

Enforcing a synthetic intermediate patent, as with any other patent, requires the patent owner to show how the alleged infringer uses the patented synthetic process or intermediate compound to make its API. If the accused infringer does not publicize their synthetic process (and accused infringers rarely do), it can be difficult to obtain this evidence before filing a lawsuit. Thus, several process patent cases have been dismissed because the patent owner could not show that the accused infringer used the patented intermediate. For example, several years ago, a textile manufacturer sued the United States government, alleging that the Department of Defense infringed a patent on making camouflage-dyed fabrics. The textile manufacturer lost the case, however, because it could not show that the Department of Defense's outside contractors actually used the patented process.

Thus, the most valuable synthetic intermediate patents are those where the particular synthetic pathway leaves a characteristic analytic 'fingerprint' on the finished API, so that a quantitative chemical analysis of the API can determine whether or not the API was synthesized using the patented pathway or another, non-patented alternative pathway.

While advantageous, the presence of an analytical fingerprint is not essential. If one is unsure about whether or not the competitive product was made using the patented pathway, there are various legal ways to address the situation. Nonetheless, it is far less expensive, and more reliable, to rely on an unambiguous and predictable scientific fingerprint than to rely on an inherently unpredictable legal procedure.

Enforcing a synthetic intermediate patent also requires complying with certain somewhat arcane procedural rules. For example, Section 287(b)(2) of the process patent statute requires the patent owner to notify the accused infringer of alleged

infringement and to do so in a particular fashion, and by a particular deadline, etc. A patent infringement lawsuit filed by Celanese Corporation was recently dismissed simply because Celanese's lawyers failed to provide notice to the accused infringer by the legally-required deadline.⁴

These kinds of failures have supported a misconception that synthetic process patents are weak. This is incorrect: these failures are on the large more procedural than substantive – they impact how your USA based law firm will accomplish a patent enforcement action, not whether or not they can accomplish it. The arcane procedural rules governing how to enforce a synthetic intermediate patent do not limit the underlying legal scope and power of synthetic process and intermediate compound patents.

How to Proceed if the API does not have These Characteristics

If the API manufacturing opportunity has these characteristics, then the API may provide an exciting opportunity, as did human growth hormone. In contrast, where the API does not have at least two of these three characteristics, certain industry statistics inform our decision on whether or not to pursue patent protection.

Patents are Expensive to Enforce

First, patents are expensive to enforce. The fixed legal costs of enforcement can exceed the value of the patent itself. For example, in a statistical sample of 28 patent lawsuits in calendar year 2007 in New York City involving minor patents - patents worth less than US\$ 1,000,000 - the legal cost to enforce these patents averaged US\$ 1,107,000. Put another way, the cost to enforce a patent worth less than US\$ 1,000,000 is more than US\$ 1,100,000. Thus, legal costs exceed the value of the patents themselves.

Further, these costs are for an average patent. Some patents involve quite simple technology: a new folding chair design (Fig. 2), for example. In contrast, pharmaceutical and biotechnology patents are the most technologically complex type of cases (Fig. 3). This greater technological complexity increases the amount of work needed to educate the judge and jury on how the relevant technology works. Thus, biotechnology and pharmaceutical lawsuits are typically more expensive than the average patent case, and define the most-expensive quartile of patent litigation cases. In calendar year 2007, the most expensive quartile of patent lawsuits

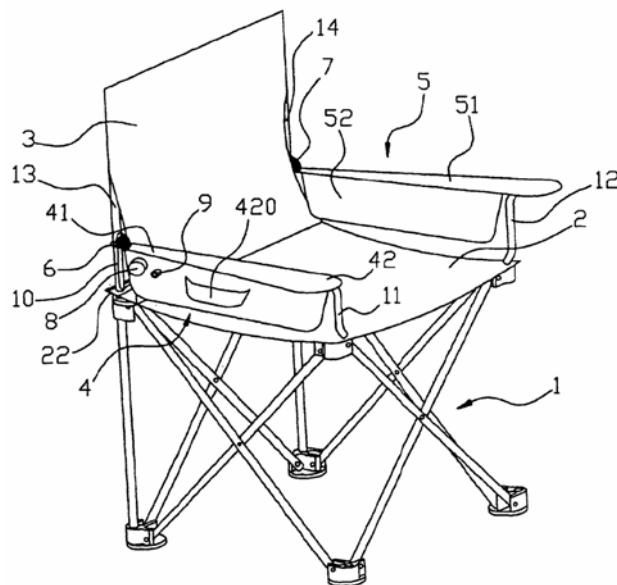
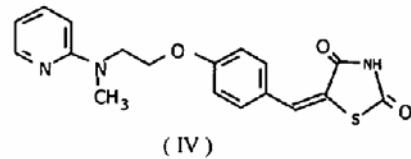
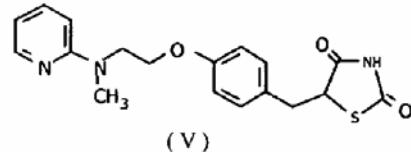


Fig. 2—New folding chair design



5-[[4-[2-[N-Methyl-N-2-(Pyridyl) amino] ethoxy] benzylidene] thiazolidine-2,4-dione.

THF / CoCl₂ / DMG / DMF / NaBH₄
↓
Methanolic ammonia



5-[[4-[2-[N-Methyl-N-2-(Pyridyl) amino] ethoxy] phenyl methyl] thiazolidine-2,4-dione.

Fig. 3—Pharmaceutical formulation

for minor patents in New York City cost US\$ 1,500,000. Put another way, the cost to enforce a pharmaceutical patent worth less than US\$ 1,000,000 is more than US\$ 1,500,000. Thus, the cost to enforce a drug patent worth less than US\$ 1,000,000 is 50% more expensive than the value of the underlying patent.⁵

Cases involving higher-value patents have legal enforcement costs which are a smaller percentage of the patent value. Legal enforcement costs, however,

increase consistently with increase in patent value. Given this economic landscape, it may be most economically rational to simply abandon certain patents rather than pay to enforce them.⁶

Patents are Risky to Enforce

Simply spending a significant amount to enforce a patent does not assure victory. To the contrary, most patent cases go against the patent owner, find the patent either invalid or not infringed.

For example, in calendar year 2007, of the cases addressing alleged obviousness (or lack of inventive step), the trial court found the patent obvious in 34 of 68 total cases, or fully half of the time. Similarly, of the cases addressing alleged anticipation (or lack of novelty) under US Section 102(b), the trial court found the patent anticipated in 20 of 34 total cases, or *over* half of the time. Similarly, in cases addressing literal infringement, the trial court found the patent not directly infringed in 167 of 228 total cases, or in fully three out of four cases. (!)

Thus, it is statistically more likely than an accused infringer will escape liability, either because the patent is found invalid or because the patent is found not infringed. Given the high cost of enforcement, and the statistical likelihood that a patent will be found invalid or not infringed, it may be most economically-rational for many patent owners to simply abandon any patent which is not worth at least several times the fixed cost of enforcement.

Patents are Expensive to Obtain

Patents are expensive to obtain. In calendar year 2007, the cost to prepare a reasonably complex United States biotechnology or pharmaceutical patent application averaged US \$15,000 in both Boston and San Francisco, two biotechnology centres. This is simply the average cost to prepare the application: in addition, a patent applicant must also pay government filing fees, and the legal fees required to respond to inquiries from the patent examiner, to amend the application, to perhaps pursue an administrative appeal, et cetera. Further, this is the average cost to prepare one application (generally, one 'independent' patent claim and nine accompanying 'dependent' claims). Most biotechnology cases, however, involve at least half a dozen independent claims which often evolve into half a dozen different patent applications.

Patents resist cost-containment efforts because of the likelihood a patent will be found valid and infringed in litigation is to a certain extent a function of cost. Cutting corners in obtaining the patent increases the risk that the resulting patent will ultimately be on the wrong side of the litigation statistics discussed above and be found invalid or non-infringed.

Further, the relation of cost to value is not a normal statistical distribution, but appears to be a discontinuous function: perhaps ninety-five percent of all US patents have a value of approximately zero. This is evidenced by patent abandonment statistics. To maintain a US patent, the owner must every four years or so pay a nominal government maintenance fee, currently about US \$1,000. A rational patent owner would pay the \$1,000 maintenance fee whenever the owner believes the patent is worth more than the \$1,000 fee due. Surprisingly, however, the overwhelming majority of US patents are voluntarily abandoned because the owner fails to pay the maintenance fee. This indicates that patent owners believe that most of their US patents are worth less than US \$ 1,000: less than the government filing fees required to file the patent application in the first place. This intimates that less-expensive patents are not merely less valuable, but are entirely valueless.

How to Minimize Patent Expense

These statistics show a need to minimize patent expense. There are several ways to do this. One approach is to impose tight budgets on all patent applications. This approach reduces the up-front cost of patenting, but creates the risk that one's patent portfolio will ultimately consist simply of a large number of weak patents, none of which is worth the expense and risk of enforcement.⁷

Another approach is to evaluate each potential patent filing before even beginning to prepare the patent, by determining whether the invention has the three characteristics described above. Inventions which do not display at least two of the three characteristics discussed above arguably should not be patented at all. These inventions, even if patented, likely will not be valuable enough to justify the additional investment required to legally enforce the patent against an alleged infringer. Every patent application which you do not file saves you perhaps US\$ 20,000 in preparation and government filing fees

alone – capital which you can use to thoroughly protect those few inventions which meet three criteria.

Conclusion

Evaluating potential new generic API manufacturing opportunities requires Research & Development professionals to collaborate with colleagues in marketing and in business development, to assess whether the API can meet each of the three factors which the most-successful generic API manufacturing opportunities share.

To learn more about the topic, you can apply to attend web-based seminar on intermediate patent prosecution strategies. To apply, send an email to newsletter@LicensingLaw.net, stating your contact

information and corporate affiliation, and the web seminar topic of interest

References

- 1 Strictly speaking the Israeli manufacturer's product was not a 'generic' product, because there was no regulatory regime for bio-similar products, so a new drug application was required.
- 2 Patent Applications Library, www.LicensingLaw.net, or email to Newsletter@LicensingLaw.net.
- 3 *Sun Pharmaceuticals Lecture*, http://www.licensinglaw.net/Patent_Applications_Library.htm.
- 4 Newsletter@LicensingLaw.net.
- 5 Litigation Library, www.LicensingLaw.net.
- 6 Another solution is provided by Pharmaceutical Patent Attorneys, LLC (Morristown, New Jersey), which finances drug patent litigation.