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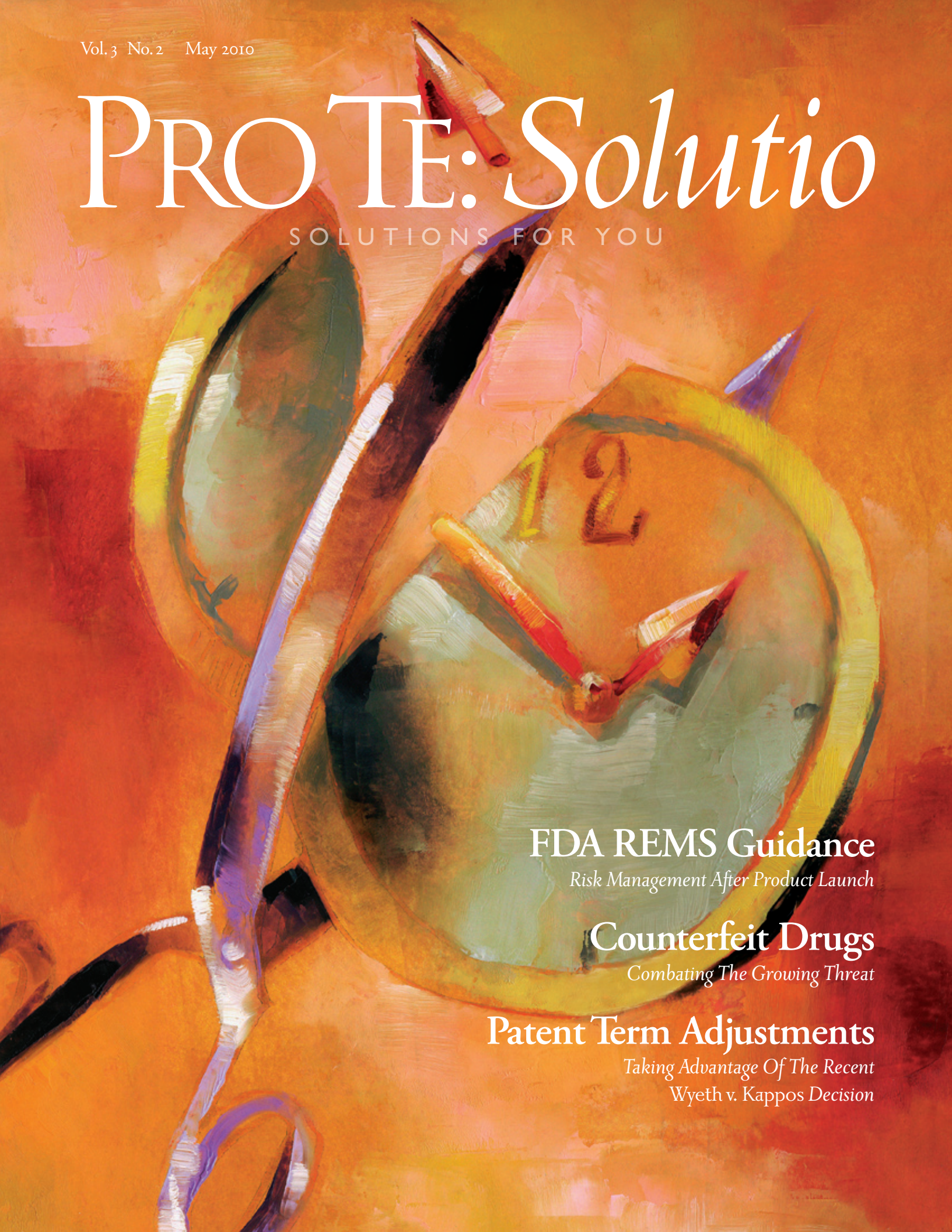
PRO TE: *Solutio*

SOLUTIONS FOR YOU



FDA REMS Guidance

Risk Management After Product Launch

Counterfeit Drugs

Combating The Growing Threat

Patent Term Adjustments

Taking Advantage Of The Recent Wyeth v. Kappos *Decision*

Dear Clients:

The pharmaceutical, medical device, and healthcare industry strives to protect the public's well-being. But, in order to provide assistance to others, companies must first be able to protect themselves. Articles in this issue of *Pro Te: Solutio* offer ideas about how to help prevent or remedy potentially harmful legal situations that companies regularly face.

The patent application process affects the bottom line of innovator companies, and the recent decision in *Wyeth v. Kappos* affects how the length of a patent is calculated based on application delays originating within the PTO. Find out how this adjustment may impact your company in *Are Your Patents Getting Their Full Term Due?*

Just as patents exist to protect valuable information, so does trademark law. In the case of counterfeit drugs, trademark law can be used to protect a company's product as well as the company's reputation and the health — even lives — of consumers. *Counterfeit Drugs* examines how trademark laws can be used to protect and defend a product from typically elusive counterfeiters.

Industry members work hard to protect those who place their trust in a company's product, and this effort continues well after a drug or device enters the market. *An Updated Guide on Managing Risks and Enhancing Prescription Drug Safety After Product Launch* provides an overview of the FDA's latest Guidance for Industry concerning risk evaluations and mitigation strategies during post-marketing.

Diligent protection of products and consumers is just another "day in the life" of this industry — and in how Butler Snow helps clients. We hope this issue of *Pro Te: Solutio* provides new insight and information that will bolster your company's defenses against potentially weakening or damaging forces.

Christy D. Jones
Co-Chair — Litigation

Charles F. Johnson
Co-Chair —
Business and Corporate Healthcare

Pro Te: *Solutio*

Vol. 3 No. 2 May 2010

Sharing Solutions

It's human nature to share problems. But how often is someone willing to share solutions? Butler Snow wants to do just that — provide scenarios and the solutions that turned a client's anxiety into relief and even triumph. That's why we created this magazine, *Pro Te: Solutio*, which explores how real-life legal problems have been successfully solved.

That's also why we at Butler Snow redesigned and expanded our unique health-oriented industry group, now comprised of two major sections that handle business and litigation. The Pharmaceutical, Medical Device, and Healthcare Industry Group has more than 50 multi-disciplinary attorneys who provide creative solutions for the complex issues of the healthcare industry. This group includes product liability and commercial litigators; corporate, commercial, and transaction attorneys; labor and employment attorneys; intellectual property attorneys; and those experienced in government investigations.

Pro Te: Solutio is a quarterly magazine available only to the clients of Butler Snow. If you have questions or comments about its articles, you're invited to contact group co-chairs Christy Jones and Charles Johnson, as well as any of the attorneys listed on the last page of this publication.

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ARE YOUR PATENTS GETTING THEIR FULL TERM DUE?

Taking Advantage of the Recent *Wyeth v. Kappos* Decision

As a result of a January decision by the Court of Appeals for the Federal Circuit, many recently-issued patents could have several months tacked onto their terms. The decision stems from a case filed by Wyeth and Elan Pharma International against the director of the United States Patent and Trademark Office (PTO) over the terms for two jointly-owned patents related to Alzheimer's treatments. Wyeth and Elan claimed that the PTO had miscalculated the patent term adjustments that were owed to them as a result of the PTO's own delays.

Patent Term Adjustments

Patent term adjustments (PTAs) were created by Congress to compensate patentees for bureaucratic delays by the patent office. Before 1995, the amount of time it took for a patent to issue did not negatively affect the length of the patent; the right to exclude others from making, using, or selling a patented device or method lasted seventeen years from the date of issue. In 1995, the United States became a party to the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (the TRIPS agreement), which greatly enhanced protection of intellectual property between countries.[1] As part of the TRIPS agreement, Congress changed how the patent terms were calculated; instead of lasting seventeen years from the date of issue, patents would expire twenty years from the date of filing.

As a result of the change in the way expiration dates were calculated, delays in the issuance of the patent became big concerns for patent applicants. A long, bureaucratic hold-up at the PTO could significantly cut into the term of the patent. Patents that took longer than three years to issue effectively had shorter terms than were available prior to the TRIPS agreement. Each day that the patent was delayed beyond three years directly cut into the patent term. For example, a patent that took seven years to issue would have only thirteen years left in its term. The patent owner was effectively being punished for delays out of his control.

To make up for these shorter patent terms, Congress included patent term guarantees in the American Inventor's Protection Act of 1999.[2] These guarantees ensured that patents which were delayed by the patent office would have their lost time tacked back onto the end of the term of the patent.

Patent term adjustments are codified in 35 U.S.C. §154(b)(1). The statute provides

for adjustments to the patent term under three different kinds of delays.

The so-called "A-delays" are delineated in Part (A) of the statute and occur when the PTO fails to respond promptly within certain prescribed deadlines. This type of delay can occur when the PTO fails to mail a first office action within fourteen months of the filing date or when the PTO takes longer than four months to respond to an applicant's reply.[3] For each day of "A-delay," the patent term is adjusted by a day being tacked onto the end of the patent term.

"B-delays" occur when the PTO takes longer than three years to issue a patent.[4] Under the patent term guarantee, each day of B-delay results in a patent term adjustment being added back onto the end of the patent term. Effectively, this guarantee ensures that a patent term would be no less than seventeen years, the same duration of a patent term prior to the TRIPS agreement.

"C-delays" are delays in issuance of the patent caused by appeals and interference proceedings or secrecy orders.[5] The statute that prescribes patent term adjustments compensates patent holders one day for each day of this type delay.

The Issue in *Wyeth*

The patent term adjustment statute also includes provisions to account for overlaps in the three types of delays.[6] In 2004, the PTO issued a notice which stated that it interpreted the statute to mean that, in situations in which both A-delays and B-delays occur, the applicant is entitled to receive only the longer of the patent term adjustments available, not both.[7] The PTO reasoned that A-delays would cause B-delays and, therefore, both should not be counted.

Wyeth concluded that the PTO was improperly calculating the patent term adjustments where there is both A-delay and B-delay and filed suit in district court for the District of Columbia, asserting that the PTO had misinterpreted the statute.[8] Wyeth argued that it was entitled to extensions for both A-delays and B-delays, minus any overlap. For Wyeth, the difference was significant: U.S. Patent 7,179,892 should have received 294 days more, and U.S. Patent 7,189,819 was owed 230 more days.

The PTO countered that Wyeth's interpretation would lead to a "windfall" for the patent applicant because the applicant would be overcompensated for the PTO's delay.[9] Furthermore, the PTO argued that Congress did not intend for the patentee to get more than seventeen years of patent protection.

The District Court, in finding for Wyeth, held that the PTO's interpretation went beyond the plain language of the statute. United States District Judge James Robertson opined that, if Congress had intended to limit the patent term to seventeen years, the statute could easily have been written that way.[10]

> Each remaining day of the patent term may be worth hundreds of thousands of dollars in potential revenue to the innovator pharmaceutical company.

The PTO appealed the decision in November 2008. The Court of Appeals for the Federal Circuit took up the case and, after hearing the arguments, decided unanimously to affirm the district court opinion that the PTO had improperly calculated the patent term.[11] The Court held that the language of the patent term adjustment statute was unambiguous that both A delays and B delays must be counted unless they occur on the same day.[12]

A Greater Impact on Biotech Companies

It is not surprising that the challenge to the PTO's 2004 interpretation of the patent term adjustment act came from two pharmaceutical companies. Patent term adjustments are particularly important for biotechnology companies because often several generic competitors are eagerly waiting for expiration of the patent so that they can enter a lucrative market. Each remaining day of the patent term may be worth hundreds of thousands of dollars in potential revenue to the innovator pharmaceutical company. When a patent on a blockbuster drug expires, the company that owns the patent potentially faces substantial losses in revenue. Pfizer, for example, has stated that it anticipates a significant drop in revenue after the patent on Lipitor®, which accounts for one-quarter of Pfizer's revenue, expires in 2011.[13]

Biotechnology companies also are likely to be affected more than other patent holders because the application process faces more delays. In 2009, the average patent in the Tech Center 1600, where Biotechnology and Organic Chemistry patents are handled, issued in 35.1 months compared to 34.6 months for all other technology groups.[14] The Average First Action Pendency was 22.8 months, 8.8 months longer than the PTO's goal of fourteen months.[15] Based on this data, on average, a patent holder for a biotechnology application could expect about 264 days of patent term adjustment for A-delays.

Finally, the value of a biotech patent is often the maximum at the end of the term because the patented product has become established in the marketplace and has developed brand recognition. Doctors and patients generally have more confidence in the product since the effectiveness of the drug has been well established. As a result, the biotechnology company generally wants to ensure that as much time is credited to a patent term as is possible.

Correcting Patent Term Adjustment Errors

In late January 2010, the PTO announced that it would not appeal the decision of the Federal Circuit; instead, it released interim guidelines on how to request a recalculation of the patent term adjustment based

on the *Wyeth* decision.[16] The guidelines provide a free alternative to the normal process for requesting reconsideration.[17]

Under the interim guidelines, there is a narrow window for obtaining a recalculation of the patent term adjustment. Only those patents which issued prior to March 2, 2010, and in which the issue is the overlapping delays are eligible for a recalculation request. The PTO has stated that the patent holder must file the request within 180 days of the patent granting date. The PTO has provided a simple form for those who are eligible, entitled, "Request for Recalculation of Patent Term Adjustment In View of *Wyeth*."[18]

The PTO updated the software that calculates PTA on March 2, 2010. If a patentee believes that the PTO has miscalculated a patent term despite the updates, a request for reconsideration should be filed within two months of the issue date. Because of strict deadlines, patentees must act quickly to request recalculations.

Conclusions

Errors in calculating patent term adjustments are not unusual. Because of the potentially strong financial impact of an error, especially for biotechnology companies, patent applicants should perform their own calculations for patent term adjustments and promptly request reconsideration if that is an option.

[1] *See* Uruguay Round Agreements Act, Pub. L. No. 103-465, §532, 108 Stat. 4809, 4984 (1994).

[2] *See* Consolidated Appropriations Act, Pub. L. 106-113, 113 Stat. 1501A-557 (1999).

[3] 35 U.S.C. §154(b)(1)(A).

[4] *Id.* §154(b)(1)(B).

[5] *Id.* §154(b)(1)(C).

[6] *Id.* §154(b)(2)(A).

[7] Explanation of 37 CFR 1.703(f) and of the United States Patent and Trademark Office Interpretation of 35 U.S.C. 154(b)(2)(A), 69 Fed. Reg. 34238 (June 18, 2004).

[8] *Wyeth v. Dudas*, 580 F. Supp. 2d 138 (D.D.C. 2008).

[9] *Id.* at 9.

[10] *Id.*

[11] *Wyeth v. Kappos*, 591 F.3d 1364 (Fed. Cir. 2010).

[12] *Id.* at 10.

[13] "Pfizer to Cut Researchers in Preparation for Lipitor Patent Expiration." Duff Wilson, *The New York Times*, Jan. 4, 2009. Available at <http://www.nytimes.com/2009/01/14/business/worldbusiness/14iht-pfizer.1.19344642.html?_r=1>. Last accessed April 21, 2010.

[14] *Performance and Accountability Report Fiscal Year 2009*. U.S. Patent and Trademark Office. Available at <http://www.uspto.gov/web/offices/com/annual/2009/oai_05_wlt_04.html>. Last accessed April 21, 2010.

[15] *Performance and Accountability Report Fiscal Year 2009*. U.S. Patent and Trademark Office. Available at <http://www.uspto.gov/web/offices/com/annual/2009/oai_05_wlt_04.html>. Last accessed April 21, 2010.

[16] U.S. Patent and Trademark Office, Interim Procedure for Patentees to Request a Recalculation of the Patent Term Adjustment to Comply with the Federal Circuit Decision in *Wyeth v. Kappos* Regarding the Overlapping Delay Provision of 35 U.S.C. 154(b)(2)(A). Jan. 26, 2010. Available at <http://www.uspto.gov/patents/announce/pta_wyeth.pdf>. Last accessed April 21, 2010.

[17] *See* 37 C.F.R. §1.705 (2010).

[18] *See* U.S. Patent and Trademark Office Form PTO/SB/131. Available at <www.uspto.gov/forms/sb0131.pdf>. Last accessed April 21, 2010.

Written *by* Hemant Gupta

Counterfeit Drugs

Counterfeit drugs have become a billion dollar business and reach consumers across the globe, affecting a gamut of products, from over-the-counter cough syrup to treatments for malaria and HIV.

Chanel purses and sunglasses from the back of a trailer, Rolex watches from a closet vendor, or a twenty-dollar bill that does not pass the invisible ink test at your local fast food restaurant. Mention the word "counterfeit" to most people and these images are the first to form. Over the past few decades, though, a more lethal form of counterfeiting has emerged. Counterfeit drugs have become a billion dollar business and reach consumers across the globe, affecting a gamut of products, from over-the-counter cough syrup to treatments for malaria and HIV. Counterfeit drugs now reach to every region of the world, but in regions where drug enforcement systems are weak, such as Africa, Asia and Latin America, the number of counterfeit drugs sold to unsuspecting consumers is greatest. Not only are counterfeit medications broad in their geographic scope, but their concentration has increased as well. According to the most recent data from the World Health Organization (WHO), approximately half of all medications purchased from illegal websites with concealed physical addresses are counterfeit.[1] The dangers of this business are apparent — both to the consumer and to the manufacturer. While consumers face the danger of the physical effects of a counterfeit drug, the manufacturer may face claims over a product masquerading under its brand, which the company did not manufacture and, often, did not even know existed.

This article examines the counterfeit drug industry with an eye to both preventative and retaliatory tactics on behalf of pharmaceutical drug manufacturers. Legitimate pharmaceutical manufacturers, armed with these measures, may provide a pivotal force to protect the industry, to combat harm to consumers, and to safeguard their own products and goodwill from future theft. The enormous implications of the counterfeit drug market are in large part a result of the complex nature of this clandestine industry. Thus, the first step in fighting its reach is to understand it.

Identify the Problem

The basic definition of a counterfeit drug is distinct from traditional uses of the term in intellectual property infringement, and the definition may vary from one country to another. To provide a working jargon, the WHO has posted the following definition:

A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products, and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.[2]

Contrast this definition to drugs that have not received regulatory approval or to generic

drugs, both of which are not considered counterfeit. The basic premise is that the counterfeit drug that reaches the hands of consumers is not the same drug as that produced for sale by the legitimate maker, either because it contains different ingredients or because it contains different packaging.

In its most virulent form, a counterfeit medication harms patients because it provides the wrong dosage of active ingredient or contains no active ingredient at all. For example, In January 2010, the U.S. Food and Drug Administration (FDA) warned consumers who purchased GlaxoSmithKline PLC's over-the-counter weight loss drug Alli® from internet sites that the "fake" Alli did not contain the correct active ingredient. Instead, the counterfeit medication contained sibutramine, the active ingredient in Abbott Laboratories' Meridia®. Further, the FDA warned that the counterfeit Alli contained concentrations twice as much as the maximum daily dosage of sibutramine, posing a serious health risk to persons taking it.[3] And while buying over-the-counter weight loss medications from internet-based distributors may not conjure the zealous advocacy needed to reverse the counterfeit drug phenomenon, consider the following examples: In 2001, a study in Southeast Asia found approximately 38% of antimalarial drugs sold in pharmacies contained no active ingredients whatsoever; in 1995, 89 deaths occurred in Haiti as a result of cough syrup prepared with a toxic chemical used in antifreeze; and in 2003, the FDA issued warnings of counterfeit Procrit® that potentially did not contain any active ingredient and may have even been tainted with bacteria.[4]

Key Stakeholders

The counterfeit drug market was first recognized officially by the international community in 1985 at the Conference of Experts on the Rational Use of Drugs in Nairobi. The result of this meeting was a commission to the WHO to implement programs intended to prevent and detect the importation, exportation, and smuggling of counterfeit drugs.[5] By collaborating with key agencies within its member states — such as Interpol, World Customs Organization, and the International Federation of Pharmaceutical Manufacturers and Associations — the WHO created the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), which seeks to improve existing legislative and regulatory infrastructures while also promoting effective technology to prevent counterfeiting as well as more efficient communication mechanisms between trading countries. Since IMPACT's initiation, it has drafted guidelines for security practices such as sampling suspect products and preparing rapid response plans by the regulatory bodies governing medicine in participating nations.[6]

Apothecary has been responsible for numerous "surge operations," including extensive examinations of suspected parcels and ICE investigations, and numerous convictions and seizures of adulterated drugs have resulted.

Within the United States, the FDA and the U.S. Department of Homeland Security, Immigration and Customs Enforcement (ICE), have implemented their own programs to help combat the increasing counterfeit drug problem. The FDA has drafted Industry Guidance that proposes a mechanism to increase drug safety. For example, pursuant to Section 505D of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §155, the FDA has submitted guidance on the use of standardized numerical identifiers (SNIs) on package labeling to promote accurate identification of the product drug through a serialized National Drug Code.[7] The FDA has also organized a Counterfeit Alert Network which alerts its participants of confirmed counterfeit cases in the United States or in another part of the world that have the potential to affect United States consumers.[8] As discussed below, the FDA has also promulgated draft guidance on the use of technology or additives to identify and tag manufacturers' products.

ICE has joined with the FDA Office of Criminal Investigations (OCI), along with other law enforcement partners, such as the Computer Crime and Intellectual Property Section of the Department of Justice and the U.S. Postal Inspection Service, to create an investigations and enforcement arm to counter the impact of counterfeiting within the U.S. In October 2007, these groups implemented Operation Guardian, which specifically targets the "importation and distribution of harmful, foreign products imported from all foreign sources."[9] As part of Operation Guardian, these member agencies have created an ongoing investigation initiative called Operation Apothecary ("Apothecary"), tailored to combat the smuggling of commercial counterfeit drugs through the internet, international mail facilities, international courier hubs, and U.S. land borders. Apothecary has been responsible for numerous "surge operations," including extensive examinations of suspected parcels and ICE investigations, and numerous convictions and seizures of adulterated drugs have resulted.[10]

Proactive Solutions

1. Pre-market Actions: Anti-counterfeit Technology

With the problem of counterfeit medications growing as quickly as the internet can connect unwary consumers to illegitimate websites, pharmaceutical manufacturers can be left holding the pieces of a broken

reputation. Combine this problem with consumer panic and heightened media attention, and pharmaceutical manufacturers immediately face the prospect of rebuilding their good name and hard-earned position in the marketplace. This unwelcomed scenario should cause the manufacturer to consider preventative measures that may be taken beforehand.

Several innovative options have appeared as this growing problem forces stakeholders to take inventory. For example, in 2004, the FDA issued industry guidance for the use of radio frequency identification (RFID) to "label" legitimate pharmaceutical products. RFID uses a small memory chip (RFID tag) which is placed on the drug and emits radio waves. This technology allows manufacturers and drug distributers to track the drug through the market supply chain to create an "electronic pedigree" as the drug moves from the manufacturer to the ultimate dispenser. The goal is to set aside patient fears as to how RFID could threaten individual privacy. In this world of technology and Orwellian fears, the RFID tag does not include information that could link any particular person to a drug, nor can any pharmacy or other drug dispenser add information to the tag once it is in place by the drug manufacturer. The tag's sole function is to track the medication to ensure that the exact drug that leaves the manufacturer reaches the proper destination.

Several drawbacks to RFID are worth mentioning. RFID adds costs to the pharmaceutical product because it encompasses more than a simple redesign of a package — it includes assimilating new technology both in the design or packaging and in the chain of commerce as the drug moves from manufacturer to distributor to retail sales. That is, those market participants receiving the product must also incorporate technology capable of reading the RFID. Further, RFID cannot logistically curb the harmful effects of tainted medication, as it primarily is available for packaging identification alone and does not "read" the actual drug product to determine if it is the correct chemical composition of that particular drug. But, with a pending FDA regulation, pharmaceutical manufacturers may have no choice but to implement RFID. Section 505D of the Food, Drug, and Cosmetic Act mandates that manufacturers select and implement a method to authenticate and trace their prescription drug products.[11] Currently, this mandate is slated to go into effect on December 31, 2010.

With the problem of counterfeit medications growing as quickly as the internet can connect unwary consumers to illegitimate websites, pharmaceutical manufacturers can be left holding the pieces of a broken reputation.

For manufacturers of solid oral dose drugs, another proactive option to protect the product is using physical chemical identifiers, including inks, pigments, flavors and molecular taggants. These identifiers are read by holography, laser scanning, fluorescent detection, etc. One of the greatest concerns in using physical chemical identifiers is how they may affect the drug itself as well as the patient. According to a 2009 guidance issued by the FDA,[12] these identifiers should be limited to permissible food additives, including those generally recognized as safe by the FDA, or ingredients listed on the FDA Inactive Ingredient Guide. Another consideration is where to insert the identifier into the drug. The FDA guidance provides that the identifier should be inserted in a section that does not control any time-released mechanisms and that it should not be inserted into an area where an active ingredient is contained. The value of this identifier depends on whether it can be adopted systematically, as there must both be a method for inserting the identifier into the medication as well as a method for detecting the identifier before dispensing to patients. This challenge points to a concern mirrored with RFID — cost control. Additionally, in dealing with chemical identifiers, the manufacturer must submit the added identifier to FDA scrutiny for toxicological concerns.

2. Post-market Actions: Using Litigation Solutions to Combat Counterfeiting

Solutions such as anti-counterfeit technology are engineered to prevent infringement and thus save the "pound of cure" spent in litigation. But, with internet sales of illegitimate drugs rampant and on the rise, a manufacturer of pharmaceuticals should understand the remedies available for moving to the offense. While the law may not have evolved to meet the issue head-on, companies are finding there are avenues available to address it.

Under current law, one viable offensive tactic a manufacturer may employ upon identifying the source of counterfeit drugs is a suit to enforce patent and trademark rights. Both patents and trademarks are intended to provide a wall of protection around a company's valuable intellectual property and, likewise, to provide a weapon of retaliation and restitution when that protection is infringed. Understanding the intrinsic differences between patents and trademarks is crucial for drug manufacturers desiring to maximize protection — as well as their goodwill — before the public and their customers.

Drug manufacturers invest vast quantities of resources and finances to ensure their products have properly registered patents in countries where those products

are manufactured or sold. Patents exclude third parties from making, using, importing, selling or offering for sale patented products or methods of manufacture for a limited period of time. To enforce the patent in litigation, the patent holder must allege the counterfeit manufacturer is making or selling a pharmaceutical that is described in the patent. A primary consideration is cost: Patent litigation is an expensive process. Expenses are manifest as the holder frequently must proffer an expert to testify to the technical language and applications included in the registered patent. Further, to enforce patent rights, the holder must prove that the counterfeit infringes the patent in an *exact* fashion or by *close copy*. Counterfeits that do not contain the exact same or similar ingredients or formulations of the patented product may not rise to the level of patent infringement.

While patent litigation is an option for those instances where the counterfeit medication is an exact copy of the patented product, manufacturers may find the better path to pursue is trademark litigation. Similar to patents, drug manufacturers generally register trademarks in the countries where the drug is made or distributed. Trademarks provide broader protections for the pharmaceutical than patents, including protections for the pharmaceutical's name, any symbols used in labeling, as well as designs, colors, logos, or packaging. Because of the flexible nature of the trademark's protections, a drug manufacturer should seek to apply its registered trademark to as much of the product as possible.

The Lanham Act, 15 U.S.C. §§1501-1141, grants to the holder of a trademark the right to sue those who infringe the mark. The Lanham Act defines "counterfeit" as a "spurious mark which is identical with, or substantially indistinguishable from, a registered mark."[13] If the counterfeit mark is "likely to cause confusion, or to cause mistake, or to deceive" in its use of a mark, a plaintiff may bring an action and immediately petition the court in an *ex parte* proceeding for injunctive relief.[14] Further, the Lanham Act provides that a court *shall* award treble damages or statutory damages of up to $100,000 per mark at the plaintiff's option in exceptional cases. The Lanham Act stipulates that, in the absence of extenuating circumstances, the court must award damages to the successful plaintiff. Damages may include "(1) defendant's profits, (2) any damages sustained by the plaintiff, and (3) the costs of the action" to prevailing plaintiffs.[15] This, along with injunctive relief, allows greater restitution for drug manufacturers over the more stringent requirements of patent litigation.

By simply purchasing the suspected product off the internet and submitting it to inspection and analysis, a manufacturer can determine whether the drug is a fake. Once this is known, the hunt begins for the owner of the website and address, both of which may be found with a search of the domain registrar's records.

The Lanham Act provides potential actions beyond the basic trademark counterfeiting/infringement scenario. For example, Section 43(a), the unfair competition arm of the Act, provides for a cause of action for false designation of origin, and under Section 43(c), a plaintiff may pursue an action for trademark dilution. Partnering these statutory claims with a variety of common law claims, such as injury to business reputation, the pharmaceutical manufacturer is well-equipped to bring a successful claim against a known maker of counterfeit drugs.

Potential Roadblocks

Of course, even though these remedies sound appealing in light of their favorable awards of both injunctive relief and high damages, a manufacturer must at this point be asking the question, "If we are to sue, who do we sue and how do we serve them with the complaint?"

Because counterfeit drugs are often purchased through the internet and often originate in foreign countries, the process for bringing a suit begins with stringent investigation. Investigation starts with an inquiry to determine that the drug at issue is, in fact, a counterfeit. By simply purchasing the suspected product off the internet and submitting it to inspection and analysis, a manufacturer can determine whether the drug is a fake. Once this is known, the hunt begins for the owner of the website and address, both of which may be found with a search of the domain registrar's records. Often in the world of counterfeits, though, the name, telephone number and other identifying information provided to the domain registrar are false, and the investigation must then proceed "on the ground," searching for a viable address for service of process. These efforts may prove fruitless, as the counterfeit web is often covered by elaborate smoke and mirrors.

Procedurally, though, all may not be lost at this point. On the contrary, after learning that the information provided to the domain registrar is false, a pharmaceutical manufacturer may still have the option of instigating proceedings by filing suit under the applicable provisions of the Lanham Act, asking for injunctive relief, money damages, and an assignment of the domain name used by the counterfeiter. A growing trend under Rule 4(f)(3) of the Federal Rules of Civil Procedure is courts' approving service of process by email. Affidavits and declarations provide proof that the counterfeit manufac-

turer's identifying information and address are false. With this proof, a plaintiff may seek permission from the court to serve process via the email address used by the counterfeiter to sell the fake drugs.[16] The counterfeiter takes orders and receives payment for the illegal drugs through its website; thus, email service via that same website ensures that the defendant receives notice of the claims against it. Unless a counterfeiter responds to these complaints, which happens only rarely, the manufacturer may be able to obtain a default judgment, along with an award of money damages and injunctive relief. And often the true victory is an assignment of the domain name, which ultimately gives the plaintiff the rights to many of the domain names that could be associated with the pharmaceutical product.

An additional roadblock the manufacturer may face is the role federal and state governments play in conducting their own investigations. Ideally these remedies should work in tandem to create an effective deterrent against counterfeiting, but pharmaceutical manufacturers who find themselves as plaintiffs in litigation to enforce intellectual property rights may find that the parallel proceedings sometimes halt and grind rather than flow.

If a manufacturer is fortunate enough to identify a counterfeiter's physical location such that traditional service of process is possible, the United States likely will instigate federal criminal proceedings. But, as often is the case, procedural issues immediately arise, some of which may put the progress of the civil suit at odds with criminal investigations. One possibility for which a manufacturer should be prepared is an indefinite stay of litigation pending the outcome of the criminal investigations. Even with this as a possibility, affected manufacturers should still consider private litigation a viable process.

While this path is not perfect and often requires a good measure of patience and perseverance, the roadblocks to successful litigation, assuming the manufacturer's goals are realistic (injunctive relief, assignment of the domain name used to market the counterfeit product) generally are not insurmountable.

Conclusion

Despite the efforts of agencies working both domestically and globally to identify counterfeiters and effectively reverse their enterprise, pharmaceutical drug counterfeiters remain a serious threat to legitimate markets, affecting manufacturer, consumer, and every step in-between. Manufacturers can take advantage of innovative pre-market technology to secure the product before it debuts in the marketplace. If those measures do not prove a perfect shield, manufacturers may want to, or have to, take aggressive action to stop a counterfeiter who might otherwise elude accountability. This path leads through an obstacle course of investigation and the inevitable starts and stops of litigation, and requires doggedness and creativity on the part of legal counsel.

The counterfeit pharmaceutical industry should not spread unchecked. Government is making strides in combating this "growth industry." Private manufacturers that want to or need to take up the mantle now have available the means to protect their products and to begin to hold these 21st century charlatans accountable.

[1] World Health Organization, Fact Sheet 275. Available at <http://www.who.int/mediacentre/factsheets/fs275/en>. January 2010. Last accessed April 15, 2010.

[2] *Id*. For sake of illustration, the United States Federal Food, Drug and Cosmetic Act defines a counterfeit drug as: A drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor. 21 U.S.C. §321 (g)(2).

[3] See FDA Warning: Counterfeit Alli. Available at <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm198557.htm>. 25 January 2010. Last accessed April 15, 2010.

[4] World Health Organization, Substandard and Counterfeit Medicines. Available at <http://www.who.int/mediacentre/factsheets/ 2003/fs275/en>. November 2003. Last accessed April 15, 2010.

[5] International Medical Products Anti-Counterfeiting Taskforce (IMPACT), *Counterfeit Drugs Kill!* PDF available at <http://www.who.int/impact/resources/en>. May 2008. Last accessed April 15, 2010.

[6] World Health Organization, Secretariat Report on Counterfeit Medical Products: International Medical Products Anti-Counterfeiting Taskforce. PDF available at <http://apps.who.int/gb/e/e_wha62.html> by clicking on A62-14. April 30, 2009. Last accessed April 15, 2010.

[7] U.S. Food and Drug Administration, *Draft Guidance: Standards for Securing the Drug Supply Chain — Standardized Numerical Identification for Prescription Drug Packages*. January 2009.

[8] *See* U.S. Food and Drug Administration, Counterfeit Alert Network. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm170315.htm>. July 8, 2009. Last accessed April 15, 2010.

[9] U.S. Immigration and Customs Enforcement, Department of Homeland Security. *Statement Regarding a Hearing on Oversight of Trade Functions: Customs and Other Trade Agencies Before the Senate Finance Committee* (2008) (statement of Julie L. Myers, Assistant Secretary, U.S. Immigration and Customs Enforcement, Department of Homeland Security). Available at <http://www.ice.gov/pi/news/testimonies/index.htm.>. August 11, 2009. Last accessed April 16, 2010.

[10] *Id*.

[11] 73 Fed. Reg. 78,371 (Dec. 22, 2008).

[12] *See Guidance for Industry Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting*, U.S. Dept. of Health and Human Servs., Food and Drug Admin., Center for Drug Evaluation and Research. July 2009.

[13] 15 U.S.C. 1127 (2009).

[14] 15 U.S.C. §1114 (1)(a)(2009).

[15] 15 U.S.C. §1117 (2009).

[16] For example, in *Rio Props. Inc. v. Rio Intern. Interlink*, 284 F.3d 1007 (9th Cir. 2002), the United States Court of Appeals for the Ninth Circuit held that court-directed service by email is proper under Federal Rule of Civil Procedure 4(f)(3) when the plaintiff demonstrates the specific facts and circumstances warranting a court's intervention such as in the scenario where an elusive international defendant evades service of process. *Id*. at 1017; *see also Chanel, Inc. v. He Zhizhong*, No. 09-2818, 2010 WL 985195 (W.D. Tenn. Mar. 16, 2010)(holding service of process by email under Fed. R. Civ. P. 4(f)(3) comports with due process when the defendant conducts a substantial portion of its business over the internet and further communicates with its clients via email); *Popular Enters., LLC v. Webcom Media Group*, 225 F.R.D. 560 (E.D. Tenn. 2004) (holding that service of process via email was proper under Fed. R. Civ. P. 4(f)(3) because it was the most likely method to reach the foreign defendant as other emails had successfully reached the defendant).

Written *by*
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THE *TWOMBLY* TRANSITION: STATES SLOW TO ADOPT *TWOMBLY'S* HEIGHTENED PLEADING STANDARD

I. Standard for Evaluating 12(b) (6) Motions According to *Twombly*

On May 21, 2007, the United States Supreme Court decided the antitrust matter of *Bell Atlantic v. Twombly*, and in the process, retired the 1957 decision in *Conley v. Gibson*. *Bell Atlantic v. Twombly*, 127 S. Ct. 1955, 1955-1966 (2007); *Conley v. Gibson*, 355 U.S. 41, 78 S. Ct. 99, 102, 45-46 (S. Ct. 1957).

The Supreme Court in *Conley* established the standard for granting a 12(b)(6) motion to dismiss, stating:

> [A] complaint should not be dismissed for failure to state a claim unless it appears beyond a reasonable doubt the plaintiff can prove no set of facts entitling him to relief under the law.[1]

In a 7-to-2 majority decision, the *Twombly* Court held that a complaint must allege something more than parallel conduct among industry competitors to state a claim for unlawful contract, combination, or conspiracy under Section 1 of the Sherman Act.[2] Specifically, the Court referred to *Conley's* "no set of facts" language stating: "[t]he phrase is best forgotten as an incomplete, negative gloss on an accepted pleading standard."[3] The Supreme Court emphasized the importance of the Rule 8 requirement that a plaintiff set forth the grounds entitling him to relief. [4] The Court stated:

> [It] requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do. Factual allegations must be enough to raise a right to relief above the speculative level on the assumption that all of the complaint's allegations are true.[5]

II. Expanding *Twombly*

While *Twombly* marked the end of a notice pleading era, the Supreme Court's opinion was unclear as to the scope of this new pleading standard. Two years later, the Supreme Court clearly held that *Twombly* "governs the pleading standard in all civil actions and proceedings in the United States District Courts."[6]

The plaintiff in *Iqbal v. Hasty*, a Muslim Pakistani pretrial detainee, brought action against current and former government officials, alleging unconstitutional actions were taken against him in connection with his confinement.[7] Defendants alleged the plaintiff failed to state his claim sufficiently according to *Twombly*.[8] The Second Circuit distinguished *Twombly*, holding that because the Supreme Court approved Fed. R. Civ. Pro. App. Form 9, the Plaintiff had sufficiently stated his claim.[9]

The Supreme Court reversed the Second Circuit, rationalizing that Plaintiff's "bare assertions […] amount to nothing more than a formulaic recitation of the elements of a constitutional discrimination claim."[10] The court further held that the complaint "does not contain any factual allegation sufficient to plausibly suggest petitioners' discriminatory state of mind. His pleadings thus do not meet the standard necessary to comply with Rule 8."[11]

III. Courts Transition to *Twombly*:

It has been over two years since the Supreme Court abolished pure notice pleading in *Twombly*. While federal district courts are bound by the *Twombly* standard, state courts are not, although states whose rules are patterned after the Federal Rules often find federal interpretation persuasive. The transition to *Twombly* has been slow; however, the following courts have considered adoption of the heightened pleading:

Courts adopting *Twombly*:

District of Columbia: *Clampitt v. American University*, 957 A.2d 23, 29 (D.C. 2008) (applying standard set forth in *Twombly* to hold, that "[a]t the same time, '[f]actual allegations must be enough to raise a right to relief above the speculative level.'")

Louisiana: *Tuban Petroleum, L.L.C. v. SIARC, Inc.*, 11 So. 3d 519, 523 (La. App. 4 Cir. 2009) (holding that "[t]he Louisiana Supreme Court has also looked to the federal jurisprudence for guidance because the federal and state antitrust statutes are virtually identical. The United States Supreme Court stated that 'a formulaic recitation of the elements of a cause of action will not' suffice.")

Maine: *Bean v. Cummings*, 939 A.2d 676, 688 (Me. 2008) (adopting *Twombly* in light of the fact that "Maine's Rules 8(a) and 9(b) are practically identical to the comparable federal rules.")

Massachusetts: *Iannacchino v. Ford Motor Company*, 888 N.E. 2d 879, 883 (Mass. 2008) (holding "we take the opportunity to retire the Conley language.")

Minnesota: *Bahr v. Capella University*, 765 N.W. 2d 428, 437 (Minn. Ct. App. 2009) (holding "[w]e are mindful that the United States Supreme Court has recently corrected this standard insofar as it suggests that the future introduction of evidence can substitute for an adequate statement of facts in the complaint; the statement of entitlement to relief must go beyond 'labels and conclusions' or the 'speculative presentation of a claim.'"

Ohio: *Gallo v. Westfield Natl. Ins. Co.*, 2009 WL 625522, *2 (Ohio Ct. App. 2009) (holding "the claims set forth in the complaint must be plausible, rather than conceivable. While a complaint attacked by a Civ. R. 12(B)(6) motion to dismiss does not need detailed factual allegations, Gallo's obligation to provide the grounds of her entitlement to relief requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do. Factual allegations must be enough to raise a right to relief above the speculative level.")

South Dakota: *Sisney v. Best Inc.*, 754 N.W. 2d 804, 809 (S.D. 2008) (holding "we adopt the Supreme Court's new standards.")

Courts declining to adopt *Twombly*:

Alabama: *Crum v. Johns Manville, Inc.*, 19 So. 3d 208, 212 (Ala. Civ. App. 2009) (holding "[t]he United States Supreme Court's interpretation of the Federal Rules of Civil Procedure is not binding on this court's interpretation or application of the Alabama Rules of Civil Procedure. Instead, this court is bound by the Alabama Supreme Court's interpretation of our Rules of Civil Procedure. Our supreme court has adopted the standard set forth in *Conley v. Gibson, supra*, for the dismissal of claims under Rule 12(b)(6), Ala. R. Civ. P. Until such time as our supreme court decides to alter or abrogate this standard, we are bound to apply it, the United States Supreme Court's decision in *Twombly, supra*, notwithstanding.")

Arizona: *Cullen v. Auto-Owners Ins. Co.*, 189 P.3d 344, 348 (Ariz. 2008) (holding "[i]f Arizona elects to revise the notice pleading standard for stating a claim under Rule 8, such revision will occur through an interpretation by this Court or through the procedures set forth in Rule 28.")

Washington: *Save Columbia CU Committee v. Columbia Community Credit Union*, 150 Wash. App. 176, 186 (Wash. Ct. App. 2009) ("reject[ing] *Twombly* until the State Supreme Court specifically holds otherwise.")

Vermont: *Colby v. Umbrella, Inc.*, 184 Vt. 1, 5 (Vt. 2008) (holding "we have relied on the *Conley* standard for over twenty years, and are in no way bound by federal jurisprudence in interpreting our state pleading rules. We recently affirmed our minimal notice pleading standard in Alger, 2006 Vt 115, ¶12, 181 Vt. 309, 917 A.2d 508, and are unpersuaded by the dissent's argument that we should now abandon it for a heightened pleading standard.")

State Split:

Tennessee:

Morris v. Grusin, 2009 WL 4931324, *4 (Tenn.Ct.App. 2009) ("[W]e are not at liberty to adopt the more liberal [*Twombly*] standard for dismissing complaints for failure to state a claim urged by Defendants.")

Hermosa Holdings, Inc. v. Mid Tennessee Bone and Joint Clinic, P.C., 2009 WL 711125, *3 (Tenn. Ct. App. 2009) ("Although the Tennessee Supreme Court has not adopted the standard announced in *Twombly*, we find it consistent with Tennessee law and therefore recognize its applicability.")

[1] *Conley*, 78 S. Ct. at 102, 45-46.
[2] *Twombly*, 127 S. Ct. at 1965-66.
[3] *Id.* at 1960.
[4] *Id.* at 1959.
[5] *Id.*
[6] *Ashcroft v. Iqbal*, 129 S. Ct. 1937, 1953 (2009).
[7] *Id.* at 1942-43.
[8] *Id.* at 1939.
[9] *Iqbal v. Hasty*, 490 F.3d 143, 156 (2nd Cir. 2007).
[10] *Id.* at 1949.
[11] *Id.* at 1951-52.

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SIDE
EFFECTS

An Updated Guide on

Managing Risks and Enhancing Prescription Drug Safety

after Product Launch

"It is simply not possible to identify all the side effects of drugs before they are marketed." [1]

INTRODUCTION

The safety vigilance that a drug manufacturer exercises to obtain approval of a new prescription drug from the United States Food and Drug Administration (FDA) continues through the life of the product.[2] An ongoing challenge faced by industry involves charting and implementing an effective strategic course for managing risks and enhancing drug safety after product launch. A vigilant, responsive drug safety system that applies the best possible science and technologies to identify and understand the risks of medication use promotes patient safety and fosters public trust and confidence in the drug manufacturer and its products.

A more formalized plan of risk evaluation and mitigation may be required by FDA under legislation added to the Food Drug and Cosmetic Act (FDCA)[3] by the FDA Amendments Act of 2007 (FDAAA).[4] The drug safety provisions of FDAAA strengthen FDA's authority to regulate the postmarket safety of drugs and mandate that the agency establish novel programs to prevent and detect adverse drug reactions to enhance drug safety.[5] Under the FDAAA, FDA may require postmarket studies and clinical trials to address safety issues, safety labeling changes, and Risk Evaluation and Mitigation Strategies (REMS) if the agency determines this is necessary to ensure that the benefits of the drug outweigh the risks.[6]

FDA has issued guidance papers to assist industry in developing and implementing effective risk management strategies. This article discusses FDA's Draft Guidance for Industry, *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* ("REMS Guidance"), September 2009.[7] FDA's REMS Guidance provides a useful blueprint for developing important strategies on risk evaluation and mitigation.[8] The article concludes with recommendations and practical tips for pharmaceutical manufacturers.

FDA REMS GUIDANCE

Overview of REMS

Section 505-1 of the FDCA authorizes FDA to require a Risk Evaluation Mitigation Strategy (REMS).[9] During the approval process, FDA will determine whether a REMS is required to ensure that the benefits of the drug or biological product outweigh the risks. If so, FDA will require the sponsor of the application to submit a proposed REMS, and the REMS will be approved when the drug is approved. If a product is already approved and FDA becomes aware of new safety information[10] that suggests a REMS is necessary to ensure that the benefits of the drug product outweigh the risks, FDA will require a REMS.[11] Among other things, a REMS may include plans for a Medication Guide, Patient Package Insert, a Communication Plan, Elements to Assure

Safe Use (ETASU), and an Implementation System. The REMS must include a timetable for assessment.[12]

Examples of drugs that may be subject to REMS are opiate drug products; products that are human teratogens; and products that may call for specialized healthcare skills, training, or facilities to manage the therapeutic or serious side effects of the medication.[13] As FDA becomes more comfortable with its new power and as more decisions regarding class-wide REMS are finalized, we can expect the number of REMS to grow significantly.

FDA may impose civil monetary penalties for violations of the REMS provisions, or the drug or biological product can be deemed misbranded and FDA could obtain injunctive relief.[14] Section 505-1 of the Act provides that the penalties may not exceed $250,000 per violation, or $1 million for all violations adjudicated in a single proceeding. If a violation continues after the sponsor receives written notice, the penalty is $250,000 for the first 30-day period (or any portion thereof) that the violation continues, not to exceed $1 million for any 30-day period and not to exceed $10 million for all violations adjudicated in a single proceeding. FDA may take into consideration whether the company is making efforts to correct the violation when determining the amount of a civil penalty.

Relationship Between REMS and RiskMAP

Some drug and biological products that previously were approved or licensed with risk minimization action plans (RiskMAPs) will now be deemed to have REMS. More specifically, before the enactment of FDAAA, FDA approved a small number of drug and biological products with RiskMAPs. A RiskMAP is "a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits."[15] In 2005, FDA issued a *Guidance for Industry on Development and Use of Risk Minimization Action Plans* that described how to develop RiskMAPs, select tools to minimize risks, evaluate and monitor RiskMAPs and monitoring tools, and communicate with FDA about RiskMAPs.[16]

Because FDA now has the authority under the FDAAA to require REMS when necessary to promote drug safety, FDA is seeking to reconcile REMS and RiskMAPs. FDA anticipates that a drug that would previously have been approved with a RiskMAP will instead be approved with a REMS if the statutory requirements for a REMS are met.[17] Further, drugs that would previously have been approved with a Medication Guide or patient package insert that meets the statutory requirements for a REMS will now be required to have a REMS. [18]

Many of the principles that were included in the RiskMAP guidance are embodied in Section 505-1 of the FDCA. The RiskMAP guidance continues to apply to products with existing RiskMAPs and to products with new RiskMAPs (*e.g.*, Abbreviated New Drug Applications, or "ANDAs," for which the reference listed drug has a RiskMAP). [19]

> A *vigilant*, responsive drug safety *system* that *applies* the *best possible* science and technologies to *identify* and *understand* the *risks* of *medication* use *promotes* patient *safety* and *fosters* public *trust* and *confidence* in the drug *manufacturer* and its *products*.

Content of REMS

A proposed REMS submission to FDA should have two parts.[20] First, the submission should contain a proposed REMS, which is a concise document that describes the goals and elements of the REMS and, once approved, will be the basis for enforcement.[21] Second, the submission should have a REMS supporting document that expands on information included in the proposed REMS.[22]

Proposed REMS

The proposed REMS should include product and contact information, goals, and elements used to achieve goals. A template for the proposed REMS is available on the FDA website.[23]

REMS goals should target the achievement of particular health outcomes related to known safety risks, such as patients on X drug should not also be prescribed Y drug.[24] In turn, these goals should be translated into pragmatic, specific, and measurable program objectives that result in processes or behaviors leading to the REMS goals."[25] For example, if the goal is the elimination of dangerous concomitant prescribing, then the objectives could consider lowering physician co-prescribing rates or pharmacist co-dispending rates or both.[26]

Potential REMS elements may include a Medication Guide, package insert, and communication plan to healthcare providers if the plan may support implementation of an element of the strategy.[27] These elements target education and outreach. They aim to increase the knowledge and behaviors of key people or groups, such as healthcare providers and consumers.

Medication Guides will be required if FDA determines that one or more of the following circumstances exist: (1) the drug product is one for which patient labeling could prevent serious adverse side effects; (2) the drug product is one that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect the patients' decision to use, or to continue to use, the product; and (3) the drug product is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness.[28] The sponsor is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed the drug.[29] Copies of Medication Guides and patient package inserts that are part of a REMS should be appended to the proposed REMS.[30]

FDA may determine that a Communication Plan targeted at healthcare providers and/or patients is a necessary element of the REMS.[31] Communication plans may include sending letters to healthcare providers, disseminating information about REMS elements to encourage implementation by

healthcare providers or to explain certain safety protocols such as medical monitoring by periodic laboratory tests, or disseminating information to healthcare providers through professional societies about any serious risks of the drug and any safety protocols.[32]

For a drug that has been shown to be effective but which is associated with a serious adverse event, there are elements required to assure safety.[33] Before requiring one or more Elements to Assure Safe Use (ETASU), though, FDA must make a determination that: (1) the drug, which has been shown to be effective but is associated with a serious adverse drug experience, can be approved only if, or would be withdrawn unless, such elements were required; or (2) for a drug initially approved without ETASUs, other possible elements of a REMS are not sufficient to mitigate such serious risk.[34]

An ongoing *challenge* faced by *industry* involves *charting* and *implementing* an effective *strategic course* for managing risks and *enhancing* drug *safety* after product *launch.*

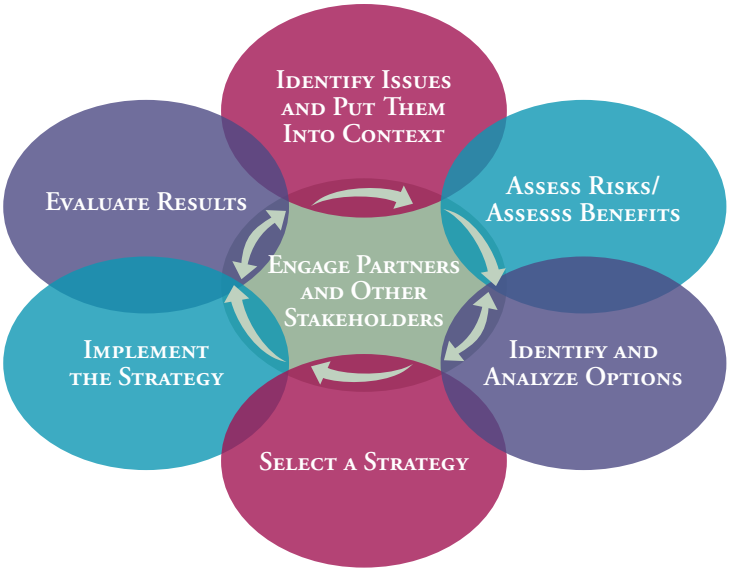
Elements to Assure Safe Use include requiring healthcare providers who prescribe the drug to have particular training or experience or to be specially certified; requiring pharmacies, practitioners, or healthcare settings that dispense the drug to be specially certified; requiring the drug to be dispensed to patients only in certain healthcare hospitals, requiring the drug to be dispensed only to patients with evidence or other documentation of safe-use conditions, such as laboratory results;[35] requiring each patient using the drug to be subject to certain monitoring; and/or requiring each patient using the drug to be enrolled in a registry.[36] Sponsors are expected to have in place an

implementation system to monitor and evaluate healthcare providers, pharmacists and other parties in the healthcare system who are responsible for implementing the elements of the ETASU.[37]

Further, these REMS elements for an NDA must have a proposed timetable for submission of assessments of the REMS.[38] Under Section 505-1(d), each timetable for submission of a REMS must at a minimum include assessments submitted by 18 months, three years and in the seventh year after the strategy is approved, with additional dates if more frequent assessments are necessary to ensure that benefits of the product continue to outweigh the potential risks.[39] For drugs with an FDA-approved ETASU, the first assessment period is typically shorter than 18 months. One example is GlaxoSmithKline's Entereg®, a medication indicated to accelerate the time for upper and lower gastrointestinal recovery following partial large or small bowel resection with primary anastomosis. One of the purposes of the REMS plan for Entereg is to reduce the risks of myocardial infarction observed with long term use. The FDA-approved REMS requires the drug manufacturer to submit assessments of the REMS on a quarterly basis during the first 18 months after REMS approval and annually thereafter.

Proposed REMS Supporting Documents

The REMS supporting document should provide a thorough explanation of the rational for and supporting information about the content of the proposed REMS. A template for a REMS supporting document is available on the FDA website.[40] The background section should describe what is known about the risk to be minimized by the REMS, such as the magnitude, severity, and frequency of the adverse event; whether there are particular populations at risk; the background incidence of the risk in the population likely to use the product; whether adverse events can be prevented or are reversible; and the benefits that would be preserved by implementation of the REMS.[41] The REMS supporting documents also should include a goals section, supporting information about proposed REMS elements, and other relevant information.[42]



Recommendations and Practical Tips

FDA REMS Guidance provides a useful blueprint for developing safety strategies and preparing a plan that will satisfy the requirements of Section 505.1 of the FDCA, as well as obtain FDA approval. As of April 15, 2010, FDA has approved 117 REMS.[43] Eighty-three REMS include only a Medication Guide. Thirty-four REMS include elements other than a Medication Guide, such as a Communication Plan and/or Elements to Assure Safe Use. Of these 34 REMS, twelve have Elements to Assure Safe Use.

A review of FDA approved REMS indicates what FDA is looking for in a proposed plan. First, it is important that the REMS specifically targets the newly identified potential risk. Second, the nature of the potential new risk determines the scope of the REMS. For instance, if the new risk concerns an increased risk of tendonitis and tendon rupture, then the goal of the REMS would be to inform patients about these potential increased risks, and the REMS elements would include a Medication Guide. If the potential risk includes medication errors because of similarities with other products on the market, then the REMS elements would include not only a Medication Guide, but also a Communication Plan.

The key to any successful plan, whether a REMS or something less formal, is to (1) identify issues and put them into context; (2) assess the risk and assess the benefits; (3) identify and analyze options; (4) select a strategy; (5) implement a strategy; and (6) evaluate results. Through this process the drug manufacturer should be working with FDA as well as keeping lines of communication open with healthcare providers and patients. The accompanying flowchart, taken from a Report to the FDA Commissioner from the Task Force on Risk Management, provides a useful illustration.[44]

Based on this flowchart, consideration should be given to the recommendations below. These are general recommendations only. The author acknowledges that circumstances related to individual drugs and issues to be addressed will vary, as will steps appropriate to addressing these circumstances or issues.

Implement Safety-Related Sections of FDAAA

- Review Framework for Tracking Adverse Experiences
- Evaluate and Improve Framework
- Increase Capacity for Postmarket Safety Monitoring
- Develop and Improve Automated Systems for Managing Adverse Event Reports
- Integrate Pre- and Postmarket Information Systems
  - Provide uniform application of analytical tools, data entry, and editing
  - Make information readily available to every reviewer

Managing the Postmarketing Surveillance

- Multidisciplinary Team-based Approach to Drug Safety
- World Class Project Management
  - Ensures company focuses the same attention on postmarket safety issues as it does on premarket review
  - Creates a culture of safety
- Most Appropriate and Best Qualified Lead Regulatory Decisions
- Ensure that Significant Postmarket Safety Issues are Highest Priority

Strengthen the Science of Drug Safety

- Advance Postmarket Drug Safety Predictions
- Advance Signal Detection and Analysis
  - Identify signals of potential safety problems database of spontaneous reports (*Distinguish noise from real concerns*)
  - Develop background incidence rates for problems in a population
  - Develop new methodological tools for inference from available datasets
  - Enhance clinical and laboratory studies to develop new methods to improve product safety (*e.g.*, biomarkers).
- Ensure Quality Manufacturing
  - Facilitate increased reliance on quality systems that will continually improve the quality of drugs and drug manufacturing.
  - Integrate enhanced quality management systems into review and inspection processes.
  - Encourage implementation of risk-based approaches that focus on critical areas. Ensure that regulatory review and inspection policies are performed by well-trained staff.

Expanding Communication and Information Flows

- Risk Communication within Company
- Risk Communication with FDA
- Risk Communication with Healthcare Providers
- Risk Communication with Patients

CONCLUSION

The vast majority of prescription drugs are safe and effective when used as labeled. As globalization, emerging areas of science, evolving technologies, and people's growing interest in managing their health and well-being present the industry with unprecedented challenges and opportunities, risk evaluation and minimization strategies keep pharmaceutical companies one step ahead.

[1] Wood, *et al.*, "Making Medicines Safer—The Need for an Independent Drug Safety Board," *N. Engl. J. Med.*, 339: 1851-1854 (1998).

[2] 21 U.S.C. §§355(k), 355 (o), 355-1 (2008).

[3] 21 U.S.C. §§301 *et seq*.

[4] Pub. L. No. 110-85, title IX, 121 Stat. 823 (Sept. 27, 2007).

[5] *See id.* §§901-21.

[6] *See* 21 U.S.C. §§355 (o), 355-1.

[7] The REMS Guidance: (a) provides FDA's current thinking on the format and content that industry should use for submission of proposed REMS; (b) describes each potential element; (c) includes preliminary information on the content of assessments and proposed modifications of approved REMS; (d) describes REMS policies for certain regulation situations; (e) informs industry about who to contact within FDA about a REMS; (f) indicates FDA websites where documents about approved REMS will be posted; and (g) provides an example of what an approved REMS might look like for a fictitious product. *See* REMS Guidance <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>. Last accessed April 21, 2010.

[8] Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research, FDA News Release dated Sept. 30, 2009. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm184399.htm>. Last accessed April 21, 2010.

[9] 21 U.S.C. §355-1.

[10] "New safety information" refers to "information derived from a clinical trial, an adverse event report, a postapproval study, or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system […] or other scientific data deemed appropriate by the Secretary about a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the REMS was required, or since the last assessment of the approved REMS; or the effectiveness of the approved REMS obtained since the last assessment of the strategy." *Id.* at §355-1 (b)(3).

[11] *Id.*

[12] *Id.*

[13] Fed. Reg. Vol. 73, No. 60 at 16313-14 (March 27, 2008).

[14] 21 U.S.C. §§331-333.

[15] REMS Guidance at 3.

[16] FDA Guidance for Industry, *Development and Use of Risk Minimization Action Plans* (March 2005), *passim*. For further discussion of RiskMAPs, see *Pro Te: Solutio* v.1, no.4, pp. 6-9.

[17] REMS Guidance at 3.

[18] *Id.*

[19] *Id.*

[20] *Id.* at 7.

[21] *Id.*

[22] *Id.* at 7.

[23] FDA's Postmarket Drug Safety Information for Patients and Providers. <www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders>. April 6, 2010. Last accessed April 21, 2010.

[24] REMS Guidance at 9.

[25] *Id.*

[26] *Id.*

[27] 21 U.S.C. §355-1(e).

[28] 21 C.F.R. Part 208.

[29] REMS Guidance at 10.

[30] *Id.*

[31] 21 U.S.C. §505-1(e)(3); REMS Guidance at 10-11.

[32] REMS Guidance at 11.

[33] *Id.* at §355-1(f).

[34] *Id.* at §355-1(f)(1).

[35] Because laboratory testing or other documentation may be burdensome and disrupt patient care, this tool should be considered when products have unique benefits but unusual risks, such as irreversible disability or death, and when other measures are known or likely to be insufficient to minimize those risks.

[36] *Id.* at §355-1(f)(3)(A)-(F).

[37] *Id.* at §355-1(f)(3)(B),(C) and (D).

[38] 21 U.S.C. §355-1(d).

[39] *Id.*

[40] FDA's Postmarket Drug Safety Information for Patients and Providers. <www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders>. April 6, 2010. Last accessed April 21, 2010.

[41] REMS Guidance at 16.

[42] *Id.* at 17-21.

[43] See FDA Approved RiskEvaluation and Mitigation Strategies. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>. April 15, 2010. Last accessed April 21, 2010.

[44] Task Force on Risk Management, Report on Managing the Risks from Medical Product Use and Creating a Risk Management Framework at 74-75. May 1999. <http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm180325.htm>. April 15, 2010. Last accessed April 21, 2010.

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