

One World, Many Regulations

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DIGITAL STOCK

WHEN ENTERING GLOBAL AGREEMENTS, PHARMA COMPANIES MUST BE INFORMED, FLEXIBLE, AND CREATIVE.

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The ability to compete globally is essential to success in the pharmaceutical industry. The current trend is to establish joint ventures, outsource various stages of the development and production of a single pharma product, and purchase or start an indigenous business in other countries. Successful companies have also moved beyond mere exploratory attendance at trade shows to gain familiarity with foreign markets and environments that are sometimes very different than their "home field." Executives sophisticated in handling cultural distinctions and regulatory nuances have a distinct advantage. (See "Culture Clashes," page 2.)

Understanding cultural differences is

part of the secret to success; the other is knowing the company's legal rights, or more significant, its lack of rights in a particular foreign country. Companies need to be familiar with broad multilateral rules to be able to recognize those rights and make informed decisions about foreign initiatives.

This article examines the broad legal framework every pharma producer faces when developing, servicing, pursuing clinical evaluation, selling, or manufacturing components in foreign countries. A general understanding of the international legal regime that governs the actions of various countries can help pharma executives know what to anticipate and how to react.

Patent Protection

Because of their high R&D and other commercialization costs, pharma companies' most compelling international need is to maximize patent exclusivity—in years and in geographic scope. Time here is measured not only in how long

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and how well a foreign country provides patent protection but also in how easily and quickly a new product can be brought in to its market. In foreign pharma markets, getting it right the first time may be the difference between success and failure. Getting it wrong can mean competing against the company's own product in places no one thought possible, sooner than expected.

The United States continues to be the leader in providing patent protection for innovative products, but the clear driving force today is the multilateral efforts under the auspices of the World Trade Organization (WTO) to promote and refine the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Although TRIPS was initiated through the Uruguay Round of multilateral trade negotiations and signed by the member-nation leaders on April 15, 1994, it continues to be the subject of much debate. Negotiations on various aspects of TRIPS continued during a second meeting in Doha, Qatar in 2001. A detailed analysis of the TRIPS agree-

ment and the pharma industry is available at www.wto.org/english/tratop_e/trips_e/pharmpatent_e.htm.

The agreement requires all WTO members to create working intellectual property systems that not only establish basic legal definitions of intellectual property rights—such as patents, trademark registrations, and copyrights—but that also implement efficient registration procedures and effective enforcement regimes. TRIPS patent protection extends to products and processes and must last at least 20 years from the date the patent application was initially filed.

The implementation of TRIPS is essential to the successful internationalization of the pharma industry. If anything, the agreement's negotiations and discussions have identified the relevant areas of weakness and controversy that need resolution both in the agreement and in the interests of developed versus developing countries. Developing country members have made progress meeting their TRIPS obligations but have yet to fully satisfy them.

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the “mailbox” provision. The process allows an early filing date so the application can satisfy a patenting criteria, such as “novelty.” Second, should the country allow the product to be marketed during the transition period, it must give the patent applicant an exclusive marketing right for five years or until a patent decision is made, whichever period is shorter. Although there may yet be others, 13 WTO members have notified the TRIPS council that they have implemented a mailbox system. They include Argentina, Brazil, Cuba, Egypt, India, Kuwait, Morocco, Pakistan, Paraguay, Tunisia, Turkey, the United Arab Emirates, and Uruguay.

India poses a particular problem. Opting for the permissible January 1, 2005 patent-protection deadline, the country has still failed to implement other TRIPS obligations, including protection for proprietary data of inventor companies and various enforcement and judicial remedies. The failure means that India's industrial property system is the default regulatory regime, which was initially structured to permit domestic companies to pirate the inventions of other countries.

As another example of particular problems, the TRIPS agreement allows member countries to provide for the use of patented inventions for R&D. Some countries take this notion further by allowing generics manufacturers to obtain marketing approval from government authorities without the patent holder's permission and before the patent protection expires. This practice is some-

Culture Clashes

Although understanding legal and business issues is obviously important to any international business deal, cultural norms are critical, too, particularly in the initial investment stage. Most US executives are familiar with what can be called the “New York style” of doing business, one that implies speed, directness and, often, impatience. Some experienced foreign counterparts may expect that approach, but it can be disconcerting, at best, to executives from an Asian, Latin American, or European country, where it is common to show reticence and to accept things that may be difficult.

Foreign business leaders often need to spend several months getting to know a prospective US company. That delay can be frustrating for executives who want to get the job done in a more “efficient” manner. It may be necessary, however, to be understanding and accommodating in such situations just to get the job done.

In Development

WTO developing country members—including Argentina, Brazil, Egypt, India, and Israel—were given a five-year grace period, until January 1, 2000, to implement most of their TRIPS obligations, but the success of such implementation remains under review and is subject to interpretation. The least-developed WTO members—primarily countries in Africa—were given an 11-year transition period, until January 1, 2006, but that deadline may be extended. Pharmaceutical products are subject to an additional waiver that allows for the delay of product patent protection by all developing countries until January 1, 2005. On June 27, 2002, the WTO TRIPS Council approved a decision extending the waiver for the least-developed countries until 2016.

The countries able to benefit from the extension have two obligations. First, they had to allow patents to be filed, starting January 1, 1995, even though they are not required to decide about whether to grant any patent until January 1, 2005—commonly referred to as

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times called the “regulatory exception” or “Bolar” provision. A Canadian law implementing the practice was upheld as consistent with the TRIPS agreement in a WTO dispute settlement panel report adopted by the WTO Dispute Settlement Body on April 7, 2000. But such provisions can be poorly implemented and counterproductive to future R&D.

In Australia, for instance, a 1998 patent-term extension law permits “springboarding,” which allows generic manufacturers to do all the required testing before the expiration for patents that were granted extensions under the 1998 law. Australia justified that Bolar provision on the grounds that the new extension for existing patents was a boon to the present patent holders, which necessitated a matching offset favorable to producers of generic products. Current patent holders complain that a springboarding compensation was not necessary considering the increasingly long delays in market approval resulting from the strict requirements for cost-effectiveness data and the difficulties of getting listed on Australia’s Pharmaceutical Benefits Scheme, the government-run prescription program.

Without immediate access to the market, patent holders that were granted extensions are unable to get sufficient returns under patent exclusivity to in-

vest in future R&D. Australia’s recent enactment of a law providing for five years of confidential data protection alleviates some of the concerns about springboarding, but it would be better if it were extended to ten years and covered already-approved chemical entities. For a review of other examples of specific problems with various countries patent regimes, see the US Trade Representative’s “Special 301” Report on Intellectual Property Barriers, www.ustr.gov/enforcement/special.pdf.

Without Permission

One potential problem is that the TRIPS agreement permits compulsory licensing in certain situations subject to certain controls. In compulsory licensing, a government permits someone other than the patent holder to produce the patented product or process without the patent holder’s consent. A compulsory license

- must not be arbitrary
- cannot be given exclusively to a single licensee
- must be granted primarily to supply the domestic market
- must pay the patent holder adequate remuneration.

Except in cases of national emergencies, other circumstances of extreme emergency, government use, or anti-competitive cases, the entity seeking a

compulsory license must have first attempted unsuccessfully to obtain a voluntary license from the rights holder on reasonable commercial terms.

Some countries abuse compulsory licensing by making it overly broad and extending it to situations for which it never was intended. In Singapore and Vietnam, for instance, a compulsory license can be granted to sanction insufficient or “unreasonable” working of the patented invention, which is ripe for abuse and unnecessary in today’s competitive atmosphere. Other countries, such as Bulgaria and Hungary, do not expressly recognize importation of a patented drug as evidence of “working the patent,” which should be made an express part of any compulsory licensing law, as the Czech Republic recently did.

Domestic manufacturing should not be necessary to satisfy the requirement. Argentina allows compulsory licenses to export patented inventions when the license was granted because of a national emergency. Granting compulsory licenses to produce products for export likely violates the TRIPS requirements that compulsory licenses be limited to allow use predominantly in the domestic market. The issue has been at the forefront of recent TRIPS negotiations because it does hamstring those countries truly lacking in manufacturing capacity from importing cheaper generics from countries where pharmaceuticals are patented.

Nevertheless, in light of the potential for abuse, US pharmaceutical companies should be careful in negotiating with foreign companies to ensure that they do not help establish the basis for a compulsory license. All negotiations with foreign competitors, suppliers, and others should be taken seriously, documented, and usually conducted with some input from legal counsel. Establishing a record of the reasonable commercial terms of the negotiation and what would qualify as adequate compensation may prove to be prescient if a compulsory license situation arises.

Spending Time

If that line from the Eagles’ song were

The Demise of Duties

During the Uruguay Round of multilateral trade negotiations, tariffs were considered the most significant problem. Consequently, as part of the Uruguay Round Agreements, the United States and 21 other major trading countries agreed to the reciprocal elimination of duties on approximately 7,000 pharmaceutical products and chemical intermediates used in the production of pharmaceuticals as well as certain derivatives of pharma products.

The 22 countries also agreed to conduct a review, at least once every three years, to identify additional products that could be covered by the pharma

duty elimination initiative. The first review added 496 items and was implemented on April 1, 1997. A second review is underway and has produced a list of 642 items under consideration. The International Trade Commission’s report on the second review provides a summary of those activities and future plans: See Advice Concerning the Addition of Certain Pharmaceutical Products and Chemical Intermediates to the Pharmaceutical Appendix to the Harmonized Tariff Schedule of the United States, www.usitc.gov/wais/reports/arc/w3167.htm.

Flexibility Under TRIPS

The Doha Declaration of the TRIPS Agreement and Public Health expressly recognizes the following flexibilities:

- In applying the customary rules of interpretation of public international law, each provision of the TRIPS agreement shall be read in the light of the object and purpose of the agreement as expressed, in particular, in its objectives and principles.
- Each member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted.
- Each member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood

that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria, and other epidemics, can represent a national emergency or other circumstances of extreme urgency.

- The provisions in the TRIPS agreement that are relevant to the exhaustion of intellectual property rights leave each member free to establish its own regime for such exhaustion without challenge, subject to the “most favored nation” and national treatment provisions of Articles 3 and 4. A complete copy of the agreement is available at www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm.

revised to “you can spend all your time making money, or you can spend all your money wasting time,” it would ring true for the pharma industry abroad. The time under patent protection is not measured solely in how long or even how well a country provides patent protection, but also in how easily and how quickly a new product can be brought to market in that country.

In other words, the period during which a drug can be sold under patent exclusivity is now a function of how long patent protection is afforded for a product and how soon the product can begin to enjoy such protection. That holds true now more than ever, because TRIPS specifies a 20-year patent protection from the patent filing, inclusive of the time it takes to get the drug to market. Although that issue was discussed during the Uruguay Round negotiations, the TRIPS agreement does not include an obligation to extend the patent term to account for commercialization delays, but some industrialized countries do compensate for the lost time in their patent laws.

The best way for pharma companies to avoid spending time wasting money and instead, spend that time making money, is to take early stock of the foreign country’s regulatory regime for drug approval. They should seek coun-

tries with transparent regulatory approval procedures coupled with predictable time frames and should use an experienced legal practitioner as their guide. Red flags to look for include

- strict data requirements, such as stability or cost-effectiveness data
- quasi-governmental approval authorities such as public hospitals rather than established agencies
- duplicative local testing and clinical trial requirements
- repetitive and costly certification documentation.

Additional study requirements also may present a time-consuming obstacle to drug approval. Compounds that must be screened for ethnic sensitivity often can be approved for use in various populations without clinical data from those populations. Sometimes there is a need to conduct a “bridging study” in the population that demonstrates ethnic sensitivity to the drug. But some countries require bridging studies that are not scientifically necessary, causing significant delays in registration. Korea, for instance, often requires bridging studies using clinical data on Koreans only, even when scientifically acceptable Asian data is available.

More Delays

Imported products may face additional

hurdles in the form of quotas, discriminatory discretionary approvals, and even border testing requirements. For example, Vietnam still imposes import quotas on pharma products. Indonesia appears to discriminate in its registration process for imported medicines by approving only life-saving and small-volume drugs and products that cannot be produced domestically for technical reasons. Indonesia also requires foreign companies to maintain a local manufacturing facility to import finished products. And the European Union continues to insist on batch testing pharmaceuticals at the point of entry, increasing costs and causing marketing delays.

Given the difficulty for individual companies to change approval schemes, forward-thinking pharmaceutical executives should draft contractual arrangements to account for regulatory hurdles. A contract for the foreign production of a product’s intermediate stage in one country, for example, should be sufficiently flexible to accommodate approval delays that postpone finished product manufacture in another foreign market.

Similarly, entering a foreign market through a joint-venture arrangement presents certain risks when regulatory approval is a prerequisite to success. Typically, joint ventures are not—nor are they meant to be—permanent relationships. Strategies, management interests, and business environments change over time, and the differing cultures of two or more countries can compound and accelerate those changes. Joint ventures are also often managed by both partners—a situation that is usually untenable as a long-term strategy. Joint ventures are more appropriately viewed as an interim step toward a business entity that is 100 percent controlled by one of the partners, or, in some cases, a third entity. It is critical for pharma companies to

- fully assess the relationship
- carefully outline control issues
- make an effort to anticipate and predict the natural life of the venture, given the regulatory uncertainties
- ensure that the agreement includes a well defined exit strategy.

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A Matter of Price

The struggle toward approval may be dwarfed by foreign regulatory frameworks that control distribution and prices. A patent is useful only if the product can be sold at a price that compensates for the initial R&D and provides funds for future R&D. Now that high tariffs in most WTO countries have been addressed, successful foreign market access is keyed to price management regimes and prescription practices. (See "The Demise of Duties," page 3.)

Those practices can vary considerably from country to country. Some of the more common are

- the use of reference pricing
- positive/negative reimbursement lists

Outsourcing APIs

To improve international competitiveness, pharmaceutical companies have long outsourced various stages of the development and production of single products. The US International Trade Commission noted that trend in its Review of Global Competitiveness in the Pharmaceutical Industry, www.usitc.gov/wais/reports/arc/w3172.htm.

The ITC also notes in its October 1999 Industry Trade and Technology Review ([ftp://ftp.usitc.gov/pub/reports/ittr/PUB3253.PDF](http://ftp.usitc.gov/pub/reports/ittr/PUB3253.PDF)) that heightened competition in the pharma industry has increased the significance of time to market, because numerous companies often are working simultaneously to develop similar products. Consequently, companies have begun outsourcing the manufacture of chemical intermediates and active pharmaceutical ingredients (APIs) to fine chemical companies. That practice allows pharma companies to avoid

- long delays resulting from scale-up production processes following final government approval of a drug for a foreign market
- the time and cost of facility upgrades and production monitoring required by increasingly stringent environmental regulations on the worldwide chemical industry.

- controls on profits, volume, or spending
- international price comparisons
- patient co-payments
- budgets for doctors.

The impact of control measures and cost-containment programs on pharmaceutical pricing is extensively outlined in the ITC report Pricing of Prescription Drugs, [ftp://ftp.usitc.gov/pub/reports/studies/PUB3333.PDF](http://ftp.usitc.gov/pub/reports/studies/PUB3333.PDF).

Many countries, including industrialized nations such as Australia, Denmark, Germany, the Netherlands, and Sweden, use reference pricing. The relevant health authorities establish a reference price for either single products or therapeutic classes for which reimbursement is permitted—although patients who prefer a more expensive drug can pay the difference. Reference pricing can diminish a patent's protection by forcing price competition with generic products within broadly grouped therapeutic classes. Discriminatory reimbursement through the use of positive and negative lists can operate in the same way when generic producers are allowed to offer discounts to the official reimbursement rate. Direct price controls, such as those employed by France, Italy, New Zealand, and Spain, require new product prices and any changes in the prices of existing products to be approved before the drug can be reimbursed by the social insurance system.

Two of the most contentious issues of the Doha multilateral trade negotiations stem from developing countries' push to have TRIPS allow them easier access to medicines in public health emergencies and to have "differential pricing" of essential drugs among countries. The debate between developing and developed countries likely will rage for some time to come. On November 14, 2001, the Doha WTO Ministerial issued a declaration affirming the basic patent protection tenets of the TRIPS agreement. But the declaration also said that TRIPS should not prevent members from taking measures to protect public health and to promote access to medicines for all. (See "Flexibility Under TRIPS," page 4.) The issue of differential pricing presents more significant analytical and legal challenges.

The struggle toward approval may be dwarfed by foreign regulatory frameworks that control distribution and prices.

Much recent media attention has centered on the unresolved differences among the member countries over the diseases that would be covered for compulsory licensing, with the United States and other developed countries seeking to limit coverage to HIV/AIDS, tuberculosis, malaria, and other infectious diseases of similar gravity versus the developing countries (led by Brazil, India, and the African group) seeking an open-ended scope covering public health problems generally.

Differential Problems

The issue of differential pricing presents more significant analytical and legal challenges. In differential pricing—also referred to as discount, equity or tiered pricing—a company charges different prices in different parts of the world according to consumer purchasing power. It can be a win-win situation when the manufacturer of a patented drug is able to recover most R&D costs in richer markets while simultaneously selling the product or licensing its production at lower prices in poorer countries. Because of pressure brought by advocacy groups, reliable and adequate financing from government or charitable sources, high-volume purchasing, and other market forces, differential pricing already exists for many commodity medicines such as vaccines, contraceptives, and condoms. Problems with differential pricing include antitrust concerns and the possibility that lower prices in developing countries may become reference targets for price controls in the industrialized countries.

But pharma companies' biggest fear in pursuing differential prices is the pos-

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vent parallel imports. GlaxoSmithKline, for instance, uses a different brand name for its well-known anti-ulcerant, Zantac (ranitidine), which it markets as Zinetac in India. Using different packaging, color combinations, and language to market to different countries may significantly reduce the opportunity for parallel imports.

Even when prices fall, poor countries still may be unable to afford to purchase a particular product, especially in the large quantities that it may need. Pharma companies may wish to explore counter-purchases, especially when cash flow and currency exchange problems undermine purchasing power. The practice usually involves a foreign company or country agreeing to buy a specified number of pharmaceutical products and, in return, the pharma company agreeing to purchase, say, a certain percentage of raw material from that country and to pay in US currency. The practice is common in large industrial transactions and makes it possible to sell one drug to a foreign country while acquiring the raw materials needed to produce another product in that same country.

Global Market

Despite such national differences, however, progress toward standardization is being made. For the past decade, the United States, the European Union, and

Japan have participated in the International Conference on Harmonization with the goal of eliminating duplicate requirements for drug development and approval within their regions. The group finalized the Common Technical Document, designed to be a single basis for drug approval in all three regions, at meetings held November 9–11, 2000.

Also, the United States and the European Union continue to implement a 1997 Mutual Recognition Agreement, under which each recognizes the other's inspections of drug and biologic manufacturing facilities, thus avoiding duplicate inspections of individual factories. Yet another trend that moves the industry closer to a true global market is the outsourcing of active ingredient manufacturing. (See "Outsourcing APIs," page 5.)

Pharma's overarching rule in dealing with foreign countries should be to remain flexible and creative but constantly aware of the practical and legal shortcomings that may exist there. The keys to international success are knowing what patent rights to expect, how long it takes to get the product to market under the protection of those rights, and what pricing and prescription regimes are in place in a particular foreign market. Pharma companies that enter global agreements based on an informed position will have a strong foundation for worldwide growth. ■

sible diversion of their most lucrative products from poor countries to wealthier countries through parallel imports. Also known as gray market imports, the situation occurs when a drug is sold in one country at a low market price and then gets shipped to a third country for sale at a higher market price. Such products are legitimate and even may have been produced under a valid patent, but they create a strong disincentive for selling drugs in countries at a low market price. It makes no sense for a company to create its own low-cost competition.

Yet, it may be advantageous for pharma companies to take the initiative in seeking opportunities to exploit differential pricing. It may be as simple as creating different marketing strategies for the different country markets to pre-

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