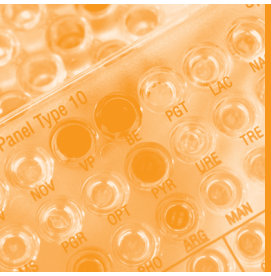

PharmaBulletin

WILMERHALE

REGULATORY

UNITED STATES

FDA Proposes Rules for Expanded Access to Investigational Drugs for Treatment Use and Charging for Investigational Drugs

On December 11, 2006, the United States Food and Drug Administration (FDA) proposed two rules designed to expand early patient access to investigational drugs, and allow sponsors to charge for such drugs in clinical trials.

The first rule seeks to make it easier for patients with serious or life-threatening diseases or conditions to gain access to experimental drugs. Under existing regulations, access to investigational drugs is permitted for patients with serious or immediately life-threatening diseases or conditions for which there is no satisfactory alternative therapy, the potential benefit justifies the risk, and providing the drug will not interfere with investigations that could support development and ultimate approval of the drug. The expanded access proposal does not alter this baseline test, but clarifies and expands the circumstances that can satisfy these criteria. In particular, the rule would create a sliding scale for the required levels of evidence of safety and potential benefit needed to allow early access, depending on the seriousness of the disease and the size of the proposed patient treatment population.

The second rule would clarify the circumstances in which patients can be charged for drugs (both experimental and approved) used in clinical trials. It would permit charging for the sponsor's own drug if the drug, a new indication for the drug or new safety data might not otherwise be developed: the trial is essential to the development of a new drug or would support a significant labeling change for an approved drug; and charging for the drug is necessary in order to conduct the trial. Sponsors would also be able to charge for use of another company's approved drug when co-administered with, or used as a comparator to, an investigational drug, or in trials evaluating a new use for an approved drug.

If adopted, these rules have the potential to benefit both patients and pharmaceutical companies. However, some patient groups have criticized the rules as not going far enough to allow greater access to promising, but as yet unapproved, drugs—and pending litigation over such access issues may further alter the dynamics of patient access to investigational drugs.

The comment period closes March 14, 2007. Sponsors who have questions about the proposed rules, or who may wish to submit comments to FDA, can contact WilmerHale's FDA Department for more information.

FDA – Expanded Access to Investigational Drugs for Treatment Use

FDA – Charging for Investigational Drugs

CHINA

China RoHS to Regulate Medical Devices

A growing trend, which began in Europe, is to limit the presence of hazardous substances and elements in the environment by regulating their use in manufacturing processes. Particular attention has been directed to six substances: lead, mercury, cadmium, hexavalent chromium, poly brominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs). Medical devices have, thusfar, enjoyed an exemption from regulations in Europe under the EC Directive on the Restriction of the Use of Certain Hazardous Substances (Directive 2002/95/EC).

However, medical devices that fall within the regulatory scope of electronic information products will be subject to regulation under China's counterpart, the Measures for the Administration of the Control of Pollution by Electronic Information Products (China RoHS). These regulations were promulgated on February 28, 2006, and take effect on March 1, 2007.

The FDA has proposed rules to allow sponsors to charge for investigational drugs in clinical trials

China RoHS will operate in a different manner than its EU predecessor. Instead of restricting or prohibiting the use of the named substances in products for which there is no exemption, China RoHS consists of a two-stage approach.

In the first stage, covered products will be subject to labeling or marking requirements with respect to the presence of such substances, the standards for which were published in November 2006. Restrictions or prohibitions will only be introduced in the second stage, based on the feasibility of substitution or reduction and/or prohibition for those products included in a Catalogue for Priority Control of Pollution by Electronic Information Products.

The first edition of the Catalogue, which is to be revised annually, has yet to be issued, therefore it is not yet known which products will be included in the Catalogue from the outset. However, the Ministry of Information Industry has stated that manufacturers will be given at least six months to comply after a product is listed in the Catalogue.

Manufacturers of medical devices to be sold in China should first determine whether their products fall within the scope of electronic information products. If so, they should then ensure that their products are properly marked or labeled (in Chinese), including instructional brochures or pamphlets. If the devices include any of the regulated substances, manufacturers will have to specify an environment-friendly use period during which, under normal conditions, such substances will not leak or mutate, resulting in environmental pollution or serious harm to persons or property.

The Court of Appeals for the Federal Circuit (CAFC) recently clarified the liablity standard for inducement of patent infringement

INTELLECTUAL PROPERTY

UNITED STATES

Inducement to US Patent Infringement Harder to Prove

In *DSU Medical v. JMS*, the Court of Appeals for the Federal Circuit (CAFC) recently clarified the liability standard for inducement of patent infringement. Similar to the CAFC's 2003 holding in *Warner-Lambert v. Apotex*, the case may have significant implications for pharmaceutical and medical device companies. Unlike Europe, the United States allows patents for methods of treating and diagnosing conditions of the human body. Although direct infringement is typically incurred only by doctors or patients, patentees seek to enforce such patents against drug and device makers on grounds that they induce infringement of the patented methods.

In *Warner-Lambert*, the CAFC held that mere knowledge that a product **may** be used for infringing purposes is insufficient to prove inducement. Rather, when a product has a substantial non-infringing use, inducement must be shown by proof of specific **intent.** In *DSU*, the CAFC clarified that the intent required is not only to induce acts that lead to or constitute direct infringement, but to induce **infringement**.

These two decisions are likely to produce a substantial amount of litigation and uncertainty. For example, what a patentee of a medical method who is unwilling or unable to sue directly infringing patients and doctors must prove will now be hotly contested by sellers of the products used in treatments that are alleged to infringe the method claims. Sellers of those products will argue that it is necessary to prove not merely evidence of the knowledge of the likelihood or occurrence of infringing acts, but evidence of an intent to cause infringement. These decisions may also cause a resurgence in noninfringement or invalidity opinions of patent counsel. Although the CAFC said in *Knorr-Bremse* that the failure to obtain those opinions is no longer evidence of willfulness, many commentators have suggested that non-infringement or invalidity opinions of patent counsel may support an affirmative defense that the alleged inducer did not have the requisite intent.

DSU Medical v. JMS

Warner-Lambert v. Apotex

EUROPE

Failure to "Clear the Way" Assists Balance in Favor of Injuncting Generic Competitor

Mr. Justice Kitchin of the English High Court has ruled in favor of the French pharmaceutical company Les Laboratoires Servier (Servier), granting an injunction pending trial for patent infringement, against Slovenian generic pharmaceutical distributor Krka d.d. (Krka). An application by Krka for summary judgment on the basis of

anticipation and/or obviousness (founded on an earlier Servier patent and/or a pre-priority date sale) was refused.

The patent in suit related to a particular crystalline form of the active ingredient perindopril erbumine and its method of preparation. Servier, acknowledged by the court as "the largest privately owned innovative pharmaceutical company in France" and "the second largest French pharmaceutical company worldwide," markets Coversyl, a drug containing this ingredient, in 108 countries worldwide. The United Kingdom is their most significant market.

Krka is the supplier of a variety of generic pharmaceutical products. Having first obtained a marketing authorization for their product in Hungary, by utilizing the Mutual Recognition Procedure, they obtained four further authorizations in the United Kingdom.

The patent has also been the subject of opposition proceedings before the European Patent Office, where it had been upheld with amended claims. Krka intended to appeal that decision.

Satisfied there was "a serious issue to be tried," Mr. Justice Kitchin considered that the following factors favored the grant of an interim injunction: (1) Krka's offer to sell its product at a lower price so that it would "quickly gain a major share of the UK market"; (2) the fact that other generic manufacturers would then promptly follow suit; (3) the likely "effect of this competition" being "a downward spiral [in] price," detrimentally affecting Servier's "market share"; (4) the then "substantial resistance to any attempt to force a substantial increase in the generic tariff rate," which, in addition, "might well lead" to the prescription of alternative products; (5) the fact that Coversyl is "crucial to Servier's business," whereas ""Krka produce[s] numerous different generic products,"there being "no reason to believe" this drug "is particularly significant to their future business plans"; (7) the fact that Krka is not presently on the market; and (8) the observation that Krka evidently "chose not to" clear the way.

Mr. Justice Kitchin noted this final factor to be particularly "important." While an application for an interim (pre-trial) injunction is by no means certain of success, in recent years the courts have shown a willingness to find in favor of pharmaceutical patentees where a generic competitor has failed to "clear the way"—either by seeking a declaration of non-infringement or by revoking the patent prior to product launch *(Smithkline Beecham v. Apotex [2003] EWHC 2556 (Pat), upheld on appeal [2003] EWHC Civ 137).*

This latest decision highlights the strategic advantage of selecting the English courts in the fight against European generic competition. With an emphasis on pre-action negotiation; the availability of a variety of pre-action relief, including pre-action disclosure; pre-trial disclosure as standard; and the potential of a six-month "speedy trial" order, the English courts are an increasingly attractive option in the armory of European pharmaceutical patentees.

Following this decision, it has been reported that the parties have reached an amicable out-of-court settlement.

Les Laboratoires Servier & Anor v. KRKA POLSKA SP.Zo.o & Anor [2006] EWHC 2453 (Pat)

Slovenia Business Week (Nov. 2006)

The English courts have shown a willingness to find in favour of pharmaceutical patentees, where a generic competitor has failed to "clear the way."

ANTITRUST/COMPETITION

UNITED STATES

Supreme Court Review Sought in Second Circuit Hatch-Waxman Patent Settlement Case

On December 15, 2006, the consumer class plaintiffs in *In re: Tamoxifen Citrate Antitrust Litigation*, filed a Cert Petition, seeking Supreme Court review of an important Second Circuit decision regarding the settlement of Hatch-Waxman patent infringement litigation. The Second Circuit had affirmed dismissal of a consumer class antitrust challenge to the patent settlement between Zeneca, the patent holder and marketer of the branded Tamoxifen drug (Novadex, a breast cancer treatment), and Barr, a generic applicant for FDA approval and the patent challenger. The settlement involved substantial payments to Barr and its supplier, and Barr's withdrawal of its patent challenge and efforts to gain FDA approval of its generic application. The Second Circuit rejected the contention that the settlement

violated the antitrust laws, finding that the settlement was no more exclusionary than the patent itself.

This Cert Petition follows on the heels of the Supreme Court's denial of a similar petition where the Federal Trade Commission (FTC) had sought review of an Eleventh Circuit decision that similarly rejected an antitrust challenge to a branded-generic patent settlement, *FTC v. Schering-Plough* (See **WH PharmaBulletin, Issue 6, Summer 2006**). The FTC supported the Tamoxifen plaintiffs in their efforts to seek a rehearing by the Second Circuit, and almost certainly will file a brief in support of the Tamoxifen Cert Petition. FTC officials have stated publicly that the Commission continues to have a strong interest in challenging Hatch-Waxman patent settlements where payment is made to a generic challenger in exchange for what the FTC views to be a "delay" in entry. However, recent court decisions, including *Schering-Plough and Tamoxifen*, have not accepted that view, reasoning that a settlement that does not exclude competition to any greater extent than the patent itself is lawful and thus legitimately prevents generic entry prior to expiration.

FTC officials have stated publicly that the Commission continues to have a strong interest in challenging Hatch-Waxman patent settlements where payment is made in exchange for a "delay" in entry

The Tamoxifen petitioners argue that the factual and procedural background of the Tamoxifen settlement make this decision a much better vehicle for review than was the Eleventh Circuit *Schering-Plough* decision, and urge a compelling public need to address the issue of determining "the appropriate antitrust standard applicable to an agreement between a brand pharmaceutical manufacturer (and patent holder) and a generic market entrant (and alleged patent infringer) whereby the patent holder shares a portion of its future profits with the alleged infringer in exchange for the latter's agreement to not market its competitive product."

In addition to an opposition by the defendants, Zeneca and Barr, and the FTC's expected amicus brief in support of the petition, the Court may well request the views of the United States Solicitor General, as it did in *Schering-Plough*. There, the Solicitor General opposed the petition, in part because the Department of Justice was not in full accord with the FTC's view of such settlements, and in part because, in its view, the case did not present the best vehicle for review of the issue.

In re: Tamoxifen Citrate

EUROPE

Hellenic Competition Commission Issues Decision in *GlaxoSmithKline* Case

The Hellenic Competition Commission ruled on September 1, 2006, that GlaxoSmithKline had not infringed Article 82 of the EC Treaty in restricting supplies of the three products (Lamictal, Imigran and Serevent) to wholesalers suspected of engaging in parallel trade.

Although the Competition Commission ruled that GlaxoSmithKline had abused a dominant position under Greek law by ceasing all supplies from November 2000 to February 2001, it failed to rule on the issue of whether a quota system—introduced by GlaxoSmithKline in order to prevent wholesalers having unrestricted supplies of the three drugs—also abused its dominant position, concluding that the issue should be dealt with by the European Commission.

GlaxoSmithKline Decision

CFI Partially Annuls European Commission Decision on GlaxoSmithKline Parallel Imports

On September 27, 2006, the European Court of First Instance (CFI) partially annulled the 2001 decision of the European Commission that GlaxoSmithKline (formerly Glaxo Wellcome) (GSK) had infringed Article 81(1) of the EC Treaty by introducing a dual pricing system to prevent parallel trade between Spain and the United Kingdom. Although the CFI found that the practice had an anticompetitive effect, it concluded that the Commission had failed to adequately consider whether the practice should be exempted under Article 81(3) of the EC Treaty. In particular, the CFI found that the Commission had failed to examine the implications of the practice on GSK's research and development activities, and acknowledged the special characteristics of the pharmaceutical sector. The Commission must now reconsider whether the practice should be exempted under Article 81(3) of the EC Treaty.

CFI – GlaxoSmithKline Decision

UK Competition Authority Confirms Investigation into Pfizer UniChem Deal

In October 2006, the UK Office of Fair Trading confirmed that it is examining the

exclusive distribution arrangement between Pfizer and UniChem (the distribution arm of Alliance-Boots). Critics of the agreement argue that it threatens patient welfare and the National Health Service. Pfizer has rejected these concerns, stating that the agreement would reduce the scope for counterfeit medicines to enter the United Kingdom, and expressing confidence that the agreement fully complies with UK and EU competition laws.

The Times Online Article – *Pfizer-UniChem* Deal

Italian Competition Authority Imposes Interim Measure Order on Pharmaceutical Wholesalers

On September 28, 2006, the Italian Competition Authority made an interim measures order to ensure that seven pharmaceutical distributors supply OTC products to non-pharmacy outlets. The distributors involved are Alleanza Salute Italia S.p.A., Alleanza Salute Distribuzione S.p.A., Galenitalia S.p.A., Comifar S.p.A., Comifar Distribuzione S.p.A., Safar Società Cooperativa and Itriafarma Società Cooperativa. The move follows complaints that the wholesalers, without objective justification, had refused to supply non-prescription medicines to retailers who were not pharmacies. The ongoing investigation is due to be completed in September 2007.

PUBLIC POLICY

UNITED STATES

Preemption of Price Controls on Patented Prescription Drugs: Federal Circuit Hears District of Columbia's Appeal

Pending before the US Court of Appeals for the Federal Circuit in *BIO & PhRMA v. District of Columbia*, No. 2006-1593 (Fed. Cir.) is an appeal with significant implications for the rights of patent holders, the constitutional limits on the power of state and local governments to regulate intellectual property, and the incentives to invent and develop potentially life-saving patented drugs.

The District of Columbia is appealing from a judgment of the US District Court for the District of Columbia that struck down the District of Columbia Prescription Drug Excessive Pricing Act of 2005 (DC Act). The DC Act represents an unprecedented attempt by a state or local government to target and cap the price of patented—and **only** patented—prescription drugs. In the overwhelming majority of its applications, moreover, the DC Act regulates transactions that occur wholly outside of DC's borders.

The DC Act prohibits a manufacturer from selling a patented prescription drug anywhere in the country if that sale results in a subsequent sale in DC at an "excessive" price. A prima facie case of excessiveness may be established based on benchmark prices in Australia, Canada, Germany and the United Kingdom, where government controls depress pharmaceutical prices. The District of Columbia or any individual or organization claiming to represent "the public interest" may file suit in DC Superior Court to enforce the DC Act. A court that finds a price to be "excessive" can impose treble damages, fines, injunctive relief, and attorneys fees and costs on the manufacturer.

The DC Act represents an unprecedented attempt to target and attempt to cap the price of patented prescription drugs

WilmerHale's David W. Ogden and Randolph D. Moss challenged the DC Act on behalf of Pharmaceutical Research and Manufacturers of America (PhRMA) in the US District Court for the District of Columbia. After consolidating the case with a subsequent suit filed by Biotechnology Industry Organization (BIO), the district court granted summary judgment to PhRMA and BIO in December 2005. The court concluded that by undermining patent holders' ability to set prices in their discretion to recoup the substantial investments in their patented products, the DC Act poses a "clear obstacle to the accomplishment and execution of the purpose and objectives set by Congress in passing federal patent laws" and "flies directly in the face of a system of rewards calculated by Congress to insure the continued strength of an industry vital to our national interests." The court therefore held that the DC Act is preempted by federal patent law and violates the Supremacy Clause. It also held that the Act's extraterritorial regulation of transactions occurring wholly outside the district violates the Commerce Clause. The district court declared the DC Act invalid both on its face and in the overwhelming majority of its applications, and enjoined DC from enforcing it.

On appeal to the Federal Circuit, DC does not challenge the district court's holding that the DC Act violates the Interstate Commerce

Clause, though it attempts to vacate that holding by challenging PhRMA's and BIO's standing to bring suit. DC also argues that the price controls it imposes on patented prescription drugs are not preempted by federal patent law.

Lawmakers around the country are watching DC's appeal, and its outcome may influence whether other states or local jurisdictions enact price-control legislation modeled on the DC Act. State and consumer groups active on drug pricing issues—including the National Legislative Association on Prescription Drug Prices and other groups—have also demonstrated their interest by submitting an amicus brief in support of DC.

WilmerHale continues to represent PhRMA on appeal. On December 19, 2006, PhRMA and BIO filed a brief in support of the district court's judgment. The case is likely to be argued this spring.

BIO & PhRMA v. District of Columbia

A Democratic majority in both chambers of Congress will bring a robust legislative agenda for the pharmaceutical and biotech industries in 2007

Congressional Update: 2007 Legislative Agenda for Pharmaceutical and Biotech

A Democratic majority in both chambers of Congress will bring a robust legislative agenda for the pharmaceutical and biotech industries in 2007. Senate and House committee chairs, including Senator Kennedy and Representatives Dingell, Waxman and Stark, have begun laying out their priorities for health-related legislative and oversight hearings. Prominent issues include FDA reform, reauthorization of pharmaceutical user-fee legislation, and the establishment of a process for approving "generic" versions of biologic agents.

According to Speaker Pelosi, legislation repealing the Medicare Part D non-interference clause is an immediate priority for the new Congress. If successful, the repeal would allow the government to intervene in the negotiations between private sector drug plans and pharmaceutical manufacturers to lower drug prices for the millions of seniors on Medicare. Hearings on the matter are likely to highlight concerns over access to medicines, government price controls and the potential impact on drug innovation. Already, scholars have begun analyzing the possible effects of such legislation. For example, a study sponsored by the Manhattan Institute found that significant reductions in prices for Medicare drugs could lead to a reduction in pharmaceutical R&D investment, and a loss of approximately 12 new medicines per year over the next decade. However, proponents of direct government negotiation highlight the cost savings that can be achieved for seniors currently in the program. Although the House seems poised to enact Medicare Part D legislation, the Senate has thus far signaled a more cautious approach, and may be less likely to pass significant revisions so early in the life of this new program.

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