
Article

Regulatory Silence at the FDA

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INTRODUCTION

Congress creates federal administrative agencies, crafts their fundamental organizational structure and mission, and bestows upon them authority to perform tasks such as rulemaking, adjudication, investigation, and licensing. Often, Congress expressly directs an agency to perform a specific task within a timeframe subject to carefully enumerated factors or considerations.¹ Many times, however, an agency is left with a great deal of discretion, either express or implied, to determine appropriate action within the scope of its authority, the statutory language, the Constitution, and procedural laws.² It is in these instances that the Supreme Court's deference precedent has flourished, setting forth when a court ought to defer to an agency's reasonable interpretation of the statute that it administers when the

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1. See, e.g., 21 U.S.C. § 355b(a) (2012).

Not later than one year after January 4, 2002, the Secretary of Health and Human Services shall promulgate a final rule requiring that the labeling of each drug for which an application is approved . . . include the toll-free number maintained by the Secretary for the purpose of receiving reports of adverse events regarding drugs and a statement that such number is to be used for reporting purposes only, not to receive medical advice. With respect to the final rule.

(1) The rule shall provide for the implementation of such labeling requirement in a manner that the Secretary considers to be most likely to reach the broadest consumer audience.

(2) In promulgating the rule, the Secretary shall seek to minimize the cost of the rule on the pharmacy profession.

(3) The rule shall take effect not later than 60 days after the date on which the rule is promulgated.

Id.

2. Administrative Procedures Act, Pub. L. 79-404, 60 Stat. 237 (1946) (codified as amended in scattered sections of 5 U.S.C.).

statute itself is silent or ambiguous.³ As muddled and disputed as this deference case law is, it seeks to clarify the scope of an agency's discretion when the agency acts to interpret law. However, agencies, especially the U.S. Food and Drug Administration (FDA), also decide *not* to interpret language within a statute or regulation even though such interpretation is authorized by Congress and would facilitate effective and consistent industry responses.⁴

Nowhere is this behavior more evident than in the FDA's regulatory authority as it relates to patent law, where the statute authorizes the agency to act but does not require a specific regulatory action. This Article uses two recent examples of high-stakes litigation in the life-sciences realm that demonstrate the FDA's reluctance to wade into issues regarding patent-related procedural mechanisms within legislation. Both case studies involve situations in which Congress directed the FDA to oversee a regulatory process and provided a statutory framework that involved the use of patent information as part of that process. The first deals with risk evaluation and mitigation strategies (REMS) in the context of drugs and biologics established in the Food and Drug Administration Amendments Act of 2007.⁵ The second deals with the Biologics Price Competition and Innovation Act (BPCIA) enacted as part of the Patient Protection and Affordable Care Act of 2009.⁶ Although both examples raise similar issues and have resulted in protracted litigation,⁷ to date

3. See *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 843 (1984).

4. There is foundational case law distinguishing an agency's failure to act and declining to act that is relevant here under an Administrative Procedure Act section 706 analysis. See *generally* *Norton v. S. Utah Wilderness All.*, 542 U.S. 55 (2004) (holding that claims to compel action under the Administrative Procedure Act when agency action is unlawfully withheld or unreasonably delayed can proceed only where a plaintiff asserts the agency's failure to take a discrete agency action that was required).

5. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85 (2007) (codified in scattered sections of 21 U.S.C.).

6. Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001-7003, 124 Stat. 119, 804-21 (2010) (codified in scattered sections of 42 U.S.C. & 21 U.S.C.).

7. See *Sandoz, Inc. v. Amgen, Inc.*, 582 U.S. ___, Nos. 15-1039, 15-1195, slip. op. (June 12, 2017); Complaint, *Mylan Pharms. Inc. v. Celgene Corp.*, (D.N.J. Apr. 3, 2014) (No. 14-2094) (No. 1) (original complaint); Order, *Mylan Pharms. Inc. v. Celgene Corp.*, No. 14-2094, (D.N.J. Dec. 23, 2014) (No. 54) (order on motion to dismiss); Order, *Mylan Pharms. Inc. v. Celgene Corp.*, No. 15-8017, (3rd Cir., Mar. 5, 2015) (No. 42) (order on motion to petition and cross petitions for permission to appeal); Order Granting Mylan's Unopposed Motion to Seal,

only the REMS example has been addressed in the legal literature.⁸

Part I of the Article discusses relevant administrative law and case precedent regarding required agency action and failure to act, including the scope of judicial review. This Part also addresses the role of citizen petitions in requesting an agency to act and the legal implications of an agency response or lack thereof. Part II examines the statutory framework for drugs and biological products, as well as the crucial relationship between the FDA and the U.S. Patent & Trademark Office (PTO) as it impacts drug and biologic development and approval. Part III delves into the two case studies, describing the relevant statutory language and connecting the language to agency behavior. Part III.A details the REMS litigation and current status in the courts, as well as congressional response in the form of proposed legislation.⁹ Part III.B details the BPCIA litigation, which culminated in the June 2017 Supreme Court decision *Sandoz v. Amgen*, and highlights the ongoing legal challenges with the statutory provisions.¹⁰ Part IV discusses broader implications and suggests several meaningful ways in which the FDA could address the current uncertainty arising from these two examples.

This Article contributes to the literature in three ways. First, it explores FDA behavior through the lens of administrative law and practice, particularly tied to the Administrative Procedure Act (APA) and relevant case law. Second, it delves into two real-time instances in which the FDA's silence has significantly contributed to anticompetitive action from life-science companies that impacts consumers. Third, it urges that the FDA

Mylan Pharms. Inc. v. Celgene Corp., No. 14-2094, (D.N.J. June 19, 2017) (No. 252).

8. Several legal scholars have examined the use of REMS by the pharmaceutical industry to thwart generic competition. *See generally* Michael A. Carrier & Brenna Sooy, *Five Solutions to the REMS Patent Problem*, 97 B.U. L. REV. 1661 (2017) (concluding that patents on REMS programs undermine generic competition); Jordan Paradise, *REMS as a Competitive Tactic: Is Big Pharma Hijacking Drug Access and Patient Safety?*, 15 HOUS. J. HEALTH L. & POL'Y 43 (2015) (exploring the tactics used to stifle competition); Darren S. Tucker & Gregory F. Wells, *Emerging Competition Issues Facing Follow-On Biologics*, 29 ANTITRUST MAGAZINE 100 (2014) (arguing that anticompetitive reactions to BPCIA will likely mirror historic ones to the Hatch-Waxman Act).

9. Creating and Restoring Equal Access To Equivalent Samples Act of 2017, S. 974, 115th Cong. (2017) (attempting to promote competition in the market for drugs and biologicals).

10. *Sandoz*, 582 U.S. ___, Nos. 15-1039, 15-1195, slip. op. (June 12, 2017).

can play a more dominant role in interpreting the statutes going forward to provide clarity to industry and explores meaningful ways to achieve that goal.

I. DEFINING FDA ACTION

Before exploring the two case studies, a brief discussion of the underlying administrative-law framework is warranted. The following Sections provide an overview of basic statutory definitions, the scope of judicial review, instances of deference to administrative agencies, and the citizen petition process.

A. THE ADMINISTRATIVE PROCEDURE ACT

Federal administrative agencies are constrained by a variety of sources, though chiefly through their enabling statute and subsequent related legislation, as well as the APA.¹¹ The APA grounds many of its provisions on the concept of agency action, which it defines as “the whole or part of an agency rule, order, license, sanction, relief, or the equivalent or denial thereof, or failure to act.”¹² Agency actions, including failures to act, are subject to judicial review, the scope of which is set forth in the APA.¹³ An agency may act in a definitive manner, by promulgating a regulation or issuing an order through adjudication. An agency also acts when it formally denies a request. There may also be a failure to act, which occurs when an agency fails to take a discrete, identifiable action that the statute requires the agency to take.¹⁴ Finally, there may be agency inaction, which can take many forms. An agency inaction (the omission of an action without formally rejecting a request) is not the same as a failure to act or a denial.¹⁵ The Court provides:

11. Pub. L. 79-404, 60 Stat. 237 (1946) (codified as amended in scattered sections of 5 U.S.C.).

12. 5 U.S.C. § 551(13) (2012).

13. *Id.* §§ 701–706. These provisions are applicable except to the extent that “(1) statutes preclude judicial review; or (2) agency action is committed to agency discretion by law.” *Id.* § 701. “A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial relief thereof.” *Id.* § 702. “Agency action made reviewable by statute and final agency action for which there is no adequate remedy in a court are subject to judicial review. A preliminary, procedural, or intermediate agency action or ruling not directly reviewable is subject to review on the review of the final agency action.” *Id.* § 704.

14. *Norton v. S. Utah Wilderness All.*, 542 U.S. 55, 64 (2004) (“[A] claim under § 706(1) can proceed only where a plaintiff asserts that an agency failed to take a *discrete* agency action that it is *required to take*.”).

15. *Id.* at 63.

A “failure to act” is not the same thing as a “denial.” The latter is the agency’s act of saying no to a request; the former is simply the omission of an action without formally rejecting a request—for example, the failure to promulgate a rule or take some decision by a statutory deadline.¹⁶

The distinction between a definitive action on the part of the agency, a failure to act, and inaction matters for purposes of judicial review. Agency actions, in whatever form, are typically reviewed by courts under an arbitrary-and-capricious standard, where the court is to hold unlawful and set aside the agency action if it is found to be arbitrary and capricious.¹⁷ The arbitrary-and-capricious test requires that agencies make decisions based on a consideration of the relevant factors including alternatives, without a clear error of judgment, and under the correct legal standard.¹⁸ While arbitrary-and-capricious inquiry is “searching and careful,” the standard of review “is a narrow one,” where the court is not empowered to substitute its judgment for that of the agency.¹⁹

However, where a party alleges that an agency has failed to act, the reviewing court is directed to “compel agency action unlawfully withheld.”²⁰ Here, the APA empowers a court to compel an agency “to perform a ministerial or non-discretionary act” or “to take action upon a matter, without directing *how* it shall act.”²¹ However, this occurs only upon the court determining that there was a failure to act—where the agency failed to take a discrete, identifiable action that the statute requires.²² For example, “when an agency is compelled by law to act within a certain time period, but the manner of its action is left to the agency’s discretion, a court can compel the agency to act, but has no power to specify what the action must be.”²³

There is a general presumption of reviewability for agency actions, yet the APA provides two circumstances in which there

16. *Id.*

17. The APA provides six standards of judicial review. Courts review most policy decisions of agencies under the arbitrary and capricious test, which applies to informal agency action and informal rulemaking, unless Congress specifies otherwise. WILLIAM F. FOX, UNDERSTANDING ADMINISTRATIVE LAW 339 (6th ed. 2012).

18. *Id.* at 339–40.

19. *Citizens to Pres. Overton Park v. Volpe*, 401 U.S. 402, 416 (1971).

20. 5 U.S.C. § 706(1) (2012).

21. *Norton*, 542 U.S. at 64 (citing U.S. DEP’T OF JUSTICE, ATTORNEY GENERAL’S MANUAL ON THE ADMINISTRATIVE PROCEDURE ACT 108 (1947)).

22. *Id.*

23. *Id.* at 65.

is no judicial review available: (1) where a statute precludes judicial review,²⁴ or (2) when there is an “agency action committed to agency discretion by law.”²⁵ The phrase “discretion by law” is a narrow exception, where “statutes are drawn in such broad terms that in a given case there is no law to apply.”²⁶ This exception is where agency inaction traditionally falls. In *Heckler v. Chaney*, the Supreme Court applied the nonreviewability section of the APA to eliminate from judicial review administrative-agency actions classified as refusals to take action, or agency inaction.²⁷ The Court held that the FDA’s decision “not to take enforcement action should be presumed immune from judicial review.”²⁸ In its reasoning, the Court stated “when an agency refuses to act it generally does not exercise its coercive power over an individual’s liberty or property rights, and thus does not infringe upon areas that courts often are called upon to protect.”²⁹ After the decision in *Heckler*, legal scholars began to shape the meaning of the agency inaction. Cass Sunstein wrote that agency actions are “committed to agency discretion by law” whenever the governing statute imposes no legal constraints on the agency with respect to the particular allegation made by the plaintiff.³⁰ Justice Antonin Scalia penned that inaction is where an agency “simply sits on its hands and does not choose to do additional things that could be done.”³¹

The case law regarding agency decisions not to initiate notice-and-comment rulemaking is a little more opaque than enforcement discretion. Agencies may refuse to promulgate a rule after receiving input from the public or industry by means of citizen petitions. However, that refusal, or decision not to act, may come in many forms. The Supreme Court has not examined the issue and two dated cases in the D.C. Circuit involving similar

24. 5 U.S.C. § 701(a)(1).

25. *Id.* § 701(a)(2).

26. *Citizens to Pres. Overland Park v. Volpe*, 401 U.S. 402, 410 (1971) (citing S. REP. NO. 79-752, at 212 (1945)).

27. *Heckler v. Chaney*, 470 U.S. 821, 832 (1985).

28. *Id.*

29. *Id.*

30. Cass Sunstein, *Reviewing Agency Inaction After Heckler v. Chaney*, 52 U. CHI. L. REV. 653, 659 (1985).

31. Antonin Scalia, *The Role of The Judiciary in Deregulation*, 55 ANTI-TRUST L.J. 191, 191 (1986).

facts reached two different outcomes based on the facts.³² However, both were decided prior to *Heckler v. Chaney*.³³ In *Natural Resources Defense Council, Inc. v. SEC*, the court held that the refusal to promulgate a rule was arbitrary and capricious.³⁴ There, the Securities and Exchange Commission (SEC) waited seven years to deny the petition, which included extensive information gathering proceedings and a detailed, written decision.³⁵ This seems as if the agency did in fact act, but later ceased action. In *WWHT, Inc. v. FCC*, decided two years later, another panel of the D.C. Circuit held that the Federal Communication Commission's (FCC's) refusal to initiate rulemaking was reviewable for the question of whether the agency abused that discretion not to initiate a rulemaking.³⁶ There, the FCC did not even begin the investigatory and information gathering process as the SEC had done in the prior case. This outcome seems to be in conflict with *Heckler v. Chaney*, in that agency discretion in the rulemaking context is subject to review, while there is a presumption that agency discretion in the enforcement context is not subject to review.

Some recent scholarship tackles the realm of agency inaction and its various forms and this Article will not attempt to recreate that literature,³⁷ although a few excerpts are useful. For example, Professor Sharon Jacobs terms this inaction "administrative restraint" and offers a taxonomy framing how agencies use restraint strategically in order to "avoid unnecessary conflict

32. See *WWHT, Inc. v. FCC*, 656 F.2d 807 (D.C. Cir. 1981); *Natural Res. Def. Council, Inc. v. SEC*, 606 F.2d 1031 (D.C. Cir. 1979).

33. See *Heckler*, 470 U.S. at 821.

34. *Natural Res. Def. Council*, 606 F.2d at 1031.

35. *Id.* at 1035–36.

36. 656 F.2d 807 (D.C. Cir. 1981).

37. See, e.g., Eric Biber, *Two Sides of the Same Coin: Judicial Review of Administrative Agency Action and Inaction*, 26 VA. ENV'T L.J. 461, 462 (2008); Lisa Schultz Bressman, *Judicial Review of Agency Inaction: An Arbitrariness Approach*, 79 N.Y.U. L. Rev. 1657 (2004) (advocating for judicial review of agency inaction and that both agency action and inaction should be subjected to the same principles of judicial review); Sharon B. Jacobs, *The Administrative State's Passive Virtues*, 66 ADMIN. L. REV. 565, 565 (2014); Michael A. Livermore & Richard L. Revesz, *Regulatory Review, Capture, and Agency Inaction*, 101 GEO. L.J. 1337 (2013) (proposing "a specific mechanism for [the Office of Information and Regulatory Affairs] to engage in review of agency inaction by examining petitions for rulemakings filed with agencies"); Daniel P. Selmi, *Jurisdiction to Review Agency Inaction Under Federal Environmental Law*, 72 IND. L.J. 65 (1996) (examining the jurisdictional parameters of judicial review of agency inaction in federal environmental law and the adverse effects of confusion over these jurisdictional boundaries); Scalia, *supra* note 31, at 194–95; Sunstein, *supra* note 30, at 653–54.

with other institutional actors.”³⁸ Professor Jacobs refutes the position that “agencies engage in inaction and delay primarily for nefarious reasons, including lassitude and narrow interest group influence.”³⁹ She argues rather that agencies “must be pragmatic and strategic in the exercise of their authority.”⁴⁰ She urges that courts should not undermine agency passivity where appropriate internal safeguards exist, as there is merit to agency decisions not to act, even in the face of apparent authority to do so.⁴¹

Professor Jacobs specifically addresses “decisions not to decide,” where agencies avoid difficult questions entirely rather than taking steps, even minimal steps, to resolve them.⁴² The chief example of this approach was reflected in the activity of the Environmental Protection Agency (EPA) leading up to the Supreme Court decision in *Massachusetts v. EPA*.⁴³ There, the EPA determined that the statute imposed no duty to exercise its judgment to regulate greenhouse-gas emissions and that doing so would not be in the interest of the Agency.⁴⁴ The Court found an abuse of discretion on the part of the Agency in declining to make a judgment on the public health and welfare effects of greenhouse-gas emissions from motor vehicles as air pollutants.⁴⁵ Others have explored judicial review of administrative action and inaction, positing that the outcomes are “doctrinally incoherent and unclear.”⁴⁶

B. JUDICIAL DEFERENCE TO AGENCY ACTION

Courts will also defer to agency actions in certain circumstances. After *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, one circumstance achieving judicial deference is where the statute that the agency administers is silent or ambiguous on a particular issue.⁴⁷ The inquiry for the court is

38. Jacobs, *supra* note 37.

39. *Id.* at 588.

40. *Id.* at 568.

41. Jacobs says “[d]eferring decisions or taking small steps rather than aggressive ones can be useful where more decisive action would expose the agency to damaging backlash.” *Id.*

42. *Id.* at 575.

43. 549 U.S. 497 (2007).

44. *Id.* at 511.

45. *Id.* at 534.

46. Biber, *supra* note 37, at 461.

47. *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 843–44 (1984).

whether Congress has spoken directly on the precise question at issue.⁴⁸ Where the statute is silent or ambiguous, courts are to defer to an agency's reasonable interpretation of the statute.⁴⁹ The Supreme Court provides:

If Congress has explicitly left a gap for the agency to fill, there is an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation. Such legislative regulations are given controlling weight unless they are arbitrary, capricious, or manifestly contrary to the statute. Sometimes the legislative delegation to an agency on a particular question is implicit rather than explicit. In such a case, a court may not substitute its own construction of a statutory provision for a reasonable interpretation made by the administrator of an agency.⁵⁰

In *Chevron*, the Clean Air Act required that nonattainment states—those considered to have air quality that is worse than the National Ambient Air Quality Standards—establish a permit program regulating “new or modified major stationary sources” of air pollution.⁵¹ The EPA had promulgated a regulation to implement this mandate allowing a state to adopt a plant-wide definition of the term “[s]tationary source.”⁵² This effectively controlled the total volume of pollutants emitted by a facility rather than individual points of emission. The EPA's vision to accomplish this was called the bubble concept, in which the facility is encased in a single bubble for purposes of measuring emissions from stationary sources.⁵³ Environmentalists immediately challenged the regulation.

The challenges ultimately reached the Supreme Court. There, the Court stated that “[w]hen a court reviews an agency's construction of the statute which it administers, it is confronted

48. *Id.* at 842.

49. *Id.* at 844.

50. *Id.* at 843–44.

51. The Clean Air Act Amendments of 1977 distinguished between nonattainment regions and prevention of significant deterioration (PSD) regions with regard to obtaining permits for building any new or modified “stationary source” of air pollution. Clean Air Act Amendments of 1977, Pub. L. No. 95-95, § 129(a)(2)(B)(i), 91 Stat. 685 (amending 42 U.S.C. §§ 4701–4772 (1976)). Applicants for a new source permit in nonattainment states had to satisfy the “lowest achievable emission rate” regardless of cost. *Id.* § 129(a)(2)(B)(i)(3). On the other hand, PSD applicants had to show they were using the “best available control technology,” taking into account the cost of installing and using such technology. *Id.* § 165(a)(4).

52. 40 C.F.R. § 51.18(j)(1)(i) (1985).

53. *Chevron*, 467 U.S. at 855–56.

with two questions.”⁵⁴ The first is “whether Congress has directly spoken to the precise question at issue.”⁵⁵ If the intent of Congress is clear, the court and the agency must give effect to the expressed intent of Congress.⁵⁶ If the statute is silent or ambiguous, the second question for the court is “whether the agency’s answer is based on a permissible,” or reasonable, “construction of the statute.”⁵⁷ Based on this analysis, the Supreme Court held “that Congress did not have a specific intention on the applicability of the bubble concept . . . and conclude[d] that the EPA’s use of that concept . . . [was] a reasonable policy choice for the agency to make.”⁵⁸ The Court looked to the overall congressional aim of the permit program as accommodating conflict between “economic interest in permitting capital improvements to continue and the environmental interest in improving air quality.”⁵⁹ The Court found the agency interpretation was a reasonable accommodation of competing interests and was entitled to deference.⁶⁰ They further noted that the regulatory scheme was technical and complex, the agency considered the matter in a detailed and reasoned fashion, and the decision involved reconciling conflicting policies.⁶¹

Other cases have examined deference in different contexts, such as when an agency interprets its own regulation⁶² or when the interpretation is contained in an informal document generated outside of a rulemaking or adjudication.⁶³ These cases are rife with controversy due to inconsistent application at the lower courts and have garnered considerable attention in Supreme Court concurrences and dissents. There is a vast literature probing this case law.

54. *Id.* at 842.

55. *Id.*

56. *Id.* at 843.

57. *Id.*

58. *Id.* at 845.

59. *Id.* at 851.

60. *Id.* at 865.

61. *Id.*

62. *See Auer v. Robbins*, 519 U.S. 452 (1997).

63. *See United States v. Mead Corp.*, 533 U.S. 218 (2001) (describing a case where a U.S. Custom Service tariff schedule imposed a tariff on day planners previously classified as duty-free); *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944) (describing a case where the Administrator used an interpretative bulletin to define working time).

C. CITIZEN PETITIONS TO CHALLENGE AGENCY ACTION

The United States Constitution protects the right of citizens to petition the government to request an action on a specific matter.⁶⁴ This right has been applied to federal agencies. Likewise, the APA requires federal administrative agencies to allow the public to petition for the issuance, amendment, or repeal of a rule.⁶⁵ Finally, the FDA explicitly allows citizen petitions and has detailed regulations identifying the scope and process.⁶⁶ Any “interested person” can file a citizen petition and request that the FDA “issue, amend, or revoke a regulation or order,” or “take or refrain from taking any other form of administrative action.”⁶⁷ All citizen petitions must include the “[a]ction [r]equested,”⁶⁸ and a “[s]tatement of [g]rounds,” including “the factual and legal grounds on which the petitioner relies.”⁶⁹

There is a broad range of grounds on which citizens submit petitions to the FDA. Often an entity will petition the Agency to promulgate a regulation, which it then typically denies formally in some type of written form. This denial of the citizen petition’s request, the refusal to promulgate a regulation, or some other decision, is itself an agency action under the APA and may be challenged in court. The citizen-petition process serves to supply standing to an individual challenging the Agency’s action in court. However, if the Agency neglects to respond with an official denial or related action, this is an instance of an agency inaction. A recent empirical study examined all citizen petitions submitted to the FDA between 2001 and 2010 and found that the Agency denied eighty-one percent of the petitions and granted nineteen percent.⁷⁰ The study also found that after legislation was passed in 2007 requiring FDA to act within 180 days on each petition, the number of citizen petition filings rose from twenty-seven to thirty-four per year.⁷¹

64. U.S. CONST. amend. I (“Congress shall make no law . . . abridging the freedom . . . to petition the government for a redress of grievances.”).

65. 5 U.S.C. § 553(e) (2012) (“Each agency shall give an interested person the right to petition for the issuance, amendment, or repeal of a rule.”).

66. 21 C.F.R. § 10.30(a) (2017).

67. *Id.* § 10.25.

68. *Id.* § 10.30(b)(A).

69. *Id.* § 10.30(b)(B). For any petition, the Commission may also require an environmental impact statement and economic impact statement. *Id.* § 10.30(b)(C),(D).

70. Michael A. Carrier & Daryl Wander, *Citizen Petitions: An Empirical Study*, 34 CARDOZO L. REV. 249, 249 (2012).

71. *Id.*

II. THE FDA'S STATUTORY SCOPE: DRUGS & BIOLOGICS

The FDA is a classic command-and-control regulatory agency with the ability to promulgate regulations as a core authority granted to it by Congress. A monstrous statute, the Federal Food, Drug, and Cosmetic Act (FDCA), directs oversight of human and animal drugs, medical devices, cosmetics, food (including dietary supplements), tobacco products, and products emitting radiation.⁷² A separate statute, the Public Health Service Act (PHSA), contains provisions for the FDA's regulation of biological products.⁷³ In all, the FDA oversees upwards of twenty-five percent of consumer products in the United States.⁷⁴ Congress frequently amends the FDCA and PHSA, with the most recent significant amendments contained in the 21st Century Cures Act, enacted in December 2016.⁷⁵

The overall mission of the FDA, as supplied by Congress, is seemingly in conflict, requiring both speed in product approvals and ample protection of the public. Many commentators have lamented this inherent tension.⁷⁶ The Agency is tasked with "promot[ing] the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner" and at the same time "protect[ing] the public health by ensuring that [among other things] . . . human and veterinary drugs are safe and effective."⁷⁷ The Director of the FDA's Center for Drug Evaluation and Research, Janet Woodcock, writing with a coauthor on the need for ongoing collaboration to improve outcomes, notes "[t]he ongoing tension between these two objectives results in assertions that FDA requirements are stifling innovation, and simultaneously that FDA standards are too low."⁷⁸ The split mission may also

72. Federal Food, Drug, and Cosmetic Act (FDCA) §§ 1–1012, 21 U.S.C. §§ 301–399d (2012).

73. 42 U.S.C. §§ 262–263 (2012).

74. FDA, GLOBAL ENGAGEMENT 2, <https://wayback.archive-it.org/7993/20170405003627/https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM298578.pdf>.

75. 21st Century Cures Act, Pub. L. No. 114-255, § 1, 130 Stat. 1033 (2016).

76. See, e.g., Ernst R. Berndt et al., *Opportunities for Improving the Drug Development Process: Results from a Survey of Industry and the FDA*, 6 INNOVATION POLY & ECON. 91, 91 (2006); Janet Woodcock & Raymond Woosley, *The FDA Critical Path Initiative and Its Influence on New Drug Development*, 59 ANN. REV. MED. 1, 2 (2008).

77. 21 U.S.C. § 393(b)(1), (2)(B).

78. See Woodcock & Woosley, *supra* note 76.

contribute to FDA policy choices, including decisions not to act in a particular situation.

The FDCA features ten chapters devoted to the various products that the FDA oversees. The PHSa, on the other hand, contains two lengthy sections regarding regulation of biological products.⁷⁹ The new drug and biological-product approval processes share similar features, owing largely to efforts from both Congress and the Agency to streamline the requirements. Each is subject to three phases of clinical trials, laboratory and manufacturing controls, human-subject protections, adverse-event disclosure, reporting and tracking, labeling requirements, post-market measures, and rigorous review and approval procedures.⁸⁰ The FDA has much discretion to require information as part of the premarket approval process for drugs and biological products, and to interpret the statutes. The FDA has promulgated a vast landscape of regulations regarding all aspects of the drug and biological product lifecycle.

The FDA statutory and regulatory regime necessarily implicates the concurrent authority of the PTO. The PTO awards patents for inventions; the pharmaceutical industry rakes in a substantial amount of patent protection as an investment-recouping strategy to offset costly product development.⁸¹ Patents must demonstrate novelty, utility, nonobviousness, and enablement, and must meet threshold patentability requirements.⁸² Drug and biological product patents typically involve the chemical or biologic compound itself, manufacturing practices, and methods of use.⁸³ In addition to patent protections and exclusivity through the PTO, Congress also provides product exclusivity through the FDA in the form of market and data exclusivities for particular types of products.⁸⁴ For example, new chemical entities receive five years of exclusivity, innovator biologics receive

79. 42 U.S.C. §§ 262–263 (2012).

80. Jordan Paradise, *The Legal and Regulatory Status of Biosimilars: How Product Naming and State Substitution Laws May Impact the United States Healthcare System*, 41 AM. J. L. & MED. 49, 64 (2015).

81. The Tufts Center for the Study of Drug Development estimates that the cost to develop a new prescription drug is nearly \$2.6 billion. Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 20 (2016).

82. 35 U.S.C. §§ 101–103, 112 (2012). Products of nature, natural phenomenon, and abstract ideas are not patentable subject matter. See *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589 (2012).

83. See 35 U.S.C. § 101 (declaring inventions are patentable).

84. For a discussion of FDA exclusivities, see generally Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH.

twelve years of exclusivity, and certain generic drugs may receive 180 days of exclusivity after successful litigation against the innovator product.⁸⁵

Both new drugs and biological products must also adhere to statutory requirements for patent disclosure and communication processes for industry dealings as a component of product review and approval. However, Congress has established different means to effectuate these dealings, one set forth in the FDCA, the other in the BPCIA. The provisions in the FDCA applying to new-drug applications (NDAs)⁸⁶ and abbreviated new-drug applications (ANDAs, otherwise known as generic drug applications)⁸⁷ require innovator drug products to submit a list of their patents and expiration dates for the chemical compound and related methods of use to the FDA.⁸⁸ The FDA maintains a public list in the *Orange Book*, which is consulted by the generic industry to identify both the relevant patents and drug compound therapeutic-equivalence ratings for innovator products.⁸⁹ The FDA disclaims any duty to independently confirm the validity and accuracy of these submitted patents.⁹⁰

A generic sponsor has four options when filing a generic-drug application to address the existing patents held by the innovator. The generic sponsor (1) may certify to the FDA that

L. REV. 345 (2007). The twelve-year exclusivity for innovator biological products was introduced in 2010, three years after the article cited.

85. For a discussion of the different types of FDA exclusivities, including biologic exclusivity, see Yaniv Heled, *Patents Vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419, 427–32, 443–74 (2012).

86. Federal Food, Drug, and Cosmetic Act (FDCA) § 505(b)–(e), 21 U.S.C. § 355(b)–(e) (2012).

87. Federal Food, Drug, and Cosmetic Act (FDCA) § 505(j), 21 U.S.C. § 355(j) (2012).

88. Federal Food, Drug, and Cosmetic Act (FDCA) § 505(b)(1), 21 U.S.C. § 355(b)(1) (2012).

89. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, FDA, <https://www.accessdata.fda.gov/scripts/cder/ob> (last visited June 18, 2018). The therapeutic equivalence ratings dictate which chemical compounds the generic sponsor must compare their compound with in the required bioequivalence studies to support product approval.

90. See Rebecca S. Eisenberg & Daniel A. Crane, *Patent Punting: How FDA and Antitrust Courts Undermine the Hatch-Waxman Act To Avoid Dealing with Patents*, 21 MICH. TELECOMM. & TECH. L. REV. 197, 211 (2015); see also *Caraco Pharms. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 405–06 (2012) (“[T]he FDA does not attempt to verify the accuracy of the use codes that brand manufacturers supply. It simply publishes the codes, along with the corresponding patent numbers and expiration dates, in a fat, brightly hued volume called the *Orange Book* . . .”).

there are no listed innovator patents in the *Orange Book*; (2) they may certify they will not enter the market until all relevant patents have expired; (3) they may certify that all relevant patents have expired; or (4) they may decide to file what is called a paragraph IV certification, claiming that although there are existing patents listed in the *Orange Book*, they are either invalid or unenforceable.⁹¹ This fourth type of certification is litigation-forcing, in that it triggers a timeframe during which the innovator product may bring an action for patent infringement against the generic sponsor.⁹² It is an act of artificial infringement created by the statute, as the generic product has not yet been approved or entered the market. The goal is to ascertain the validity of the patent; a successful paragraph IV challenger is awarded 180 days of exclusivity.⁹³

The biologic and biosimilar product provisions are contained in the PHSA, recently amended by the Patient Protection and Affordable Care Act, that establishes the biosimilar pathway to market.⁹⁴ These provisions for biological products differ significantly from the requirements for innovator and generic drug sponsors discussed above, largely attributable to the existing statutory frameworks and the complexity of biological products. The patent disclosure and industry processes are distinct for biological products. There is no requirement to submit patents and expiration dates to the FDA for public listing and the patent process is a private back-and-forth between the innovator biologic and the biosimilar sponsor.

The next Part will examine specific aspects of each of these FDA statutory frameworks that implicate patents, using two case studies.

III. AGENCY SUBTERFUGE OR REASONED RESTRAINT?

The following two case studies highlight inaction on the part of the FDA at various stages of the regulatory process. The first involves recent statutory provisions establishing REMS requirements for drugs and biological products. The second involves the

91. Federal Food, Drug, and Cosmetic Act (FDCA) § 505(b)(2)(A)(vii)(I)–(IV), 21 U.S.C. § 355(b)(2)(A)(vii)(I)–(IV).

92. 35 U.S.C. § 271(e).

93. Federal Food, Drug, and Cosmetic Act (FDCA) § 505(j)(5)(B)(iv), 21 U.S.C. § 355(j)(5)(B)(iv).

94. See Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010); see also Paradise, *supra* note 80, at 50.

legislative changes that created the abbreviated pathway to market for biosimilar biologics, including patent exchanges between innovator and biosimilar sponsors.

A. RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The pharmaceutical industry is well known for its arsenal of anticompetitive tactics, including entering into reverse payments (also known as pay-for-delay settlements, in reference to the innovator paying the generic product to stay off the market during the 180 days of exclusivity);⁹⁵ product hopping or evergreening (shifting market demand to a new formulation of a drug);⁹⁶ using authorized generics to retain market share;⁹⁷ and filing frivolous citizen petitions in order to delay generic market entry.⁹⁸ As watchdog to anticompetitive behavior, the Federal Trade Commission (FTC) routinely asserts antitrust laws against the pharmaceutical industry. The 2012 case *Federal Trade Commission v. Actavis, Inc.* is one chief example, where the Supreme Court scrutinized a pay-for-delay settlement entered into between an innovator-drug patent holder and a generic, holding that such agreements were not per se illegal but instead subject to a rule of reason test.⁹⁹

Drug and biologic innovators are now utilizing REMS to interfere with generic drug entry. Amendments to the FDCA in 2007 introduced new statutory REMS provisions that bolster the FDA's post-approval authority.¹⁰⁰ The FDA can require REMS either as a condition of approval¹⁰¹ or, in the case of already approved products, as a subsequent condition for continued marketing.¹⁰² The FDA may require a medication guide for patients; additional physician prescribing information; communications

95. See Fed. Trade Comm'n v. Actavis, Inc., 133 S. Ct. 2223, 2229 (2013); *Pay for Delay*, FTC, <https://www.ftc.gov/news-events/media-resources/mergers-competition/pay-delay> (last visited June 18, 2018).

96. See, e.g., Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167, 171 (2016); M. Sean Royall et al., *Antitrust Scrutiny of Pharmaceutical "Product Hopping,"* ANTITRUST, Fall 2013, at 71, 71.

97. See FTC, AUTHORIZED GENERIC DRUGS: SHORT-TERM EFFECTS AND LONG-TERM IMPACT 66–69 (2011).

98. See Matthew Avery et al., *The Antitrust Implications of Filing "Sham" Citizen Petitions with the FDA*, 65 HASTINGS L.J. 113, 124–27 (2013).

99. *Actavis*, 133 S. Ct. at 2237.

100. Federal Food, Drug, and Cosmetic Act (FDCA) §§ 505(p), 505-1, 21 U.S.C. §§ 355(p), 355-1 (2012).

101. See Federal Food, Drug, and Cosmetic Act (FDCA) § 505-1(a)(1).

102. See *id.* § 505-1(a)(2).

to healthcare providers and pharmacies; limitations on labeling, promotion, and prescribing to assure safe use by patients; patient registries and tracking; and a REMS implementation plan.¹⁰³ Violations trigger civil money penalties and subject manufacturers to litigation under misbranding provisions within the FDCA.¹⁰⁴ To date, the FDA has implemented over seventy REMS, more than half of which include elements to assure safe use (ETASU) that often take the form of distribution restrictions; training and recordkeeping requirements for prescribers and pharmacists; and prescribing and administration limitations.¹⁰⁵

REMS are being used in two distinct ways by innovators. First, innovators are patenting their ETASU and asserting patent infringement against generic or biosimilar versions of their product where the manufacturer attempts to utilize aspects of the patented ETASU in their own label.¹⁰⁶ One example of this is Celgene's patented distribution system for thalidomide, described in the patent abstract as "[m]ethods for delivering a drug to a patients [sic] in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated."¹⁰⁷

This assertion of patent rights poses a major problem for generics. To obtain FDA approval through the ANDA process, generic applicants, among other things, must demonstrate bioequivalence to the innovator products through pharmacodynamic and pharmacokinetic comparison studies and also must have the same proposed label.¹⁰⁸ If the generic cannot acquire permission to use the same label, including the ETASU that are considered part of the labeling, and the FDA does not grant a waiver from a

103. *See id.* § 505-1.

104. *Id.* § 303(f)(4)(A).

105. *See Approved Risk Evaluation and Mitigation Strategies (REMS)*, FDA, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemisData.page> (last visited June 18, 2018).

106. For a detailed discussion of the REMS provisions and the associated patent problems, see Paradise, *supra* note 8.

107. U.S. Patent No. 7,141,018 B2 (filed Nov. 28, 2006).

108. Federal Food, Drug, and Cosmetic Act (FDCA) § 505(j)(A)(v). The statute requires many elements as part of the ANDA, including a demonstration of the same conditions of use, route of administration, dosage form, and strength. Federal Food, Drug, and Cosmetic Act (FDCA) § 505(j)(A).

shared REMS system,¹⁰⁹ then marketing and selling that generic drug would violate the law.¹¹⁰

The statute emphasizes the preference of innovator and generic companies agreeing to implement a single, shared REMS system rather than separate systems each for the branded drug and the generic. However, this is proving difficult as innovator companies strategically refuse to negotiate or stall negotiations on development of a single, shared system.¹¹¹ In the face of industry uncertainty, the FDA has denied several citizen petitions requesting them to act to interpret the statute regarding the facilitation of a single, shared REMS system.¹¹² The FDA did recently publish a draft guidance establishing a two-prong approach to address issues raised by the statute and industry behaviors.¹¹³ However, this guidance does not address situations in which the innovator threatens patent infringement or denies a license to use the ETASU.

Second, innovators subject to REMS for an NDA drug product claim that they cannot make samples of that drug available to the generic applicant because they would be in violation of distribution restrictions placed on the products by the FDA through ETASU REMS. One such case involves Celgene Corporation and Mylan Pharmaceuticals, where Mylan alleges that

109. The FDA maintains the authority to waive the use of a single, shared REMS system, though to date it is unclear how often they have done this, what products were involved, and whether there was a failure to negotiate due to innovator refusal. Such a waiver is possible where a relevant part of the innovator reference listed drug (RLD) REMS is the subject of a patent and the generic was not able to obtain a license. The generic sponsor must certify to the FDA that they attempted to obtain a license and were refused. Federal Food, Drug, and Cosmetic Act (FDCA) § 505-1(i)(1)(B), 21 U.S.C. § 355-1(i)(1)(B). The FDA recently published a draft guidance establishing a two-prong approach to address issues raised by the statute and industry behaviors. Use of a Drug Master File for Shared System Risk Evaluation and Mitigation Strategy Submissions; Draft Guidance for Industry; Availability, 82 Fed. Reg. 52,058 (2017) [hereinafter Use of a Drug Master File].

110. Federal Food, Drug, and Cosmetic Act (FDCA) 21 U.S.C. § 352(y).

111. Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on New Steps to Improve FDA Review of Shared Risk Evaluation and Mitigation Strategies to Improve Generic Drug Access, (Nov. 8, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584259.htm>.

112. Kurt R. Karst, *FDA Largely Denies Citizen Petition on Single, Shared REMS System, but Outlines Agency Standards and Processes*, FDA LAW BLOG (Oct. 21, 2013), <http://www.fdalawblog.net/2013/10/fda-largely-denies-citizen-petition-on-single-shared-rems-system-but-outlines-agency-standards-and-p>.

113. Use of a Drug Master File, *supra* note 109.

Celgene is refusing to distribute Thalomid and Revlimid for bioequivalence testing.¹¹⁴ The FDA has invoked ETASU REMS for both innovator products because of their teratogenic nature, including requirements to prevent embryo-fetal exposure.¹¹⁵ The ETASU involve extensive requirements for distribution only through authorized dispensing pharmacies. Celgene asserts that the distribution imposed by the FDA prohibits the transfer of drug samples to Mylan for any purpose, including studies to demonstrate bioequivalence to the innovator product.¹¹⁶ At least two previous generic companies have alleged similar claims, although those situations have resulted in settlements.¹¹⁷

The FTC filed a June 2014 amicus brief in the case, arguing that Celgene is engaging in exclusionary conduct in violation of the Sherman Act by “refusing to sell to rivals.”¹¹⁸ The FTC identified potential violations of the Sherman Act by Celgene not only refusing to directly provide samples to Mylan, but also implementing restrictions that prevent Mylan from purchasing samples through customary distribution channels.¹¹⁹ The U.S. District Court for the District of New Jersey denied Celgene’s motion to dismiss.¹²⁰ Celgene has appealed.

The statute does not specifically prohibit the exact behavior at issue in the case but provides generally:

No holder of an approved covered application shall use any element to assure safe use required by the Secretary under this subsection to block or delay approval of an application under section 355(b) or (j) of this

114. Complaint, Mylan Pharms., Inc. v. Celgene Corp., No. 14-2094 (D.N.J. Apr. 3, 2014).

115. *Revlimid (lenalidomide) Risk Evaluation Mitigation Strategy (REMS) Modification*, FDA (Feb. 17, 2015), <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM222644.pdf>; *Thalomid (thalidomide) Risk Evaluation and Mitigation Strategy (REMS) Modification*, FDA (Sept. 2014), <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM222649.pdf>.

116. Complaint at 28, Mylan Pharms. Inc. v. Celgene Corp., (D.N.J. Apr. 3, 2014) (No. 14-2094) (No. 1).

117. *Actelion Pharm., Ltd. v. Apotex, Inc.*, No. 12-5743, 2013 WL 5524078 (D.N.J. Sept. 6, 2013); *Lannett Corp., Inc. v. Celgene Corp.*, No. 08-3920, 2011 WL 1193912 (E.D. Pa. Mar. 29, 2011).

118. Brief for Fed. Trade Comm’n as Amicus Curiae, Mylan Pharms., Inc. v. Celgene Corp., No. 14-2094 (D.N.J. June 17, 2014).

119. *Id.* at 6.

120. Order on Motion to Dismiss, Mylan Pharms., Inc. v. Celgene Corp., No. 14-2094, (D.N.J. Dec. 23, 2014). The Third Circuit rejected Celgene’s request for immediate review in March 2015. Vin Gurrieri, *3rd Circ. Declines to Hear Mylan, Celgene Antitrust Fight*, LAW360 (Mar. 6, 2015), <http://www.law360.com/articles/628588>.

title or to prevent application of such element. . . to a drug that is the subject of an abbreviated new drug application.¹²¹

The statute does not instruct on how this provision relates to the bioequivalence requirements generally. Nor does it contain any civil money penalties for violation of this provision or a private cause of action. The FDA has informed generic companies that they would exercise enforcement discretion and specifically told Mylan that they “would not consider the provision of samples of an RLD [reference listed drug] to a generic manufacturer a REMS violation.”¹²²

The FDA held a public meeting in July 2017, seeking input on the performance of the generic drug program and its goals of achieving a balance between access and innovation.¹²³ Included in the *Federal Register* notice announcing the meeting were topics specific to anticompetitive behavior enabled by the REMS provisions.¹²⁴ Specifically, the FDA solicited comments on how the Agency should utilize its authority to address challenges encountered by generic companies attempting to reach agreements for shared REMS systems; what actions the FDA should take to address difficulties acquiring sufficient samples for testing; and what marketplace dynamics exist that may be disincentivizing the marketing of generics.¹²⁵ Meeting materials, recordings, and presentations from the public meeting are available at the FDA’s website.¹²⁶ Coverage and commentary resulting from the public meeting are ongoing in the legal media realm and blogosphere as the FDA continues to contemplate how to implement any changes to policy.

In November 2017, FDA Commissioner Scott Gottlieb issued a statement announcing FDA’s new approach to improve the review of shared REMS programs, noting the “need to make sure that REMS programs maintain their role in serving public health and don’t become a tool companies can use to delay or

121. Federal Food, Drug, and Cosmetic Act (FDCA) 21 U.S.C. § 355-1(f)(8) (2012).

122. Complaint, Mylan Pharms., Inc. v. Celgene Corp., No. 14-2094, at 12 (D.N.J. Apr. 3, 2014).

123. U.S. Food & Drug Admin., Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access; Public Meeting; Request for Comments, 82 Fed. Reg. 28,493 (June 22, 2017).

124. *Id.* at 28,495.

125. *Id.*

126. *Administering the Hatch-Waxman Amendments; Ensuring a Balance Between Access and Innovation; Public Meeting*, FDA (last updated Sept. 18, 2017), <https://www.fda.gov/Drugs/NewsEvents/ucm563986.htm>.

block competition from generic products entering the market.”¹²⁷ As part of the new approach, Gottlieb assures the FDA “will explore new steps . . . to reduce the likelihood that branded drug companies can use the existence of REMS as a way to slow the entry of generic competition.”¹²⁸ Gottlieb has also stated that Agency letters to brand companies that convey that selling samples to a generic company for testing is acceptable under a REMS may be made public.¹²⁹

Congress is also contemplating mechanisms to remedy the rampant problems with innovator bad actors in the REMS realm. Notably, an early draft of 2012 legislation had contained a provision to curb REMS abuses, but was removed following lobbying activity.¹³⁰ The Creating and Restoring Equal Access to Equivalent Samples Act (CREATES Act), introduced in the Senate in April 2017 by Senator Patrick Leahy of Vermont, would create a cause of action for generic and biosimilar sponsors to obtain restricted product samples.¹³¹ Two of the bill’s enumerated findings explicitly address the scope of FDA authority as motivation for the bill:

The [FDA] has testified that some manufacturers of covered products have used REMS and distribution restrictions adopted by the manufacturer on their own behalf as reasons to not sell quantities of a covered product to generic product developers, causing barriers and delays in getting generic products on the market. The [FDA] has reported receiving significant numbers of inquiries from generic product developers who were unable to obtain samples of covered products to conduct necessary testing and otherwise meet requirements for approval of generic drugs.¹³²

The antitrust laws may address actions by license holders who impede the prompt negotiation and development of a single, shared system of elements to assure safe use, and the [FDA] has some authority to waive the requirement of a single, shared system. Clearer regulatory authority to approve different systems that meet the statutory requirements to ensure patient safety, however, would limit the effectiveness of bad faith negotiations over single, shared systems to delay generic

127. Press Release, *supra* note 111.

128. *Id.*

129. Derrick Gingery, *FDA Exploring Whether Public Sharing Can Stop REMS Abuses*, PINK SHEET (July 18, 2017), <https://pink.pharmaintelligence.informa.com/PS121134/FDA-Exploring-Whether-Public-Shaming-Can-Stop-REMS-Abuses>. This move would increase transparency and remove a company’s ability to blame the FDA for restricting access. *Id.* Agency review to determine whether such a letter is warranted typically takes eighteen months. *Id.*

130. *Id.*

131. S. 974, 115th Cong. § 3(b) (2017).

132. *Id.* at § 2(6).

approval. At the same time, clearer regulatory authority would ensure all systems protect patient safety.¹³³

The bill would require that innovator products provide sufficient quantities of the product to generic drug or biosimilar applicant (termed “eligible product developer”) in order to conduct clinical testing to support their application to the FDA.¹³⁴ The term sufficient quantities is defined as an amount that would allow the product sponsor to conduct testing to support an abbreviated application for either a drug or biological product and “fulfill any regulatory requirements relating to such an application for approval or licensing.”¹³⁵ Where an innovator refuses to provide sufficient quantities following a request and offer to purchase from the eligible product developer, the eligible product developer may then bring a civil action for failure to supply on “commercially reasonable, market-based terms.”¹³⁶ Where the innovator product is the subject of a REMS with ETASU, there is also an authorization process through the FDA to achieve access.¹³⁷ There are affirmative defenses identified,¹³⁸ along with remedies where the eligible product developer prevails, including an order to provide access to sufficient quantities, reasonable attorney’s fees, and additional monetary amounts for delay or failure to comply.¹³⁹ A similar bill was introduced in the House.¹⁴⁰

Effectively, this bill aims to fix the problem inherent in the more general current language of the statute imploring that “no holder or an approved covered application shall use any [ETASU] . . . to block or delay approval” of a generic drug or biosimilar product.¹⁴¹ It would create a cause of action, provide remedies, and compel compliance. However, while the new language provides some direction, there is still ample authority and discretion to the FDA on how to carry out the statute. For example,

133. *Id.* at § 2(10).

134. *Id.* at § 3(b)(1).

135. *Id.* at § 3(a)(9).

136. *Id.* at § 3(b)(2)(A)(iv).

137. *Id.* at § 3(b)(2)(B). The bill authorizes the Secretary of Health & Human Services to perform this, though this would be delegated to the Commissioner of the FDA.

138. *Id.* at § 3(b)(3).

139. *Id.* at § 4(A).

140. Fair Access for Safe and Timely (FAST) Generics Act, H.R. 2051, 115th Cong. (Apr. 6, 2017).

141. Federal Food, Drug, and Cosmetic Act (FDCA) 21 U.S.C. § 355-1(f)(8) (2012).

the eligible product developer is authorized to submit to the Secretary of Health & Human Services a written request to obtain sufficient quantities, and the Secretary is given 90 days to authorize the ability of the eligible product developer to obtain a specific quantity for testing and bioequivalence purposes. It is unclear how this will function to allow access to the product held by another manufacturer without court intervention.¹⁴²

B. THE BIOSIMILAR PATENT DANCE

The second case study is a more recent development, arising subsequent to the enactment of the Patient Protection and Affordable Care Act in 2010.¹⁴³ As part of the new abbreviated route to market for biosimilar biological products, the statute appears on its face to require a disclosure by the biosimilar sponsor to the innovator product sponsor of its application to the FDA as well as manufacturing information. The statute states:

Not later than 20 days after the Secretary notifies the . . . applicant that the application has been accepted for review, the . . . applicant—
(A) shall provide to the reference product sponsor a copy of the application submitted to the Secretary . . . and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application.¹⁴⁴

Following such disclosure, the statute provides for a private exchange between the biosimilar applicant and the reference biologic sponsor that identifies patents for potential litigation.¹⁴⁵ The statute imposes good-faith negotiations between the two parties; if there is no agreement resulting from the negotiations, the innovator is to bring a patent infringement action against the biosimilar applicant.¹⁴⁶ These provisions are known as the patent dance.

In addition, the biosimilar applicant “shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k).”¹⁴⁷ After receiving notice of first commercial marketing from the biosimilar sponsor, the innova-

142. S. 974, 115th Cong. § 2(B)(i)–(ii) (Apr. 27, 2017).

143. Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010) (codified in scattered sections of 42 U.S.C. and 21 U.S.C.).

144. 42 U.S.C. § 262(l)(2).

145. *See id.* § 262(l)(1), (l)(3)(A) (2012).

146. *Id.* § 262(l)(4)–(6)(B).

147. *Id.* § 262(l)(8)(A).

tor (reference product sponsor) may seek a preliminary injunction to prevent the manufacture or sale of the biosimilar product until all patent disputes are resolved.¹⁴⁸

The provisions immediately sparked controversy and made their way to the Supreme Court in June 2017. Amgen and Sandoz disputed both provisions of the statute with regard to Sandoz's product Zarxio, the biosimilar version of Amgen's Neupogen (filgrastim).¹⁴⁹ The FDA accepted the biosimilar application for Zarxio on July 7, 2014. Sandoz then notified Amgen that it had submitted the application and intended to commercially market Zarxio immediately after FDA approval.¹⁵⁰ However, Sandoz refused to disclose both the application and the manufacturing information.¹⁵¹ Amgen filed suit in October 2014 in the Northern District of California, citing both state unfair-competition law and patent infringement.¹⁵² The complaint asked for injunctive relief for Sandoz's noncompliance with the disclosure provisions in the statute. Sandoz argued that Amgen's patent was invalid and denied any violation of the statute's disclosure provision. Separately, the two parties were involved in litigation regarding the 180-day notice of commercial marketing requirement.¹⁵³

The Federal Circuit addressed both issues, affirming the dismissal of the state unfair competition claims, declaring that an injunction was not available as a remedy,¹⁵⁴ and as for the notice issue, holding that a biosimilar must be licensed at the time the applicant gives the reference sponsor the requisite 180-day notice.¹⁵⁵ In July 2017, the Supreme Court thus addressed two related questions on certiorari: (1) whether the statutory language instructing a biosimilar applicant to provide its application and manufacturing information to the reference biologic sponsor after FDA acceptance of the application is enforceable

148. *Id.* § 262(l)(8)(B).

149. Zarxio (filgrastim-sndz) was approved by the FDA on March 6, 2015. *Approval Package for: Application Number: 125553Orig1s000*, FDA (Mar. 6, 2015) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125553Orig1s000Approv.pdf.

150. *Sandoz, Inc. v. Amgen, Inc.*, 582 U.S. ___, Nos. 15-1039, 15-1195, slip. op. at 8 (June 12, 2017).

151. *Id.*; 42 U.S.C. § 262(l)(9)(C).

152. *Sandoz, Inc.*, slip. op. at 8; *Amgen, Inc. v. Sandoz, Inc.*, 2015 WL 1264756, at *7-9 (N.D. Cal., Mar. 19, 2015).

153. Order Granting Defendant's Motion to Dismiss, *Sandoz, Inc. v. Amgen, Inc.*, No. 3:13-cv-02904-MMC (N.D. Cal. Nov. 12, 2013).

154. *Amgen, Inc. v. Sandoz, Inc.*, 794 F.3d 1347, 1357-58 (Fed. Cir. 2015).

155. *Id.*

by injunction; and (2) whether the biosimilar applicant must give notice of intended commercial marketing to the reference biologic sponsor only after obtaining an approved license from the FDA.¹⁵⁶

The Supreme Court held that the biosimilar statute¹⁵⁷ was not enforceable by injunction because Sandoz disclosed neither the application nor manufacturing information for the biosimilar to Amgen, and thus there was no “artificial infringement” triggering those remedies as available in the generic drug context.¹⁵⁸ The Court held that the exclusive statutory remedy was an action for declaratory judgment.¹⁵⁹ The Court remanded to the Federal Circuit both the issue of whether California unfair competition law provides a separate remedy¹⁶⁰ and the issue of whether the BCPIA preempts state law remedies.¹⁶¹

The Court also held that the statute allows a biosimilar applicant to give notice of first commercial marketing prior to obtaining a license from the FDA.¹⁶² The Court relied on a plain-language statutory interpretation and structural analysis of other timing provisions in the statute.¹⁶³ This holding provides a significant advantage to biosimilar applicants because they can enter the market much earlier. Most interesting to this second question faced by the Court, Justice Breyer penned a brief concurrence harkening to judicial deference, and perhaps nudging the FDA to act:

The Court’s interpretation of the statutory terms before us is a reasonable interpretation, and I join its opinion. In my view, Congress implicitly delegated to the Food and Drug Administration authority to interpret those same terms. That being so, if that agency, after greater experience administering this statute, determines that a different interpretation would better serve the statute’s objectives, it may well have authority to depart from, or to modify, today’s interpretation, though we need not now decide any such matter.¹⁶⁴

This is not the end of the story. Much confusion remains as to the application of the Supreme Court’s holding on both points and whether the FDA will step in and make policy choices to fill

156. *Sandoz, Inc. v. Amgen, Inc.*, 582 U.S. ___, Nos. 15-1039, 15-1195, slip op. (June 12, 2017).

157. Specifically, 42 U.S.C. § 262(l)(2)(A) (2012).

158. *Sandoz, Inc.*, slip op. at 10–13. *See* 35 U.S.C. § 271(e)(4).

159. *Sandoz, Inc.*, slip op. at 12 (citing 42 U.S.C. § 262(l)(9)(C)).

160. *Id.* at 14.

161. *Id.* at 15.

162. *Id.* at 16 (citing 42 U.S.C. § 262(l)(8)(A)).

163. *Id.* at 16.

164. *Id.* at 19 (Breyer, J. concurring) (citation omitted).

in some of the details. The lower courts will be reviewing cases on BPCIA-related issues for the foreseeable future. For example, the Federal Circuit reviewed a dispute between Amgen and Hospira in August 2017, where Amgen sought to compel discovery from Hospira of manufacturing information for their biosimilar version of the innovator biologic Epogen. Hospira had filed their biosimilar application with the FDA in December 2014, provided a copy of the application to Amgen, yet did not separately provide information regarding “the process . . . used to manufacture the biological product” as the statute requires.¹⁶⁵ The Federal Circuit denied Amgen’s requests, citing a lack of jurisdiction¹⁶⁶ and general concepts of civil procedure.¹⁶⁷

Similarly, in *Genentech, Inc. v. Amgen, Inc.*, filed in October 2017, Genentech asserted patent infringement and sought a declaratory judgment for Amgen’s refusal to provide manufacturing information independent of the limited information provided in the application itself.¹⁶⁸ The litigation involved Amgen’s Mvasi, the biosimilar to Genentech’s lucrative innovator anti-cancer therapy Avastin (bevacizumab).¹⁶⁹ Amgen continued to refuse this manufacturing information as an additional submission to Genentech, arguing the statute does not require it. This is an interesting position, given that Amgen sued for a similar refusal as the innovator in the previous case. Genentech notes this seemingly contradictory position in this case and chastises the actions in “stonewalling” as “particularly brazen.”¹⁷⁰ The fact that companies are altering their interpretations of the statute depending on their financial stake and position as either the innovator or biosimilar product sponsor should be a clear signal that clarity is needed to rectify the ambiguity.

As for the fate of the questions remanded by the Supreme Court, a unanimous Federal Circuit ruling on December 14, 2017 held that Congress “fully occupied” the field of patent litigation for biosimilars with passage of the BPCIA.¹⁷¹ This federal

165. *Amgen, Inc. v. Hospira, Inc.*, 866 F.3d 1355, 1357 (Fed. Cir. 2017).

166. *Id.* at 1363.

167. *Id.* at 1361.

168. Complaint at 5–10, *Genentech, Inc. v. Amgen, Inc.*, No. 1:17-cv-01471-GMS (D. Del. Oct. 26, 2017).

169. *Id.*

170. *Id.* at 5.

171. *Amgen, Inc., Amgen Mfg. Ltd. v. Sandoz, Inc.*, 877 F.3d 1315, 1328 (Fed. Cir. 2017).

preemption holding means that state laws cannot compel disclosure of manufacturing information.¹⁷² Accordingly, going forward, pioneer biologic companies have neither federal injunctions nor state laws to turn to when a biosimilar sponsor refuses to provide this information. Patent infringement actions remain available.

IV. TOWARD MEANINGFUL FDA ACTION: INITIAL MUSINGS

The widespread uncertainty resulting from the two case studies generates several implications that may prove damaging for access and innovation, as well as patient safety. These include hefty litigation costs as courts continue to wrestle with the case law and statute. Despite the Supreme Court decision in *Sandoz, Inc. v. Amgen, Inc.* and the Federal Circuit's decision regarding federal preemption in the context of the BPCIA, for example, procedural questions resulting from the legislation promise future litigation. Likewise, litigation is pending on varying aspects of the REMS statutory provisions. Given industry uncertainty about the law, generic and biosimilar sponsors may decide to delay development until there is more resolution, or abandon development efforts entirely. There may be a direct impact on drug costs, as the longer an innovator product enjoys the totality of the market, the higher the overall costs for that drug or biologic will be for consumers. In fact, one study published in July 2014 estimated that approximately \$5.4 billion per year has been lost in prescription-drug savings due to distribution restrictions imposed by brand manufacturers under the auspices of REMS.¹⁷³ Last, and perhaps most troubling, is that industry behavior using REMS to block competitor uses may also be detrimental to the long-term safety of users. Physicians have already identified refusing access to products for bioequivalence studies and the blocking of REMS through patents as a direct threat to patient safety.¹⁷⁴

However, where FDA authority interacts with patent protections, the FDA has been historically reluctant to take actions that may be viewed as aggressive, or outside their expertise

172. *Id.*

173. ALEX BRILL, MATRIX GLOB. ADVISORS, LOST PRESCRIPTION DRUG SAVINGS FROM USE OF REMS PROGRAMS TO DELAY GENERIC MARKET ENTRY 1 (July 2014), http://www.gphaonline.org/media/cms/REMS_Studyfinal_July2014.pdf.

174. See, e.g., Ameet Sarpawatri et al., *Using a Drug Safety Tool To Prevent Competition*, 370 NEW ENG. J. MED. 1476 (2014).

reading product safety and efficacy.¹⁷⁵ Some commentators assert that the FDA has no authority to act in particular situations, including biologic patent disputes.¹⁷⁶ However, undeniably, the FDA is now considering best practices in each of these areas and Commissioner Gottlieb has prioritized issues impacting competition. Public meetings and continued communications with industry reflect real concern with the problems. The current momentum within the FDA may be shifting the longstanding hands-off approach to issues connected to patent protections.

Complicating things is the fact that both the REMS and bi-similar case studies raise jurisdictional questions. As discussed above, the FDA is a single agency, with a product-safety mission, as well as a mission to speed innovations. The FDA is universally looked upon as the stalwart agency shaping drug and biologic law and policy. However, the PTO and FTC play a large role in restricting and guiding the behavior of the drug and biologic industry. Often it appears that the FDA defers to these agencies on particular issues despite the agency's broad authority. This is problematic given the roles of the PTO and FTC. The PTO acts to reward innovation with patent exclusivities at the outset of invention. Their statutory role includes granting good patents that satisfy the core statutory requirements of novelty, utility, nonobviousness, and enablement, including patentable subject matter. The PTO also plays an active role in assessments of issued patents through newly created post-grant review challenge procedures.¹⁷⁷ These mechanisms may in a given scenario be well-suited to challenge a potentially invalid or unenforceable individual ETASU REMS, yet they do not provide industry-wide certainty and resolution.

The FTC monitors industry behavior once on the market, assuring that companies do not violate statutes such as the Sherman Act¹⁷⁸ and the Lanham Act¹⁷⁹ that prohibit various forms

175. Eisenberg & Crane, *supra* note 90, at 211.

176. "Unlike the Hatch Waxman Act, pursuant to which the FDA plays at least *some* ministerial role in publishing Orange Book patents, the FDA is *wholly without power* to address biologic patent disputes." Michael A. Carrier & Carl J. Minniti III, *Biologics: The New Antitrust Frontier*, 2018 ILL. L. REV. 1, 43 (2018).

177. *Post Grant Review*, U.S. PATENT & TRADEMARK OFFICE, <https://www.uspto.gov/patents-application-process/appealing-patent-decisions/trials/post-grant-review> (last visited June 18, 2018).

178. 15 U.S.C. §§ 1–7 (2012).

179. Lanham Act, Pub. L. No. 79-489, 60 Stat. 427 (codified in scattered sections of 15 U.S.C.).

of anticompetitive activity. The FTC has routinely exercised this function in the drug and biologic realm, most notably with pay-for-delay settlements. But this reactive watchdogging occurs after a product has entered the market and is not best situated to proactively address the structural problems that foster the activity in the first place. Recent legal-media analysis notes that the FDA's increasing focus on problems with competition in the pharmaceutical realm may be "paving the way for the [FTC] to bring more novel enforcement actions."¹⁸⁰ An expert within the FTC's healthcare unit describes this recent FDA activity addressing competition as "an elevation of these issues to the highest levels of the FDA."¹⁸¹

The FDA, on the other hand, has immense latitude to say what the statutory provisions mean for industry as part of the review and approval process, and provide direction to industry prior to entering the market. In a sense, by not acting in these two situations the FDA is in fact violating *both* of its core missions: to protect the public safety and speed innovation. As noted above, the FDA has rejected citizen's petitions urging that the agency take action to formulate clear rules for the single, shared REMS systems. The FDA has issued guidance on various aspects of REMS,¹⁸² though they have not addressed the significant problems discussed earlier in a meaningful way through regulations or clear guidance. The FDA has also expressed that they would exercise enforcement discretion by not penalizing innovators for providing samples for bioequivalence studies where distribution restrictions via ETASU were in place.¹⁸³ This, as in *Heckler v. Chaney*, is an example of an agency merely declining to take enforcement action where the statute imposes civil penalties for violations of shared REMS systems, well within the "committed to agency discretion by law" language in the APA. Yet it provides no direction to guide industry behavior.

With regard to the biosimilar patent provisions, Justice Breyer himself explicitly nudged the FDA to take their role in interpreting the statute to heart. Justice Breyer states that the agency could act to interpret the statutory terms (e.g., regarding

180. Melissa Lipman, *FDA's Focus on Competition May Boost FTC Enforcement*, LAW360 (Dec. 1, 2017), <https://www.law360.com/articles/990139/fda-s-focus-on-competition-may-boost-ftc-enforcement>.

181. *Id.*

182. *See, e.g.*, Use of a Drug Master File, *supra* note 109.

183. Complaint at 12, *Mylan Pharms. Inc. v. Celgene Corp.*, No. 14-2094 (D.N.J. Apr. 3, 2014).

the timing of the 180-day first commercial marketing notice). This could be done through notice-and-comment rulemaking to provide the needed clarity and process. It would be time consuming, and would be certain to be subject to legal challenge, and then subject to judicial deference as Justice Breyer offers in his concurrence. Perhaps these two case studies illustrate agency restraint at its finest, or agency reluctance at its worst. Patients, and innovation, deserve concerted attention at the FDA going forward as to how agency action could best be calibrated to remedy these problems.