

I N S I D E   T H E   M I N D S

# Food and Drug Litigation Strategies

*Leading Lawyers on Building Strong Defenses  
and Adapting to Evolving FDA Regulations*



ASPATORE

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A Primer: Recent Developments  
and Strategies in Petitions and  
Lawsuits Challenging FDA  
Approval of Generic Drug  
Products Under the  
Administrative Procedure Act

Bruce S. Manheim Jr.

*Partner*

Wilmer Cutler Pickering Hale and Dorr LLP



ASPATORE

## **Introduction**

During the past thirty years, much attention has been focused on patent litigation arising under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). These cases typically pit brand-name pharmaceutical companies against generic drug competitors over patents covering blockbuster drug products. The outcome of such litigation frequently involves billions of dollars for the parties. Much less attention has been given over the years to equally high-stakes litigation involving challenges to approval by the US Food and Drug Administration (FDA) of generic versions of brand-name drug products. In these cases, brand-name manufacturers are concerned about the non-patent exclusivity they are entitled to under the law. They also seek to redress the reputational harm their products may sustain if FDA approves generic versions they believe are not as safe or effective as the brand-name product. Like patent litigation, these cases have enormous financial consequences for the litigants.

This chapter explores the challenges surrounding a citizen petition and lawsuit against FDA over the approval of a generic drug product. In the first place, brand-name manufacturers of drug products are understandably often loath to file a lawsuit against FDA—an agency that maintains jurisdiction over that company’s existing products and that must act to approve a brand-name manufacturer’s applications to market new drug products. Litigation against FDA is also frequently complex and difficult. As described more fully in the sections that follow, brand-name manufacturer petitions and lawsuits against FDA are challenging, but they have been successful when they are carefully prepared and focus on significant legal and scientific issues that may have clinically meaningful impacts on patients. Engaging FDA early in the administrative process to raise concerns about the safety or efficacy of a proposed generic product through a citizen petition is often critical to the outcome of any litigation brought thereafter. While this chapter focuses on drug products, many of the principles outlined here will be equally applicable to challenges involving FDA approval of biosimilars under the Public Health Service Act.

## Statutory and Regulatory Background

The Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to regulate the manufacture, distribution, and sale of drugs in the United States.<sup>1</sup> Those seeking approval to market a new drug must file a new drug application (NDA) with the agency.<sup>2</sup> To secure approval of an NDA, an applicant must undertake an extensive and costly array of animal and human tests, including clinical investigations, demonstrating that the drug is both safe and effective for its proposed use.<sup>3</sup> Only after FDA approves an NDA may the applicant market the drug product in the United States.<sup>4</sup> Typically, the process of obtaining approval of an NDA involves extensive testing and an investment of hundreds of millions of dollars by the brand-name manufacturer.<sup>5</sup>

In 1984, with passage of the Hatch-Waxman Amendments, Congress amended the FDCA to allow FDA to approve, in certain instances, generic drugs that are the same as drugs previously approved by FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application (ANDA) to the agency.<sup>6</sup> In support of such applications, a generic manufacturer may reference FDA's findings with respect to the preclinical and clinical testing previously conducted for a drug product approved under an NDA, known as the reference listed drug (RLD). To reference that information, however, the ANDA applicant must demonstrate, and FDA must conclude, that the generic drug does, in fact, perform in the same way as the brand-name drug it purports to copy.<sup>7</sup>

Unlike NDA applicants, ANDA applicants are not required to undertake comprehensive safety and efficacy studies; rather, approval is based on a demonstration of sameness and equivalence to the brand-name product for

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<sup>1</sup> 21 U.S.C. § 355(a) (1938).

<sup>2</sup> 21 U.S.C. § 355(b).

<sup>3</sup> 21 U.S.C. § 355(d).

<sup>4</sup> See n. 3, *supra*.

<sup>5</sup> See generally, *Drug Approval Process*, FDA Approvals, available at <http://www.drugs.com/fda-approval-process.html> (last visited Jul. 23, 2013) (“It takes on average 12 years and over US \$350 million to get a new drug from the laboratory onto the pharmacy shelf.”).

<sup>6</sup> 21 U.S.C. § 355(j).

<sup>7</sup> 21 U.S.C. §§ 355(j)(2)(A) and 355(j)(3).

which such studies have already been completed. Specifically, for an ANDA to be approved, FDA must find that the generic version is identical to the brand-name drug product with respect to the active ingredients, route of administration, dosage form, strength of the drug, and labeling.<sup>8</sup> At the same time, FDA must also determine that the generic drug is “bioequivalent” to the innovator drug.<sup>9</sup> Under the statute, a generic drug is bioequivalent to a RLD if “the rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the [reference] listed drug...”<sup>10</sup>

Under the Hatch-Waxman Amendments, FDA may not approve an ANDA until any applicable period of non-patent or data exclusivity for the brand-name drug product has expired. The FDCA provides a period of five years of non-patent exclusivity for new drug containing a new chemical entity. In such cases, an ANDA may not be filed until the expiration of five years.<sup>11</sup> The FDCA also provides for an additional period of three years of data exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of certain changes to the brand-name product. In addition, FDA is authorized to grant additional periods of non-patent exclusivity for, among other things, pediatric studies and the development of orphan drug products.<sup>12</sup>

Thus, with passage of the Hatch-Waxman Amendments, Congress struck a trade-off between two competing interests: the desire to spur innovation and development of new pharmaceuticals on the one hand and the desire to cabin the cost of pharmaceuticals and incentivize development of generic products on the other. As one court put it, the Hatch-Waxman Amendments “set up a statutory system to balance the need to stimulate

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<sup>8</sup> 21 U.S.C. § 355(j)(2)(A)(ii)-(iii).

<sup>9</sup> 21 U.S.C. § 355(j)(2)(A)(iv).

<sup>10</sup> 21 U.S.C. § 355(j)(8)(B)(i).

<sup>11</sup> If the submission is accompanied by a paragraph IV certification, the applicant may submit its application four years following the original product approval.

<sup>12</sup> 21 U.S.C. §§ 360aa-360dd (West).

innovation against the goal of furthering the public interest.”<sup>13</sup> This trade-off may result in a debate—a “chess game”—played out over time between brand-name manufacturers and generic manufacturers over whether a generic drug may be approved by FDA under the relevant standards and, if so, when it may reach the market.

This tension is especially heightened because, upon approval of an ANDA, FDA indicates that the generic product is “therapeutically equivalent” to the brand-name drug and assigns such a rating to the approved generic drug in its publication “Approved Drug Products with Therapeutic Equivalence Evaluations” (the “Orange Book”). Physicians and pharmacists consider a therapeutic equivalence rating to mean that a generic drug is fully substitutable for the brand-name product. In addition, by operation of certain state laws and numerous health insurance programs, FDA’s designation of a therapeutic equivalence rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

### **Building the Administrative Record through the Citizen Petition Process**

The debate over approval of a generic product typically begins at the administrative adjudication stage, when brand-name manufacturers learn or believe that an ANDA has been or will soon be filed with the agency. Brand-name companies generally seek to ensure that FDA requires the generic drug applicant to conduct all studies necessary to demonstrate that the generic version is the same as, and bioequivalent to, the brand name or reference product. For relatively simple drug products, such tests may not be especially burdensome or complex. But, for products that raise more difficult questions about sameness or bioequivalence, the studies that FDA requires of a generic drug applicant are often critical to a determination of whether and, if so, when the generic product may be approved. In this context, brand-name manufacturers often provide FDA with information concerning the potential differences that may exist for generic drugs and the clinical significance of those differences. They may then assert that,

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<sup>13</sup> *Momenta Pharmaceuticals Inc. v. Amphastar Pharmaceuticals Inc.*, 686 F.3d 1348, 1354 (Fed. Cir. 2012).

unless a generic drug manufacturer can assure FDA that the generic product is the same as the brand-name product, FDA may not, as a matter of law or science, approve the ANDA.

*Citizen Petitions—Engaging FDA Early in the Process*

In determining whether to approve a generic drug product, FDA is required to compile all information, including test results, expert statements, and correspondence, in an administrative record. The agency must make its decision on the ANDA solely on the basis of information in this record. If litigation ensues at some point in the future over FDA's decision, it is the information in the administrative record that was before FDA at the time of its decision—and not other evidence, such as that one would normally amass in civil discovery—that will be considered by the court.<sup>14</sup> As a result, to the extent that a brand-name manufacturer wishes to engage FDA in its consideration of a generic drug product, it is critical that the company develop a strategy to supplement the administrative record with information supporting its position. This may frequently require brand-name companies to begin thinking about the prospect of generic competition many years before an ANDA is approved.

Submission of a citizen petition to FDA is the principal mechanism through which brand-name manufacturers supplement the administrative record. The FDA has issued regulations prescribing specifically the types of information that an interested party must include in a citizen petition.<sup>15</sup> Any individual, organization, or corporation, regardless of the place of their actual citizenship, may file a citizen petition with the agency.<sup>16</sup> Such petitions have become a routine means through which stakeholders submit requests and express concerns to FDA. They may focus on the approval requirements governing proposed generic versions of a company's product, such as questioning whether the active ingredient in a generic product is identical to the active ingredient in the brand-name company's product or whether FDA's proposed method for determining bioequivalence is applicable to a particular ANDA.

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<sup>14</sup> 5 U.S.C. § 706 (1966).

<sup>15</sup> 21 C.F.R. § 10.30 *et seq.* (1979).

<sup>16</sup> 21 C.F.R. § 10.30(a).

Upon receiving a citizen petition, FDA will establish a docket for the submission (which can be accessed at [regulations.gov](https://www.regulations.gov)), and the petition is available to the public for review and comment. The submission of a citizen petition and any supporting materials will become part of the administrative record that is before FDA.<sup>17</sup> In addition, any individual, entity, or company may submit comments to citizen petitions, which will also become part of the administrative record. These comments may disagree with or support the petition or point out other considerations that FDA should consider when making a decision on the substantive issue at hand. It should be noted that, while citizen petitions create a public process to ventilate certain issues with FDA, a generic manufacturer may be able to avoid publicly disclosing its response to a citizen petition by responding to the concerns raised in a petition in a submission directly to the ANDA. ANDAs are confidential submissions.

The FDA's obligations with respect to responding to a citizen petition bifurcate, depending on the type of citizen petition that is filed with the agency. Under Section 505(q) of the FDCA, FDA must respond to citizen petitions within 150 days of receipt of the submission. A "505(q) petition" is generally one that is filed when there is a pending ANDA or Section 505(b)(2) application currently before the agency at the time of submission of the petition, and the petitioner requests that FDA take an action that could delay approval of the pending ANDA or 505(b)(2) application.

Alternatively, if a citizen petition does not meet these criteria, then FDA's obligations to answer the petition are much different. For this latter category, FDA's regulations require the agency to respond to a citizen petition within 180 days. The FDA may, however, issue an "interim response" stating that it has been unable to reach a decision on the substantive issues raised in the petition because it raises complex issues requiring extensive review and analysis by agency officials.

Inasmuch as FDA receives numerous petitions and because its regulations allow for the issuance of tentative responses, companies that file citizen petitions that are not treated as 505(q) submissions may not obtain any substantive response from the agency for a period of months or even years.

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<sup>17</sup> *E.g.*, 21 C.F.R. § 10.3(a) (defining administrative record for FDA decisions).

Although the petitioner may seek judicial action to compel FDA to answer a citizen petition more quickly, such efforts generally fail. Typically, in cases where FDA grants approval of an ANDA, the agency will answer the citizen petition from the brand-name manufacturer the same day. On the other hand, in cases where FDA has decided not to grant an ANDA, FDA may not answer the petition for an extended period or at all.

*Shaping the Record with Both Scientific and Legal Arguments*

No matter which type of citizen petition a brand-name manufacturer may file, a petitioner must introduce strong scientific evidence and persuasive legal arguments into the record if it is to be successful with FDA. Submitting such materials to the record is fundamental and ultimately becomes central to a court challenge. Moreover, as a matter of practice, the burden has typically fallen on the brand-name manufacturer to present information or evidence that moves FDA not to approve an ANDA. While the FDCA's provisions can certainly be read to place the burden on the generic company to demonstrate that its ANDA satisfies the requirements for approval, that has not generally been the approach that FDA has taken in responding to requests in citizen petitions to withhold approval of a generic drug product. Hence, the importance of shaping the record cannot be understated.

Moreover, it will be important for petitioners to present evidence that the public health or patient safety may be compromised by a generic drug product if FDA does not grant the action requested in the petition. That is, petitions that raise serious issues and may involve clinically meaningful impacts will have a greater chance of success over submissions that challenge differences between brand-name and generic products where the differences are minor and will not potentially affect patients. In this context, petitioners should also recognize that regulatory precedents at FDA are critical. Hence, petitions will have a greater likelihood of success if the actions requested therein are supported by, or at least consistent with, earlier decisions by FDA. Those earlier decisions by FDA on citizen petitions are readily accessible.

At the same time, successful petitioners often frame their arguments based on *both* scientific grounds and statutory requirements. Indeed,

because the courts will generally defer to FDA's technical expertise on questions of science, citizen petitions or other submissions to the record should be grounded in legal arguments regarding FDA's actions and how they comport (or do not comport) with the law and regulations binding the agency. To be sure, brand-name manufacturers will need to be sensitive to the potential anti-competitive effects of a citizen petition in terms of the timing of the submission, as well as its contents. But as long as the petitioner has a defensible and reasoned basis for its request to the agency, it should not be reluctant to bring those concerns to the attention of FDA.

Finally, parties contemplating submission of a citizen petition to FDA should anticipate arguments they might make someday in court. They must also consider their own actions on their NDAs to ensure consistency in the position they are taking with respect to the generic product. It is important for such parties to consider how a potential case would develop in court when drafting or submitting a citizen petition or providing information to FDA. Crafting a citizen petition with an eye toward potential litigation can be challenging and requires a sophisticated knowledge of relevant case law, the legal bases for a challenge under relevant statutory and regulatory authority, and the impact those authorities may have on the specific factual and evidentiary elements of the case.

This foregoing is especially true because, in contrast to patent litigation, there is generally no discovery in cases challenging FDA decisions. Rather, to the extent that a brand-name manufacturer may seek to file a lawsuit against FDA, that action will be decided solely on the basis of the information in the administrative record established by the citizen petition and supplements thereto.<sup>18</sup> To be sure, a litigant may ask the court to order FDA to supplement the record. But in administrative record cases involving challenges to federal agency action, "supplementation is the exception, not the rule."<sup>19</sup> A litigant would need to rebut the presumption

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<sup>18</sup> See 21 C.F.R. § 10.3(a) (defining administrative record for FDA decisions). 30(h) (defining the administrative record for citizen petition determinations); see also *King v. Leavitt*, 475 F.Supp.2d 67, 72 (D.D.C. 2007) ("The Court notes that if plaintiffs renew their APA claims against an FDA action, such claims must be based on the proper administrative record.")

<sup>19</sup> *Comprehensive Community Development Corp. v. Sebelius*, 890 F. Supp. 2d 305 (S.D. N.Y. 2012).

of administrative regularity and show that the materials it seeks to discover were before the agency decision-maker. Alternatively, a party may ask that the court consider extra-record evidence if it can demonstrate that there has been “bad faith or improper behavior on the part of the agency decision-maker” in excluding such evidence.<sup>20</sup> Accordingly, a brand-name manufacturer that wishes to preserve the option of suing FDA if its petition is denied must build a robust administrative record from which the agency and, later, the court can make its decision.

If a citizen petition is denied by the FDA, a brand-name manufacturer must decide whether to accept that decision or challenge it. At the administrative adjudication level, a petitioner may ask FDA for a stay of its action and/or seek reconsideration of the decision.<sup>21</sup> Such efforts, however, are generally futile. They also may work to the disadvantage of the brand-name manufacturer. The generic manufacturer may be launching its product, and the petitioner may be reluctant or unable to seek injunctive relief in court against such actions while its request for a stay or reconsideration is pending before FDA. Requests for a stay or reconsideration must be filed within thirty days of the agency’s denial of a petition, but there is no time period by which FDA must respond to these requests. As a result, the only meaningful recourse, in most cases, is to seek judicial review of FDA’s denial of the citizen petition and approval of the ANDA.

### **Getting into Court: Finality, Ripeness, Standing, and Exhaustion**

The federal courts have authority to review and set aside FDA’s actions pursuant to the Administrative Procedure Act (APA). Cases brought under the APA are typically resolved on cross motions for summary judgment, based on the administrative record. Understanding the bases and limitations of federal court review under the APA can be critical in framing a successful challenge to FDA’s actions. Indeed, a lawsuit challenging FDA’s approval of an ANDA and/or denial of a citizen petition presents special challenges. As a threshold matter, a plaintiff must demonstrate that the case at hand is justiciable and that the plaintiff has standing and has exhausted its

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<sup>20</sup> *Nat’l Audubon Soc’y v. Hoffman*, 132 F.3d 7, 14 (2d Cir.1997) (citing *Overton Park*, 401 U.S. at 420).

<sup>21</sup> 21 C.F.R. § 10.30(j).

administrative remedies. Although such questions are not merit-based, their importance cannot be overstated. The sections that follow review the law and recent developments concerning finality, ripeness, standing, and exhaustion in the context of litigation against FDA.

### *Finality and Ripeness*

A court will generally limit its review of an agency decision to final agency action. That is, a court will not expend judicial resources to review an action that is interim, only decided partially, or merely representative of the unofficial views of an agency official.<sup>22</sup> Based on FDA's regulations governing citizen petitions, the denial of a citizen petition is described as final agency action and, therefore, would appear to allow for immediate judicial review.<sup>23</sup> Yet FDA denial of a citizen petition is typically not enough for a court to entertain substantive review of FDA's decision. Courts have dismissed cases where FDA has denied a citizen petition but not yet approved the generic product.<sup>24</sup> In those cases, courts generally take the view that judicial resources should not be spent reviewing a matter when it is not clear that FDA will, in fact, ever approve the product. Moreover, even when FDA has denied a petition and approved a product, a court may still decline to review the action if there is no evidence that the product will launch imminently.<sup>25</sup>

In determining whether to consider the merits of a particular action, a court will evaluate whether an agency decision is ripe for review. Ripeness "probes the fitness for review of the legal issue presented, along with the hardship to the parties of withholding court consideration."<sup>26</sup> In considering whether a matter is "fit" for judicial review, a court will determine "whether the issue is purely legal, whether consideration of the issue would benefit from a more concrete setting, and whether the

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<sup>22</sup> *Den-Mat Corp. v. FDA*, CIV. A. MJG-92-444, 1992 WL 208962 (D.Md. Aug. 17, 1992) (non-final letters from FDA not actionable).

<sup>23</sup> *E.g., Holistic Candlers and Consumer Ass'n v. US Food & Drug Admin.*, 770 F. Supp. 2d 156 (D.D.C. 2011).

<sup>24</sup> *Pfizer v. Shalala*, 158 F.3d 1313(D.C. Cir. 1999).

<sup>25</sup> *Cephalon Inc. v. Sebelius*, 796 F. Supp. 2d 212 (D.D.C. 2011).

<sup>26</sup> *See Teva Pharmaceuticals USA Inc. v. Sebelius*, 595 F.3d 1303, 1308-1311, (D.C. Cir. 2010) (quoting, in part, *Abbott Laboratories v. Gardner*, 387 U.S. 136 (1967)).

agency's action is sufficiently final.”<sup>27</sup> A recent case involving the blockbuster product Seroquel illustrates the difficulties of timing a lawsuit challenging FDA's denial of a citizen petition so that it is filed at a time when the suit is ripe for review, but before significant harm is done to the plaintiff's position.

There, AstraZeneca, the manufacturer of Seroquel, sought judicial review of FDA's denial of its citizen petition asking FDA to withhold approval of generic versions of Seroquel.<sup>28</sup> With the denial of the citizen petition in hand, but before approval of any ANDAs, AstraZeneca filed suit against FDA and requested that the court enjoin FDA from approving generic versions of Seroquel. AstraZeneca argued that temporary injunctive relief was necessary because, in harmony with FDA's consistent and prior practice, FDA would issue a final approval of ANDAs within days, if not hours, of deciding the citizen petition. AstraZeneca demonstrated that generic companies had already begun producing generic Seroquel in an effort to release it to the market as soon as final approval was granted.

Notwithstanding the evidence that AstraZeneca submitted, the federal district court dismissed AstraZeneca's complaint as unripe for review, finding that “despite AstraZeneca's fervent belief to the contrary, there is no reason to presume that the FDA will necessarily grant final approval to one or all of the potential generic competitors seeking” to market generic versions of Seroquel and Seroquel XR or that it would do so in the time period in which AstraZeneca was entitled to exclusivity. Following dismissal of the case and only days later, FDA granted final approval to ANDAs allowing marketing of generic versions of Seroquel. AstraZeneca then filed suit to challenge FDA's decision and, having satisfied the ripeness hurdle, was able to obtain a merits determination. But, by then, generic versions of Seroquel were already on the market.

The AstraZeneca case underscores the potential difficulties that brand-name manufacturers may confront when positioning and timing their challenges to FDA's decisions. Brand-name companies may gain knowledge of FDA's acceptance for filing of certain ANDAs when they receive a Paragraph IV

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<sup>27</sup> *Id.*

<sup>28</sup> *AstraZeneca Pharmaceuticals LP v. Food & Drug Admin.*, 850 F. Supp. 2d 230 (D.D.C. 2012).

certification from the generic manufacturer pursuant to the Hatch-Waxman patent litigation provisions. But other ANDAs may not require a generic company to provide this notice to the brand-name manufacturer. Moreover, while recent passage of legislation establishing user fees and timetables for review of generic drug applications may provide further insight, brand-name companies will still not know with specificity the day on which an ANDA will be approved. On the other hand, manufacturers of generic medications usually have a good idea as to when FDA will approve their products, and they may stock up in anticipation of launching the product immediately upon approval. As a result, because ripeness requirements may generally compel a brand-name manufacturer to wait until an ANDA is approved, plaintiffs challenging FDA's decision often do so after the generic product has reached the market.

### *Standing and Exhaustion*

In addition to satisfying the requirements of ripeness and finality, a plaintiff challenging an FDA decision must demonstrate that it has standing to bring a lawsuit in the first place. Under Article III of the Constitution, federal courts must ensure that a plaintiff demonstrates injury-in-fact, that the injury in question is fairly traceable to the defendant's challenged action, and that the injury could be redressed by a favorable decision (constitutional standing requirements). At the same time, the federal courts adhere to certain prudential principles when considering the standing of a plaintiff to bring an action. These principles do not allow litigants to assert the rights of third parties, and courts should refrain from adjudicating matters of wide public significance that amount to generalized grievances. Moreover, to satisfy prudential standing requirements, litigants should demonstrate that their asserted interests are arguably within the zone of interests intended to be protected by the statute on which the claim is based.

Under these doctrines, the courts have generally found that a brand-name manufacturer has standing to challenge FDA's decision to approve an ANDA and deny a citizen petition.<sup>29</sup> In support of that finding, brand-

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<sup>29</sup> The FDA's regulations expressly provide that the agency will take the position that an interested party is affected by, and thus has standing to obtain judicial review of, final agency

name manufacturers typically allege in their complaints that FDA's approval of a generic product will result in imminent and irreparable harm to the reputation the company maintains for safe and effective products. Specifically, the complaint will allege that patients who are exposed to an inferior generic version of the brand-name product will be exposed to unacceptable risks, and physicians will inevitably begin to associate the brand-name product with a safety or efficacy problem. That will, in turn, lead physicians and patients to seek other medications for treatment of the disease. In addition to this type of harm, brand-name manufacturers also allege that approval of an inferior generic product will result in immediate and irreparable economic consequences. This allegation is usually supported by an estimate of the loss of market share once a generic product reaches the market.

While these types of allegations are often sufficient for plaintiffs to survive a motion to dismiss on standing grounds, there are certain situations where standing requirements may be more difficult to satisfy. For example, in *ViroPharma v. Hamburg*, ViroPharma challenged FDA's decision on a citizen petition submitted by another company in which the agency interpreted certain bioequivalence requirements for generic products.<sup>30</sup> ViroPharma claimed that FDA's interpretation would pave the way for approval of generic versions of ViroPharma's product. The court found that ViroPharma lacked standing to bring such claims because they were too hypothetical—there was no evidence that FDA would approve generic versions of ViroPharma's product on the basis of FDA's interpretation of the bioequivalence requirements for another product. Such alleged harms, the court declared, were “a far cry from the type of concrete and particularized injury required for Article III standing.”<sup>31</sup>

The *ViroPharma* case suggests that, to the extent that a company wishes to challenge FDA action in court, it should file a citizen petition with the agency in advance of bringing that action. In fact, for certain types of challenges, citizen petitions would appear to be required by statute before a party may file a lawsuit challenging FDA's approval of a generic drug.

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action. 21 C.F.R. §10.45(d)(1)(ii). That has not stopped the Department of Justice from raising questions of standing. Moreover, courts have an obligation to consider such issues *sua sponte*.

<sup>30</sup> *ViroPharma Inc. v. Hamburg*, 777 F.Supp.2d 140, 144 (D.D.C. 2011).

<sup>31</sup> *Id.*

Specifically, under Section 505(q) of the FDCA, FDA may not delay approval of a pending ANDA or 505(b)(2) application unless a citizen petition has been submitted to FDA and the agency determines (after reviewing the petition) that a delay is necessary to protect the public health. This provision further declares that if a civil action is filed against FDA with respect to any issue raised in the petition before FDA has taken final agency action on the petition, the court shall dismiss without prejudice the action for failure to exhaust administrative remedies.

The express application of an exhaustion provision in the FDCA to certain types of petitions—505(q) petitions—may create some confusion for brand-name manufacturers because it is not always clear whether an ANDA is pending before FDA and therefore whether a petition would be subject to the statutory exhaustion requirement. In any event, it is prudent for brand-name manufacturers to file petitions and thereby avoid arguments that they failed to exhaust administrative remedies before filing a lawsuit. If a plaintiff does not file a petition and FDA asserts that the exhaustion requirement is not satisfied, a court will consider whether:

1. The litigant is flouting legally established administrative processes,
2. The action promotes judicial economy by avoiding repetitious administrative and judicial fact-finding,
3. Exhaustion would be futile, and
4. The litigant would suffer irreparable harm if it were required to go through the administrative process prior to filing a district court action.<sup>32 33</sup>

To avoid this inquiry and set up a viable lawsuit, most brand-name manufacturers file citizen petitions with FDA.

### **Pursuing Preliminary Relief and the Importance of Venue**

Plaintiffs challenging a decision by FDA to approve a generic drug product typically must seek immediate injunctive relief, since the generic competitor

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<sup>32</sup> See *Bracco Diagnostics Inc. v. Shalala*, 963 F.Supp. 20, 30 -31 (D.D.C. 1997).

<sup>33</sup> Courts have dismissed cases based on the exhaustion doctrine when a party has failed to raise the issues first in a citizen petition. *Ass'n of Am. Physicians & Surgeons Inc. v. FDA*, 539 F.Supp.2d 4, 23 -24 (D.D.C. 2008).

may have already launched its product by the time a lawsuit is ripe and may be filed. But seeking temporary relief comes with its own set of challenges. Indeed, upon approval of an ANDA, the brand-name manufacturer has only FDA's denial of its citizen petition and any other materials that may have been submitted to the docket established by filing of the citizen petition. It does not have the full administrative record governing FDA's decision to approve the ANDA. Moreover, the plaintiff may not want to represent, at least publicly, that it will sustain irreparable harm from approval of the ANDA. There is also the risk that a negative decision on a request for injunctive relief might influence a decision later on summary judgment, if pursued. These and other challenges surrounding a request for injunctive relief are discussed next.

### *Moving for Temporary Relief without the Full Record*

Upon approval of an ANDA, a plaintiff may rush to the courthouse and ask the court to enter a temporary restraining order (TRO) and/or preliminary injunction directing FDA to suspend approval of the generic product. The courts have fashioned a four-part test to determine whether such relief is warranted:

1. Is there a substantial likelihood of establishing that FDA violated the FDCA when it approved the generic product?
2. Will the plaintiff sustain imminent and irreparable harm unless that approval is stayed by the court?
3. Does a balancing of the harms strongly favor such relief?
4. Will the public interest be furthered by a temporary stay?

Historically, these four factors have been evaluated through a "sliding scale" approach; that is, a strong showing on one of the factors, such as the merits, could lessen the need for a strong showing on another factor, such as irreparable harm.

A recent decision from the Supreme Court, *Winter v. NRDC*, casts some doubt on the viability of this "sliding-scale" approach to evaluating requests for a TRO and applications for a preliminary injunction.<sup>34</sup> Specifically, in *Winter*, the Court appeared to hold that merely demonstrating a

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<sup>34</sup> *Winter v. Natural Res. Def. Council Inc.*, 555 U.S. 7, 20 (2008).

“possibility” of irreparable harm is not sufficient to meet the standards for a preliminary injunction, even when the plaintiff had demonstrated a likelihood of success on the merits. In the aftermath of *Winter*, the D.C. Circuit has suggested, although it has not held, “that a likelihood of success on the merits is an independent, free-standing requirement for a preliminary injunction,” meaning that a plaintiff may need to make a strong merits showing and a strong showing on the other elements.<sup>35</sup> Other courts have similarly called into question the sliding-scale approach.

This line of cases may be especially relevant in litigation involving FDA’s decisions, since it may be more difficult for plaintiffs to mount a challenge on the merits at the outset of the case. That is because the full administrative record will typically not be available upon filing of the lawsuit. Rather, the materials before the court will likely be the citizen petition, other materials in the public docket (including materials submitted by the generic company in opposition to the petition), and FDA’s response. In the absence of the full administrative record, plaintiffs may be hard-pressed to make certain substantive arguments, including a challenge that the agency failed to consider all of the information in the record. Plaintiffs also may not have access to internal correspondence at the agency concerning the generic product and reports from various divisions on aspects of the ANDA. These materials might show internal tension within the agency on key issues.

### *Supporting a Request for Relief by Demonstrating Irreparable Harm*

To be sure, a plaintiff may still be able to make a compelling showing on the merits by, for example, basing all of its initial arguments solely on questions of statutory construction. But plaintiffs may still be faced with significant challenges if the sliding-scale approach is abandoned, since they will still need to demonstrate that they have sustained irreparable harm from FDA’s approval of a generic product. “To demonstrate irreparable injury, a plaintiff must show that it will suffer harm that is more than simply irretrievable; it must also be serious in terms of its

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<sup>35</sup> *Mylan Pharmaceuticals Inc. v. Sebelius*, 856 F.Supp.2d 196, 206-207 (D.D.C. 2012) (citing and discussing *Greater New Orleans Fair Housing Action Ctr. v. US Dep’t of Housing and Urban Dev.*, 639 F.3d 1078, 1089 (D.C. Cir. 2011)).

effect on the plaintiff.” Recent case law from the D.C. Circuit appears to suggest that financial harm may not be enough to demonstrate irreparable injury unless one can establish that the economic harm is so severe as to “cause extreme hardship to the business” or threaten its very existence. Yet large companies with multiple product lines may find it difficult to demonstrate that a loss of sales and revenue for one product would threaten the entire operations of the business.<sup>36</sup> As a result, plaintiffs should also consider allegations involving irreparable harm both to the company and the brand-name product stemming from FDA’s approval of a generic product.

In light of these considerations, plaintiffs contemplating litigation against the FDA should carefully consider the law in various jurisdictions where they may file a lawsuit. The federal venue statute provides that a case against a federal agency may be filed in the venue where the agency is located or in the venue where the party resides.<sup>37</sup> Generally, a case may be filed in Maryland (where the FDA resides) or the District of Columbia (where the Secretary of the Department of Health and Human Services resides) or the venue where the plaintiff resides. Venue decisions are important strategically because the law governing temporary relief (as well as the justiciability doctrines discussed above) may vary. Most cases challenging FDA’s decisions on ANDAs are filed in the D.C. Circuit, where judges have significant experience with litigation under the APA. Nonetheless, any party considering a lawsuit against FDA must carefully evaluate the law and possible venues to understand its likelihood of success on winning both temporary and permanent relief.

### **The Merits: Substantive Arguments and Judicial Deference**

Once a plaintiff has established that its action is suitable for judicial review, it must, of course, assemble substantive arguments to persuade a court to overturn FDA’s decision. Under Section 706(2)(A), a district

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<sup>36</sup> When plaintiffs move a court to enter a preliminary injunction, they must file a declaration from a company official that describes the irreparable harm the company will suffer from marketing of the generic product. To protect the confidentiality of that commercial information, plaintiffs may move the court to file such declarations under seal.

<sup>37</sup> 28 U.S.C. § 1391 (1948).

court may set aside agency action that is “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.” In connection with its consideration of the plaintiff’s arguments, a court will invariably need to consider the extent to which it must or should defer to the agency’s decisions. As described next, that determination may often dictate the outcome of a case. Indeed, for certain types of questions, a court will typically defer to an administrative agency unless its decision is clearly erroneous. These principles governing deference and judicial review may be particularly applicable to lawsuits brought by brand-name manufacturers against the FDA, where decisions involving generic drugs may frequently involve highly technical matters. As a result, any party considering a challenge to FDA’s approval of a generic drug product must understand and appreciate the circumstances and extent to which a court will defer to FDA’s determinations.

*Deference to FDA’s Statutory Interpretation—The Chevron Doctrine*

In *Chevron USA Inc. v. NRDC*, the Supreme Court outlined a two-step test for determining whether a court should defer to an agency’s construction of a statute it administers.<sup>38</sup> First, “is the question whether Congress has directly spoken to the precise question at issue.” The court explained that “[i]f the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress.” This inquiry is commonly known as “*Chevron* step one.” On the other hand, if the court finds that Congress “has not directly addressed the precise question at issue,” then the court considers “whether the agency’s answer is based on a permissible construction of the statute.” This inquiry is commonly known as “*Chevron* step two.” At the step-two stage of the *Chevron* test, the court will defer to the agency’s interpretation as long as it “represents a reasonable accommodation of conflicting policies that were committed to the agency’s care by the statute” and does not appear to be an interpretation that Congress would not have sanctioned.<sup>39</sup>

Two recent cases from the Court of Appeals for the D.C. Circuit illustrate the approach that courts will take to questions of statutory interpretation.

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<sup>38</sup> *Id.*

<sup>39</sup> *Id.*

In *AstraZeneca Pharmaceuticals LP v. FDA*, the court considered AstraZeneca’s claim that the data included on Seroquel’s labeling (and, thus, data that would be used in the generic’s labeling) were entitled to exclusivity and should not be used by generic companies until the period of exclusivity expired.<sup>40</sup> The question of whether the data were entitled to exclusivity ultimately turned on the meaning of the language “supplement to a drug application” in the FDCA. Although AstraZeneca argued that this phrase was unambiguous, the court disagreed after finding that a supplement could have various meanings. Turning to *Chevron* step two, the court noted that the FDCA “leaves to the FDA the interpretation” of what constitutes a “supplement to a drug application” and that FDA’s interpretation of that term was reasonable and permissible.

In another recent case, *Cook v. FDA*, the Court of Appeals for the D.C. Circuit reached a different conclusion about FDA’s interpretation of a particular provision in the FDCA.<sup>41</sup> There, the plaintiffs alleged that FDA violated the APA by improperly allowing shipments of a misbranded and unapproved new drug (thiopental sodium) to enter the United States, contrary to Section 801(a) of the FDCA. In pertinent part, that provision declares that “[i]f it appears from the examination of such [imported] samples or otherwise” that the product violates the FDC Act’s misbranding or new drug approval requirements, “then such article shall be refused admission.” Turning to an analysis of this provision under *Chevron* step one, the court found this language to be “plain and unambiguous” and rejected FDA’s interpretation to the contrary.

As these and other decisions make clear, plaintiffs challenging FDA actions are more likely to be successful if they can persuade a court that the case turns on an erroneous interpretation of an unambiguous statutory provision by FDA. If a party is concerned that FDA’s actions are based on interpretations of the relevant statute that are clearly contrary to the express intent of Congress, the party should present those arguments in a citizen petition to the agency and, thereby, preserve its ability to make that argument in court under *Chevron* step one. If it does not appear that Congress spoke to the precise issue at hand, then an aggrieved party must

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<sup>40</sup> See *AstraZeneca*, *supra* note 31.

<sup>41</sup> *Cook v. Food & Drug Admin.*, Case No. 12-5176 (D.C.C. Jul. 23, 2013).

ascertain whether FDA's interpretation of the statutory provision is at odds with what Congress would have intended and does not constitute a reasonable construction of the statute. If so, it should also raise those concerns in a citizen petition. Under *Chevron* step two, a court may disagree with FDA's interpretation, but still uphold it if it constitutes a permissible construction of the statute. As a result, it will be more difficult to persuade a court to overturn FDA's decision on such grounds.

### *Deference to FDA's Scientific and Technical Judgments*

In addition to deferring to administrative agencies on certain questions involving statutory interpretation, the courts also defer to agencies on questions that involve highly technical issues or scientific questions. Indeed, "[o]rdinary deference may be heightened even further in cases involving scientific or technical decisions."<sup>42</sup> This may be particularly true of a decision by FDA to approve a generic product, since such questions are frequently characterized by FDA and the courts as falling within the agency's "technical, complex, and dynamic" expertise, and they "rest on the agency's evaluations of scientific data within its area of expertise." Given this deference, brand-name manufacturers challenging approval of an ANDA on technical or scientific grounds may often have a difficult time prevailing in litigation solely on those grounds.

That is not to say, however, that such actions always fail. Rather, litigants have been successful when they can persuasively characterize FDA's decision-making as inconsistent with the agency's procedural regulations and, thus, arbitrary and capricious and in violation of the APA.<sup>43</sup> This approach was recently successful in a case brought by Bayer challenging approval of generic versions of that company's animal drug product, Baytril 100.<sup>44</sup> In advance of filing its lawsuit, Bayer submitted a citizen petition to FDA

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<sup>42</sup> *Serono Labs. Inc., v. Shalala*, 158 F.3d 1313, 1320 (D.C.Cir.1998) (noting that an agency is entitled to a "high level of deference" when its regulatory determination rests on its "evaluation [ ] of scientific data within its area of expertise").

<sup>43</sup> *Doe v. Rumsfeld*, 341 F.Supp.2d 1, 8-9 (D.D.C. 2004) ("Although FDA's scientific expertise is due great deference, it is well within this Court's scope of authority to ensure that the agency adheres to its own procedural requirements.") (citing *Service v. Dulles*, 354 U.S. 363 (1957)).

<sup>44</sup> *Bayer Healthcare LLC v. FDA*, CIV. A. 13-487 RMC, 2013 WL 1777481 (D.D.C. Apr. 17, 2013).

outlining, in detail, safety concerns surrounding generic versions of Baytril. And, in support of these contentions, Bayer submitted affidavits from three veterinarians discussing the risks presented by certain generic versions of Baytril. While these materials formed part of the administrative record, FDA failed to respond substantively to the concerns raised in Bayer's citizen petition when it approved generic versions of Baytril.

In its lawsuit seeking to enjoin FDA's approval of the generic product, Bayer focused the court's attention on the agency's failure to consider key parts of the administrative record. In response, FDA argued that the court should defer to its scientific expertise and presume regularity of its decision-making. The court rejected FDA's claims and found that "FDA entirely failed to consider" key aspects of the record Bayer had put before it. As a result, the agency's decision was not entitled to deference, and, as the court concluded, FDA acted arbitrarily and capriciously in violation of the APA by failing to consider important information in the record. The Bayer case, thus, demonstrates that litigants may overturn FDA's actions by focusing on the agency's consideration (or lack of consideration) of key information in the record, as opposed to challenging directly FDA's decisions on scientific or technical matters.

## **Conclusion**

In light of the foregoing discussion, any party that is concerned about FDA approval of a generic drug product (or, for that matter, biosimilar) will need to consider a number of factors and take particular actions in building a possible lawsuit against the agency. The following takeaways are designed to help parties and their counsel think through the key decision points and steps to challenging FDA's actions concerning approval of a generic drug product or biosimilar.

## **Key Takeaways**

- What are the repercussions of both a citizen petition and possible lawsuit against FDA? After all, the agency maintains jurisdiction over my company's products and my applications for approval to market new products.

- If we decide to file a citizen petition or possibly a lawsuit against FDA, will those actions potentially undermine or conflict with positions and arguments we may advance in patent litigation against generic companies involving the same product?
- How will my earlier submissions to FDA in connection with approval of an NDA influence what we can say in a citizen petition to FDA? We will want to be consistent in the positions we take with the agency.
- If we do file a petition, have the materials my company submitted to FDA fully captured the central arguments that we would like to make to the agency and, if necessary, to a court if FDA denies our petition?
- Are there expert views and materials that my company should submit to FDA in the form of affidavits or other literature or scientific evidence that FDA needs to fully consider in making its determination and that will ultimately make any lawsuit against the agency more persuasive?
- Do the arguments raised in my citizen petition focus on potentially significant differences between my product and a potential generic version, and would those differences potentially have a clinically meaningful impact on patients receiving the generic product? Do we have the burden of making this case?
- Have we raised both credible and fully defensible arguments in the petition that are based on both the law and science and that do not implicate anti-trust or anti-competitive issues?
- If FDA has denied our citizen petition, what further steps (if any) must we take with the agency to appeal the petition denial or, if we decide to do so, can we directly file suit in federal court?
- If we do file a lawsuit, how do we determine what venue is most favorable for a positive decision and specifically which defendants to sue? Will generic companies be allowed to intervene in the case, and, if so, how will that impact the case?
- How can we show that the harm from FDA's decision to approve a generic product is direct and imminent so as to bolster our standing and ripeness positions? Can we do so without having to disclose this harm publicly? Is financial harm enough, or do we need to show more?

- If FDA has issued its decision before a generic product has been approved, should we file a suit in court directly or wait until approval is imminent? That is, should my company risk a dismissal of its action based on justiciability, or should it wait until a dismissal is less likely, but where harm is more imminent?
- What steps can my company take to obtain FDA's production of the administrative record as early as possible in the litigation, and should we wait for production of the record, before moving for certain types of relief? Are there certain arguments I should make in a request for injunctive relief that are not dependent on immediate access to the record?
- Is the administrative record that FDA produced complete, or should my company consider moving to supplement the record, and is it possible to frame the potential litigation against FDA to challenge the agency's failure to consider key aspects of the administrative record?
- How and when can I get the administrative record after I have filed the lawsuit? Will the FDA and the generic company insist on a protective order to govern our review of certain materials in the record? If so, will that delay my ability to review key portions of the record?
- How do we overcome the deference that a court will generally give to FDA's approval of a generic drug product, both on legal questions and on scientific determinations? Can I make arguments in this context that I did not raise earlier in my citizen petition or other filings with the agency?

*Bruce S. Manheim Jr. is a partner at Wilmer Cutler Pickering Hale and Dorr LLP in Washington, DC. He is a member of the Litigation/Controversy and Regulatory and Government Affairs Departments, and a member of the Investigations and Criminal Litigation, Government and Regulatory Litigation, Life Sciences and Strategic Response and Counseling Groups. Mr. Manheim has filed numerous citizen petitions to the Food and Drug Administration (FDA) on behalf of clients, and served as lead counsel in litigation challenging FDA's decisions to approve generic drug products. He also has developed expertise on FDA review and approval of biosimilars.*

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*Skye L. Perryman is a senior associate at Wilmer Cutler Pickering Hale and Dorr LLP in Washington, DC, where she is a member of the Litigation/Controversy group. Ms. Perryman has handled litigation on behalf of pharmaceutical and biotechnology companies, including litigation challenging FDA's actions.*



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