

ANDA Approval Litigation: Arguing for Practical Exclusivity

By Lance L. Shea

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. Partner Lance Shea discussed litigation that arises near the end of exclusivity periods.

Lance Shea's portion of the presentation focused on litigation arising near the end of drug marketing exclusivity periods (exclusivity or exclusivity periods). Such litigation typically is brought by companies that develop or "pioneer" a drug (pioneer companies) against the Food and Drug Administration (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). Of course, if a pioneer company could demonstrate that the ANDA approval were improper – or could not be proper given the pioneer drug's attributes – the company could obtain a longer period during which to exclusively market the pioneer drug (also called the reference listed drug or RLD).

Shea discussed the need to consider exclusivity issues early in a drug product's life cycle, even at the earliest stages. 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.

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 do not have the force of law (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. 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 for an RLD. 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 as to approval, 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. The FDA must issue a response to a citizen petition in 180 days; however, courts have held that such responses may be tentative rather than substantive. Often, the FDA does not substantively respond to a pioneer company's citizen petition raising ANDA concerns until the agency approves the ANDA at issue.

Additionally during the exclusivity period, pioneer companies can engage in formal meetings with the FDA to discuss bioequivalence and other ANDA approval issues. Recently, the FDA issued guidance on seeking

formal meetings. *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry – Draft Guidance* (2015), is available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf>

Litigation Issues

After his introductory remarks, Shea reviewed the merits issues that often are litigated in ANDA approval cases. Of course, ANDA approval requirements imposed by the FFDCAs often are contested: 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 with 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, a court will consider the following elements: (1) the likelihood of success on the merits (e.g., the approval issues listed above); (2) whether the plaintiff will suffer irreparable harm if the FDA is not enjoined; (3) whether harm to the defendant from injunction issuance outweighs the harm to the plaintiff; and (4) whether public interest weighs in favor of injunction issuance.

Litigation Pitfalls to Avoid

By discussing several precedent cases, Shea presented litigation pitfalls to avoid in ANDA approval litigation. The following highlights four pitfalls that he covered.

Pitfall 1 – Failing to bring sufficient scientific evidence: Courts often defer to the FDA's technical decisions. See, e.g., *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 19 (D.C. Cir. 2009) (hereinafter, *Astellas*) (“The Circuit has noted that the FDA’s ‘evaluations of scientific data within its area of expertise . . . [are] entitled to a ‘high level of deference.’”); *Sanofi-Aventis U.S. LLC v. Food and Drug Admin.*, 733 F. Supp. 2d 162, 171 (D.D.C. 2010) (“[b]ecause the FDA’s determination of what is required to

assess the ‘purity’ of a generic drug for purposes of the FFDCAs ‘rests on the “agency’s evaluations of scientific data within its area of expertise,” it is ‘entitled to a “high level of deference”’ from this court.” (citations omitted)).

Thus, legal arguments over technical issues such as “sameness” or bioequivalence must be supported by compelling scientific evidence. Although this may seem obvious, both plaintiffs and the FDA have failed to bring such support. Compare *Astellas*, 642 F. Supp. 2d at 20 (“the court concludes that the plaintiff has presented insufficient evidence to suggest that the FDA acted in an arbitrary and capricious manner in setting the bioequivalency guidelines for generic tacrolimus. Accordingly, the plaintiff has failed to demonstrate a likelihood of success on the merits . . .”), and *Bayer Healthcare, LLC v. United States Food and Drug Admin.*, 942 F. Supp. 2d 17, 25 (D.D.C. 2013) (hereinafter, *Bayer*) (“[F]DA presents only legal argument that the Court should presume regularity and defer to its expertise. But, while agency action may generally be ‘entitled to a presumption of regularity,’ . . . here FDA itself acknowledges that its action has not been regular: it failed to respond to the Citizen Petition for years and failed to provide a reasoned basis for rejecting it before approving Enroflox.” (citations omitted)).

Pitfall 2 – Advancing tactics over substance: There should be no indication that the pioneer company is attempting to “game the system,” (e.g., by pursuing citizen petitions in untimely fashion) or taking actions having the appearance of unfair tactics. As to citizen petitions, filing late in the exclusivity period can backfire, as a party must certify that it can account for the dates on which it received relevant data or information that it is presenting in the petition. See FFDCAs Section 505(q); 21 U.S.C. Section 355(q). As to gaming the process, removing an RLD from the market for mere tactical reasons, or stretching regulatory arguments until thin, can backfire. See, e.g., *ISTA Pharm., Inc. v. Food and Drug Admin.*, 898 F. Supp. 2d 227 (D.D.C. 2012) (noting that “ISTA’s [labeling] position is, at best, disingenuous—at worst, intentionally misleading. . . . ISTA pulled [the RLD] from the market only the day before it filed its Citizen’s Petition arguing against approval of Coastal’s generic [based on there being no currently approved labeling, given that the RLD was no longer marketed.]”).

Pitfall 3 – Failing to develop evidence of a candidate generic’s human health risk: A critical mistake seen in several cases is failing to fully develop evidence of human health risk posed by a candidate generic drug. See, e.g., *Biovail Corp. v. U.S. Food and Drug Admin., and Anchen Pharm., Inc.*, 448 F. Supp. 2d 154, 164-165 (D.D.C. 2006) (“The plaintiff argues that it will suffer ‘inevitable and irreparable harm’ if a generic form of Wellbutrin XL has a higher risk than the original of serious

side effects. . . . Absent evidence that the generic drug pending approval will actually cause harmful health effects, however, these allegations fail to meet the requisite standard. . . . In fact, the plaintiff lays nothing but speculation before the court, stating that “[i]f a generic drug posing [the risk of grand mal seizures] reaches the market, the potential harm to Biovail is enormous’”); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 221 (D.D.C. 1996) (hereinafter, *BMS*) (“[B]ristol’s claim that its reputation will suffer if there is any adverse health effect that ensues from the use of Prevalite™ is insufficient to establish the requisite harm. There is nothing before the court which would lead it to conclude that Prevalite™ will cause any harmful health effects.”); *Astellas*, 642 F. Supp. 2d at 23 (“The plaintiff’s concerns about the potential loss of goodwill and reputation are founded entirely on its belief that the approved generic tacrolimus may be more harmful than Prograf®, a belief that, as has already been discussed, lacks evidentiary support and is entirely speculative.”).

Pitfall 4 – Failing to adequately support irreparable financial injury claims: Also seen is failure to support irreparable financial injury claims with evidence, such as data or qualified expert testimony demonstrating the type and extent of financial injury to be caused by ANDA approval. Compare *BMS*, 923 F. Supp. at 221 (“Moreover, Bristol’s claim that it will lose between 50 and 70 percent of its market share of the cholestyramine market is supported by mere speculation concerning the encroachment of Prevalite™ into its market share.”), and *Bayer*, 942 F. Supp. 2d at 25-26 (“As its basis for irreparable harm, Bayer points to the effect on its market share, arguing that the launch of Norbrook’s generic ‘will change the market irreversibly if not reversed by the requested interlocutory relief.’ . . . Bayer includes a declaration from Cary R. Christensen, the senior director of the Food Animal Products business unit of Bayer’s Animal Health Division, to support its claims of irreparable harm Indeed, Mr. Christensen explains specifically how Bayer will experience a decline in market share The Court concludes on this record that Bayer is likely to suffer irreparable harm”).

Closing this section of his presentation, Shea summarized those and other litigation pitfalls as follows:

- Relying on legal argument rather than data or testimonial evidence;
- Gaming the process, such as bringing citizen petitions unreasonably late or making specious 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 when final agency action has not occurred.

Practical Strategies to Consider

Following his review of litigation pitfalls, Shea discussed several practical strategies that parties (pioneer companies or ANDA applicants) should consider. A common theme throughout the presentation was to have early communication with the FDA about ANDA approval issues, such as bioequivalence. Of course, 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 will 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.

Hypothetical Example of Early Knowledge Development

To illustrate the approach of early knowledge development, Shea discussed a hypothetical based on *Serono v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998). He gave an overview of the case: Serono’s RLD, Pergonal, was approved by the FDA in 1969. One of Pergonal’s active ingredients was follicle-stimulating hormone (FSH). In 1990, an ANDA was filed, seeking approval of a generic version of Pergonal, now known as Repronex. In December 1992, Serono filed a citizen petition arguing that the FSH in the proposed generic drug was not the “same as” the FSH in Pergonal because of differences in isoforms of the two products. (Isoforms are different structural forms of the same protein.) Based on that difference, Serono argued that the Repronex ANDA could not be approved. In January 1997, the FDA approved the ANDA for Repronex. In May 1997 Serono sued in Federal District Court, seeking preliminary injunction rescinding the ANDA approval. Serono won in the District Court, but lost in the D.C. Circuit Court.

Of interest for Shea's presentation was the following position taken by the FDA: To be considered to have the same active ingredient for ANDA approval purposes, the generic drug must have: (1) the same primary structure as the RLD (i.e., the same protein backbone and amino acid sequence, assured by using the same natural source material); (2) the same potency; and (3) the same degree of batch-to-batch uniformity from manufacturing. The FDA prevailed by arguing that it had applied this test and found it to be satisfied by Repronex.

As a hypothetical, Shea discussed whether evidence that potency differed between isoforms of FSH would have driven a different result. If such evidence were known early enough, it could have been made known to the FDA through formal meetings or, failing same, through a citizen petition. Although such evidence may not have been specific to the isoform in the hypothetical generic drug, the strategy may have caused the FDA to look very hard at any ANDA. If evidence could have been developed demonstrating that the hypothetical RLD and generic isoforms had different potencies, it is obvious that the FDA's "sameness" test might not have been satisfied. Today, such evidence could be brought to the FDA by the previously mentioned avenues, or through comments on Recommendations pertaining to the RLD. Additionally, if evidence could have been developed that the hypothetical generic isoform raised safety concerns not shared by the RLD isoform, the evidence of different isoform potency could have been made more persuasive. If the matter went to litigation, such safety evidence could have been introduced under the public interest element of the injunction cause of action.

Concluding his remarks, Shea articulated a few questions to ask before moving forward with litigation, emphasizing a deep knowledge of the drug in question as well as an evaluation of the type of data needed to make a bioequivalence argument.

bakerlaw.com

One of the nation's leading law firms, BakerHostetler helps clients around the world to address their most complex and critical business and regulatory issues. With five core national practice groups – Business, Employment, Intellectual Property, Litigation, and Tax – the firm has more than 900 lawyers located in 14 offices coast to coast. For more information, visit bakerlaw.com.

Baker & Hostetler LLP publications inform our clients and friends of the firm about recent legal developments. This publication is for informational purposes only and does not constitute an opinion of Baker & Hostetler LLP. Do not rely on this publication without seeking legal counsel.

© 2016 BakerHostetler®