

# Brief

## Pharmaceutical Life Cycle Management: Navigating the New IP, FDA and Antitrust Terrain



Efforts to extend the life cycle of pharmaceutical products frequently involve innovations and improvements in product design, formulation, route of administration and treatment indications. In addition, negotiation of agreements with competitors, including generic and biosimilar manufacturers, is frequently employed as part of a life cycle management strategy. However, recent changes in patent, regulatory and antitrust laws have introduced greater complexity and higher risk into these strategies.

On October 23, 2015, a distinguished panel of BakerHostetler partners led an exclusive seminar in person and online at which they discussed these and related issues and provided suggestions for developing successful life cycle management strategies. Carl W. Hittinger, Lee Rosebush, Lance Shea and Maurice Valla are all deeply knowledgeable attorneys with decades of experience in helping clients meet their pharmaceutical business objectives.

# Patent-Based Exclusivity

“You have to pay attention as you’re going through the prosecution of your patent cases, because you can end up with a patent that doesn’t actually cover the indication that you’re getting. It’s not going to be an Orange Book-listable patent, and that’s going to make it significantly less valuable to you in terms of staving off generic competition.”

– S. Maurice Valla, Partner

Maurice Valla discussed several broad categories with regard to patent-based exclusivity:

- Early-stage development
- Developmental candidate identification
- Clinical development
- Approaching approval
- Prior to launch and follow-on indications
- Active pharmaceutical ingredient characteristics and new formulations
- Additional protection strategies

Selected highlights:

**Early-stage development:** Patent practitioners have historically focused on obtaining protection for therapeutic targets such as isolated DNA sequences, or for research tools used to identify compounds that interact with those isolated DNA sequences. But Valla also explained that patent practitioners now face a legal landscape in which isolated sequences are no longer patentable unless the sequence has a markedly different characteristic from its naturally occurring counterpart.

He also discussed how patent practitioners regularly sought patent protection for correlations between a therapeutic target and disease. For example, a claim might be directed to a method of treating a disease by interacting with a particular target. The current § 112 jurisprudence forecloses these types of claims unless the specification provides sufficient examples of the therapeutic compound to inform one of ordinary skill in the art. Valla suggested that such target/disease correlation claims might still be allowable when the target is well-characterized and the contemplated method of treatment is the administration of a biologic such as an antibody or an oligonucleotide. Unlike small molecule therapeutics, the prevailing view is that one of skill in the art could design an antibody or an interfering RNA to a sufficiently definite target.

**Developmental candidate identification:** Valla said that freedom to operate should be a consideration from the very beginning of the patenting process. He advised looking at what already exists in the patent landscape in terms of

the therapeutic target, drugs and competing companies. If patents exist, ask whether those patents are still valid under the latest legal standards and how much of the patent term remains.

Valla explained that the primary concern from a legal standpoint is how broadly to draft a claim. In the past, practitioners drafted broad generic claims to cover a vast universe of species. Valla noted that the current practice involves starting with a broad generic claim then narrowing the scope of the claim. If the field is very crowded, it may be desirable to claim a narrower genus, especially where that narrow genus has unexpected advantages over the prior art.

He cautioned that many countries require the applicant to limit the scope of the claims to only those compounds that have actually been synthesized. This is a significant shift from the conception-focused practice in the United States. In certain countries, like China, Japan and Taiwan, it is necessary to submit data for a representative number of compounds that shows that the compounds actually work for their claimed purpose. Such requirements are in direct tension with the “first to file” system in the United States and elsewhere. Determining when to file may come down to a business decision where the applicant balances timing considerations with the importance of capturing the international markets.

**Clinical development:** Valla said that it is desirable to claim as broadly as possible from the outset to anticipate future changes to the product. He advised that in a situation where protection is later sought for a particular salt form of the compound, such claims may face obstacles where the compound is already known and there are a limited number of pharmaceutically acceptable salts. Similarly, it may be difficult to get a claim directed to a particular isomer where the racemic mixture is known in the art.

**Approaching approval:** 35 U.S.C. § 156 provides for an extension to the patent term to compensate for any delay introduced by the regulatory approval process. Valla advised that the applicant should carefully consider which patent to extend as it is only possible to extend the term for one patent per product. He suggested considering which patent is strongest in terms of validity and which patent will give the longest period of exclusivity if extended. He also noted that the extension does not apply to the patent as a whole, but only to the product for which approval was sought. Interpreting what qualifies as the same product becomes particularly difficult when dealing with biologics, where the marketed product is similar, but not identical, to the claimed product.

**Prior to launch and follow-on indications:** Valla stressed the importance of reassessing the intellectual property landscape and the client’s portfolio throughout the approval process, as the transition to commercial-scale manufacturing might yield methods of treating additional conditions. However, diagnostic-style claims may face

greater scrutiny under some newly developed case law. Valla suggested looking for novel testing methods or reagents, or simply drafting the claims as a method of treatment. Method of treatment claims are valuable to the drug manufacturer insofar as they provide support for a product label, but they may be less valuable to third parties given the complexities of distributed infringement.

**Active pharmaceutical ingredient characteristics and new formulations:** Valla said that it might also be possible to claim new formulations. For example, the applicant may wish to draft claims covering new coatings or new routes of administration, keeping in mind that the new formulation must overcome an obviousness challenge or problems stemming from a lack of written description in the specification.

Valla advised that when seeking protection for a method of treatment using two drugs, the key to patentability will lie in the applicant's ability to convince the Patent Office that the drug combination yields unexpected or synergistic results.

**Additional protection strategies:** In addition to drug/drug combinations, the applicant may pursue drug/device combinations such as a loaded syringe or inhaler. Such a combination would be separately patentable and listable in the Orange Book, and could provide an attractive avenue for gaining protection for an old drug.

## Conclusion

Valla concluded with the observation that the applicant also may wish to seek patent coverage for an approved Risk Evaluation and Mitigation Strategy (REMS), though courts are increasingly viewing these sorts of patents as directed to the abstract idea of a method of distributing or controlling the risk in a population.

## FDA Exclusivity

"From the application perspective, we're really looking at two potential exclusivity issues for brand-name applications. These are the two that we're really trying to get into – the NCE for five years or for the NCI for three years."

– Lee H. Rosebush, Partner

## Five Types of Exclusivities

In addition to the patent rights that a drug sponsor should use to protect its products in the increasingly competitive pharmaceutical marketplace, there are powerful regulatory exclusivities that should be considered. Understanding the different exclusivities and the pathways to obtain them

will help shape a pharmaceutical company's research and development strategy and enhance its competitive advantage.

Rosebush discussed five types of Food and Drug Administration (FDA) exclusivities available for pharmaceutical products:

- New chemical entity (NCE) exclusivity
- New clinical investigation (NCI) exclusivity
- Orphan drug exclusivity
- Pediatric exclusivity
- Biologics license application (BLA)

Each exclusivity has specific criteria that an applicant/sponsor must meet. In addition, each exclusivity has its own limitations on what competitive activities are excluded.

**New chemical entity exclusivity (NCE):** A sponsor may apply for NCE exclusivity for "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act." The active moiety of a drug is the molecule or ion responsible for the physiological or pharmacological action of the drug.

NCE exclusivity can be obtained by submitting either a 505(b)(1) or 505(b)(2) application. A 505(b)(1) applicant will submit to the FDA safety and efficacy data generated in clinical trials performed by the applicant to support its request for exclusivity. A 505(b)(2) applicant relies at least partially on prior clinical data that the sponsor did not generate.

NCE exclusivity typically lasts five years and prevents the submission of any 505(b)(2) or abbreviated new drug applications (ANDAs) for drugs containing the same active moiety.

**New clinical investigation exclusivity (NCI):** NCI exclusivity can be granted to applicants submitting 505(b)(1), 505(b)(2), or supplemental applications. The sponsor must perform clinical studies, which the FDA defines as "an investigation in humans, the results of which (1) have not been previously relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety in a new patient population and (2) do not duplicate the results of another investigation relied upon by FDA to demonstrate a previously approved drug's effectiveness or safety in a new patient population."

NCI exclusivity prohibits the FDA from approving a 505(b)(2) or ANDA application for three years, but it does not prevent applicants from submitting their applications. NCI exclusivity is available for "recycled" or "rebranded" drugs, or those drugs deemed to have the same active moiety as previously approved drugs, provided the new product relies on a new clinical study. "Recycled" drugs can include extended-release versions of drugs currently on the market or new salt forms of the drugs. NCI exclusivity also

is granted for new indications, dosage regimens, patient populations and formulations of products previously on the market.

**Orphan drug exclusivity:** Orphan drug designation, or drugs intended for conditions that affect fewer than 200,000 people in the United States, may be eligible for seven years of market exclusivity. Originally intended for sponsors who would be unable to recoup the costs associated with developing an orphan drug, this designation provides full market exclusivity, which means the FDA will not approve another sponsor's marketing application for the same drug with the same indication for seven years from the date of the orphan product's approval letter from the FDA.

In addition to the seven years of market exclusivity, Rosebush explained that a sponsor can apply for and receive orphan drug status before the drug gets full FDA approval. Applying early for orphan drug designation is advisable because sponsors receive certain incentives such as 1) tax advantages, 2) additional representatives at meetings with FDA, and 3) possible reduced filing fees for drugs that receive orphan designation.

Rosebush noted that receiving an orphan drug designation does not limit the sponsor to the orphan indication. While the drug will enjoy the market exclusivity for the orphan indication, the sponsor also may pursue a more broadly applicable indication. He gave the example of Viagra, a well-known treatment for erectile dysfunction (ED), which was initially used to treat pediatric pulmonary hypertension, a condition affecting fewer than 200,000 people in the United States. Viagra received orphan drug designation for the pediatric pulmonary hypertension indication, while Pfizer also was able to get a broad label for ED.

**Pediatric exclusivity:** This is only available for a drug if the FDA requests a sponsor to undertake pediatric studies for a specific indication. But Rosebush emphasized that the sponsor can initiate contact and ask the FDA to request the pediatric studies. If a sponsor complies with the request to perform pediatric studies, the drug will likely receive the six-month pediatric exclusivity even if the drug is never approved for the pediatric indication studied by the sponsor. The six-month pediatric exclusivity period is added to any FDA exclusivity the drug enjoys, as well as the patent rights covering the drug.

**Biologics license applications exclusivity (BLA):** Biologics also are entitled to FDA-regulated exclusivities. Section 7002 of the Patient Protection and Affordable Care Act (PPACA) provides 12 years of exclusivity for approved BLA. BLA exclusivity is not available for supplements

or subsequent applications by the same sponsor for a change that results in a new indication, dosing schedule, dosage form, delivery system, delivery device or strength. Only applications by the same sponsor for changes to an existing biologic that result in a modification of safety, purity or potency can be granted an additional 12 years of exclusivity. Biologics can also receive orphan drug and pediatric exclusivities.

## Conclusion

In conclusion, Rosebush said sponsors need to be aware of the regulatory exclusivities that are available in addition to patent protection. These exclusivities are designed to encourage the development of new, safe and effective treatments. While taking advantage of these exclusivities may help a sponsor realize a return on investment, Rosebush warns that failure to utilize the regulatory exclusivities can result in increased competition and sponsors using potential research and development resources to fund expensive litigation.

## Antitrust Considerations

"Patent law and antitrust law are in constant tension. . . . That tension exists because a patent is by definition a monopoly. Exclusivity and monopoly are things that the antitrust laws were aimed at preventing or at least controlling, and therefore the ebb and flow of that over the past hundred years in the courts and in Congress has been one of increased tension."

– Carl W. Hittinger, Partner

Carl Hittinger discussed antitrust considerations raised by pharmaceutical life cycle management strategies. He noted the inherent historic tension between exclusivities – including patent exclusivity – and antitrust law, which in part seeks to prevent or control monopolies.

## Three Important Cases

**FTC v. Actavis:** In its 2013 decision in *Actavis*, the U.S. Supreme Court held that "reverse payment" settlements in Abbreviated New Drug Application (ANDA) matters may violate the antitrust laws, rejecting the view adopted by some Circuits that settlements within the "scope of the patent" were immune from antitrust scrutiny. This type of settlement involves payment from the plaintiff (the patent holder) to the defendant (the generic company accused of infringement) even though the defendant has no claim for damages. Hittinger called this case "a game changer," noting that the import of the decision was reflected in the powerful dissent by Chief Justice John Roberts,

who believed that the precedential decision undermined established relationships between patent law and antitrust law and would weaken incentives to innovate.

Since the decision, courts have addressed the question of whether Actavis also applies to noncash payments. In 2015, the Third Circuit held that Actavis does apply to a noncash settlement involving a branded company's agreement not to market its own "authorized generic" during the first ANDA filer's 180-day exclusivity period. Such an agreement may have extremely significant financial value to the generic company, though it is not a straightforward transfer of money. Hittinger also noted that, post-Actavis, companies should be prepared to justify "side deals" accompanying settlement, because they may be scrutinized by the FTC to assess whether they reflect genuine business transactions for fair value as opposed to a cover for an anticompetitive payment unrelated to the litigation at issue.

Hittinger further suggested that the Actavis analysis might also be implicated by settlements of inter partes reviews or post-grant reviews involving competitors, because, as in the Hatch-Waxman context, these would also involve a transfer of value from the patentee to a challenger with no damages claim.

**New York v. Actavis:** Hittinger next discussed recent cases involving antitrust claims based on "product hopping" – the strategy of moving customers from an older drug product losing exclusivity to a similar modified product for which exclusivity still is available. The key case in this area is the Second Circuit's 2015 decision in *New York v. Actavis*. In that case, the defendant manufacturer had removed from the market an older immediate-release version of its Alzheimer's drug Namenda in connection with the launch of a new extended-release version with patent protection until 2029. The older product was withdrawn from the market before generic competition entered, preventing existing patients from moving to a generic version of the drug under state laws requiring automatic substitution when a generic is available. Instead, patients would be switched to the extended-release form, which would not be subject to generic competition for many years.

The Second Circuit upheld an injunction that required the manufacturer to continue to make the older product available, finding that generic companies were entitled to a fair opportunity to take advantage of generic substitution laws. Importantly, though, Hittinger noted, the court suggested that certain "soft switch" tactics, such as discounts, rebates or refocusing of promotional efforts, would be permissible.

**In re Suboxone and Mylan v. Warner:** Hittinger also discussed the 2014 case from the Eastern District of Pennsylvania involving the drug Suboxone, in which an antitrust claim based on product hopping survived

summary judgment even though the older drug was not taken off the market before generic entry. The plaintiff alleged various other actions, including filing a "sham" citizen petition that raised false safety concerns about the older drug. In the aggregate, the court believed, these allegations sufficiently evidenced conduct intended to stymie competition in violation of the antitrust laws. By contrast, in the recent *Mylan v. Warner* case, also from the Eastern District of Pennsylvania, the court dismissed the generic plaintiff's antitrust claims based on repeated incremental product changes over a series of years, coupled in some cases with the withdrawal of the earlier product from the market. The *Mylan* case is on appeal to the Third Circuit, where the Federal Trade Commission (FTC) has filed an amicus brief highly critical of the district court's decision.

Hittinger emphasized that the FTC has broader powers than the Department of Justice or private litigants under the Sherman Act because it can act against "unfair methods of competition" under Section 5 of the FTC Act, which, the agency maintains, reaches some conduct that would not otherwise constitute an antitrust violation under established Sherman Act precedent.

## REMS Programs – Antitrust Considerations

Hittinger closed with a discussion of antitrust claims that have been brought based on alleged abuses of Risk Evaluation and Mitigation Strategies (REMS) programs. In both cases, the plaintiffs alleged that branded manufacturers used REMS restrictions and related safety concerns as a pretext to refuse to provide drug samples to potential generic competitors who needed the samples to undertake required bioequivalence testing. In the 2014 case *Mylan Pharms. v. Celgene Corp.*, the court did not allow a claim based on allegations that the defendant refused to cooperate in good faith with the plaintiff, a generic competitor, in developing a shared REMS program, per the FDA's instructions. That court pointed out that the FD&C Act expressly prohibits manipulating the REMS process for purposes of delay, and that this provision lessens the need for judicial antitrust scrutiny.

## Conclusion

In closing, Hittinger suggested an approach that he acknowledged might be counterintuitive. When entering into settlements or other actions involving competitors that might implicate antitrust issues, he said companies should consider being proactive and asking for the FTC's views through its relatively expeditious formal review procedures before engaging in questionable conduct. This can potentially spare the company the battle and expense of litigation that might otherwise follow.

# ANDA Approval Litigation

Shea emphasized the need to consider exclusivity issues early in a drug product's life cycle. Because ANDA approval hinges on demonstration of bioequivalence, decisions made about a potential drug's attributes and modes of action can affect the potential, and evidence needed, for ANDA approval.

Lance Shea focused on litigation arising near the end of drug marketing exclusivity periods. Such litigation typically is brought by companies that develop or "pioneer" a drug (pioneer companies) against the FDA. Plaintiffs seek preliminary injunctions against Abbreviated New Drug Application (ANDA) approval, focusing their claims on whether the FDA followed, or could follow, applicable laws during the approval process. Often at issue are ANDA approval criteria required by the Federal Food, Drug and Cosmetic Act (FFDCA). If a pioneer company can demonstrate that the ANDA approval was improper – or could not be proper given the pioneer drug's attributes – the company can obtain a longer period during which to exclusively market the pioneer drug, also called the reference listed drug (RLD).

## Arguing for Practical Exclusivity

The exclusivity period begins with approval of a New Drug Application (NDA) and runs for a period of years as provided by the FFDCA. Once exclusivity ends for an RLD, the FDA may approve an ANDA for a generic version of that RLD as a final agency action. Between those points, the FDA often issues "product-specific recommendations for generic drug development" as draft guidance documents (Recommendations). Each Recommendations guidance document describes how a generic drug product can be proven bioequivalent to a specific RLD. Because Recommendations are not binding on the FDA or the ANDA applicant, ANDA applicants are free to submit bioequivalence evidence different from that called for by the Recommendations. Yet ANDA applicants usually follow the Recommendations because they set forth the FDA's current thinking and expectations. The FDA seeks comments on each Recommendations document and establishes a docket to receive those comments.

An ANDA usually is submitted after Recommendations are issued. It is not unusual for the FDA to tentatively approve an ANDA before the exclusivity period has expired. Tentative approval does not ensure final approval, however, because the FDA can change its opinion and even approve another ANDA instead. Also during the exclusivity period, pioneer companies may bring citizen petitions requesting that the FDA require certain bioequivalence evidence for approval of ANDAs, contesting Recommendations,

or raising other ANDA approval issues. Often, the FDA does not substantively respond to a pioneer company's citizen petition raising ANDA approval concerns until the agency approves the ANDA at issue. Additionally, pioneer companies can engage in formal meetings with the FDA during the exclusivity period to discuss bioequivalence and other ANDA approval issues. Recently, the FDA issued guidance on seeking formal meetings.

When considering ANDA litigation, Shea provided a breakdown of important components:

## Merits issues

ANDA approval requirements imposed by the FFDCA often are litigated in ANDA approval cases: the generic drug must have the same active ingredient, route of administration, dosage form, strength, conditions of use, and labeling as the RLD. Also, the generic must be bioequivalent to the RLD. Simply put, this means that there must not be a significant difference in the rate and extent to which the generic's active ingredient reaches the site of action when compared to the RLD's active ingredient – given that both drugs are administered at the same dose and under similar conditions. Alternatively, the generic must be in the same pharmaceutical or therapeutic class, and have the same therapeutic effect as the RLD. Further, the ANDA applicant must demonstrate that:

- The manufacture, processing and packaging of the generic drug is adequate to assure and preserve its identity, strength, quality and purity;
- The inactive ingredients of the generic drug must be safe for use under the label indications; and
- The composition of the generic drug must be safe under label indications given the type or quantity of inactive ingredient.

As with any action for preliminary injunction, Shea noted, a court will consider:

- The likelihood of success on the merits (e.g., the approval issues listed above);
- Whether the plaintiff will suffer irreparable harm if the FDA is not enjoined;
- Whether harm to the defendant from injunction issuance outweighs the harm to the plaintiff; and
- Whether public interest weighs in favor of injunction issuance.

## Litigation Pitfalls to Keep in Mind

Shea presented litigation pitfalls to avoid in ANDA approval litigation, using precedent cases as illustration. He summarized those and other litigation pitfalls as:

- Relying on legal argument rather than data or testimonial evidence;
- Gaming the process, such as bringing citizen petitions unreasonably late or making arguments that would appear to be made only to stall the approval process;
- Failing to address issues of risk to human health posed by the generic, or making risk arguments that are not evidence based;
- Arguing that the generic is not the “same drug” without an argument that the drug is not bioequivalent to the RLD;
- Alleging irreparable injury without strong supporting evidence; and
- Bringing the matter too early, where the matter is not ripe, or final agency action has not occurred.

## Practical Strategies for Communication

A common theme throughout the presentation was to have early communication with the FDA about ANDA approval issues, such as bioequivalence. This can be

done through formal meetings. If the formal meeting approach is not successful, a citizen petition can be filed. As noted before, citizen petitions should be submitted as early as is practical. Not only will such give the FDA time to fully consider the petition, but also it will limit the defense in ANDA approval litigation that the agency lacked adequate time to address complex issues raised by the petition. Of course, filing a citizen petition may limit open communication with the FDA on the issues covered.

Additionally, parties should consider submitting substantive comments to Recommendations. While certain proprietary intellectual property should be withheld, comments should be supported by compelling data and opinion evidence rather than mere conclusory statements. Also, the arguments should be clear and succinct, rather than mired in overly technical language.

## Conclusions

Shea closed by noting that before moving forward with litigation, companies need a deep knowledge of the drug in question as well as an evaluation of the type of data needed to make a bioequivalence argument. The chances of a successful litigation are improved when companies present reliable data and have reached out to the FDA through formal talks or filed thoughtful and timely citizen petitions.

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