

# REFORMING JUDICIAL REVIEW OF BIOEQUIVALENCE DETERMINATIONS

CHRISTOPHER J. KOICHEVAR\*

*This Note discusses the regulatory regime developed by the Food and Drug Administration (FDA) to ensure generic drug quality through premarket approval. The Hatch-Waxman Act effectively created the contemporary generic drug industry in 1984, and today, this industry saves the United States billions of dollars in medical costs. The legal-scientific concept of “bioequivalence” is central to the Hatch-Waxman regime, and its meaning has developed through statutory, regulatory, and advisory pathways in Congress and at the FDA. In this Note, I argue that the FDA’s current approach to promulgating standards for bioequivalence—largely based on guidance documents—threatens the agency’s ability to sustain comprehensive and authoritative regulation in the future. Guidance documents and petition responses are not subject to public input according to the standards of the Administrative Procedure Act (APA), and may create confusion among regulated entities and trouble for consumers. Nevertheless, courts repeatedly have deferred to the FDA’s choice of policymaking form and have found challenges under the APA to be nonjusticiable for lack of standing and ripeness. I argue that this deference should be attenuated and justiciability should be restored, not because generic drugs approved under the current regime are demonstrably dangerous to patients, but because systematic foreclosure of public input and judicial oversight is an unsustainable regulatory approach.*

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## INTRODUCTION

When the average American patient fills a prescription, there is an almost three in four chance that the drug she receives is a generic copy of a formerly market-dominating innovator drug.<sup>1</sup> By some estimates, generic drugs have saved the health care system up to \$193 billion per year,<sup>2</sup> and reduce the annual prescription drug burden on Medicare by as much as \$33 billion.<sup>3</sup> The quality of and access to health care that Americans enjoy today would be diminished if laws promoting generic production were not in place.

Generics operate on the fundamental notion that first-to-market producers, especially those with patent protection, charge a premium within their market niche. Even when patents expire and competitors enter the market, producers can continue to charge higher prices because consumers remain familiar with the name, advertising, and

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<sup>1</sup> See OFFICE OF SCI. & DATA POLICY, U.S. DEP'T OF HEALTH & HUMAN SERVS., ASPE ISSUE BRIEF: EXPANDING THE USE OF GENERIC DRUGS 2 (2010), available at <http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.pdf> ("The rate of generic prescribing for all prescriptions reached almost 75 percent in 2009.").

<sup>2</sup> See GENERIC PHARM. ASS'N, GENERIC DRUG SAVINGS IN THE U.S. 3 (2012), available at <http://www.gphaonline.org/sites/default/files/IMS%20Study%20Aug%202012%20WEB.pdf> (explaining that "the use of generic drugs saved American consumers, taxpayers, federal and state governments and other payers" \$193 billion in 2011).

<sup>3</sup> CONG. BUDGET OFFICE, EFFECTS OF USING GENERIC DRUGS ON MEDICARE'S PRESCRIPTION DRUG SPENDING vii (2010), available at <http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/118xx/doc11838/09-15-prescriptiondrugs.pdf> ("CBO estimates that dispensing generic drugs rather than their brand-name counterparts reduced total prescription drug costs in 2007 by about \$33 billion.").

appearance of the innovator product. Consumers may remain loyal to a brand regardless of cheaper, functionally identical, but unbranded alternatives.

However, generic producers, with no responsibility to build and establish a market identity, also risk mounting a race to the bottom based on cheap manufacturing and marginal quality. For most consumer products, the stakes of this race are relatively low. But in the realm of prescription drugs, minute changes in drug quality or potency can create immediate adverse effects—sometimes severe ones. Furthermore, in contrast to most generic products, which consumers can evaluate at a glance, drugs must be introduced into the body to determine their effectiveness.

This Note discusses the regulatory regime that the Food and Drug Administration (FDA) has developed to ensure generic drug quality through premarket approval. The Hatch-Waxman Act of 1984 is the foundation for this regime.<sup>4</sup> The Act effectively created the contemporary generic drug industry by lowering the clinical trial requirement for quality generic drugs and by providing immunity from patent infringement for generic drug developers.<sup>5</sup> Today, the generic drug industry serves millions of consumers per year and saves the United States billions of dollars in medical costs largely by virtue of the FDA's unique regulatory treatment. This treatment revolves around evaluations of "bioequivalence"—an approximation of identity between a generic drug and an approved innovator product.<sup>6</sup>

In this Note, I argue that the FDA's current approach to promulgating standards for bioequivalence and courts' treatment of these standards threaten the FDA's ability to sustain comprehensive and authoritative regulation in the future. The FDA's current approach relies on a series of guidance documents that are not subject to the public input that is generally required under the Administrative Procedure Act (APA).<sup>7</sup> Nevertheless, courts have repeatedly deferred to the FDA's choice of policymaking form and have found challenges under the APA to be nonjusticiable for lack of standing and ripeness. I

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<sup>4</sup> Pub. L. No. 98-417, 98 Stat. 1585 (1984) (relevant sections codified as amended within 21 U.S.C. § 355 (2006) as "New drugs" and 35 U.S.C. § 156 (2006) as "Extension of patent term").

<sup>5</sup> See Michelle Meadows, *Greater Access to Generic Drugs*, FDA CONSUMER, Sept.–Oct. 2003, at 14 ("The Hatch-Waxman Act essentially created the generic drug industry," says [former director of the FDA Office of Generic Drugs, Gary] Buehler."); see also *infra* Part I.B (discussing the Hatch-Waxman Act in detail).

<sup>6</sup> See *infra* notes 28–31 and accompanying text (defining and discussing bioequivalence).

<sup>7</sup> Pub. L. No. 79-404, 60 Stat. 237 (1946) (codified as amended at 5 U.S.C. §§ 500–504, 551–559, 701–706 (2006)); see also *infra* Part I.C (discussing current guidance practices).

argue that courts should curtail this deference and restore justiciability, not because generic drugs approved under the current regime are demonstrably dangerous to patients, but because systematic foreclosure of public input and judicial oversight is dangerous as a regulatory approach. Furthermore, modifying the FDA's treatment of bioequivalence will set a precedent for future regulatory endeavors such as defining the standard for "biosimilarity"—approximate similarity between complex "biologics" like vaccine and antibody formulations.<sup>8</sup>

Part I of this Note discusses the Food, Drug, and Cosmetic Act (FDCA), the Hatch-Waxman Act, and the FDA's current approach to promulgating bioequivalence determinations. Part II reviews administrative law doctrine and discusses the line of cases in which bioequivalence, and thus the underpinnings of Hatch-Waxman and the generic drug industry, first came under attack. In these cases, courts granted extensive deference to the FDA in determining bioequivalence and also increased justiciability requirements for challenging these determinations. Two recent cases also are discussed as evidence that innovator companies continue to challenge the FDA in court and that the agency's approach to bioequivalence has left substantial questions unanswered. Part III proposes that courts loosen standing requirements and roll back deference to the FDA's bioequivalence determinations. The political upshot of this move would be to inspire reform in agency decisionmaking procedures and to promote transparency and accountability in the realm of generic drug and biologic approval.

## I

### THE FDCA AND HATCH-WAXMAN

In this Part, I introduce the fundamentals of food and drug regulation before describing the market-engineering goal of the Hatch-Waxman Act and how bioequivalence is a key concept for premarket generic drug approval. I then describe the FDA's current regime for implementing the bioequivalence provisions of the amended FDCA.

#### A. *The Food, Drug, and Cosmetic Act*

In 1938, Congress created the Food and Drug Administration to address the problem of consumer product quality and safety in the realm of food and drugs. The agency's enabling statute, the Food,

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<sup>8</sup> See *infra* Part III.C (discussing biosimilarity).

Drug, and Cosmetic Act,<sup>9</sup> was passed in the wake of the 1937 “Elixir Sulfanilamide” disaster, in which more than one hundred patients died after being treated with a presumably safe solution of sulfanilamide (an antimicrobial) in diethylene glycol (a toxic solvent).<sup>10</sup> Concurrently with the rise of modern medicine—and consumers’ willingness to pay for it—the FDA was intended to serve as a premarket watchdog for potentially toxic products.

In 1962, the Kefauver-Harris Amendments established contemporary FDA drug regulation by requiring premarket proof of efficacy in addition to safety.<sup>11</sup> Although Congress passed Kefauver-Harris partly in response to the Thalidomide tragedy, in which a popular drug for morning sickness caused widespread birth defects,<sup>12</sup> the new efficacy requirement addressed a different problem: drugs that do not work.

The complexity and potency of modern medicine often necessitate a single balancing test for safety and efficacy. Many effective drugs are also toxic.<sup>13</sup> In such cases, the FDA must decide how effective the drug must be to outweigh its dangerousness, and, if approval is still warranted, what information must be delivered to consumers about the risks associated with the drug. At the center of this regulatory task is the data that the FDA uses to carry out its evaluations. And since many aspects of a drug’s safety and efficacy are impossible

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<sup>9</sup> Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C §§ 301–399 (2006)).

<sup>10</sup> See Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER, June 1981, at 18 (explaining that the disaster “hastened final enactment in 1938 of the Federal Food, Drug, and Cosmetic Act”). The elixir was sold by the S.E. Massengill Company, which had tested the product for flavor, appearance, and fragrance, but not for toxicity. *Id.*

<sup>11</sup> Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended in scattered sections of 21 U.S.C. (2006)).

<sup>12</sup> See *Legislation*, FDA.GOV, <http://www.fda.gov/RegulatoryInformation/Legislation> (last updated July 9, 2012) (describing the events that led to the passage of the Kefauver-Harris Amendments).

<sup>13</sup> One example is the chemotherapy drug Avastin, the approvability of which was the subject of a heated FDA hearing in 2011. See U.S. FOOD & DRUG ADMIN., FDA-2010-N-0621-0537, TRANSCRIPT OF PUBLIC HEARING, PROPOSAL TO WITHDRAW APPROVAL FOR THE BREAST CANCER INDICATION FOR BEVACIZUMAB (AVASTIN) (2011), available at <http://www.fda.gov/downloads/NewsEvents/MeetingsConferencesWorkshops/UCM261611.pdf>. The Oncologic Drugs Advisory Committee ultimately ruled that Avastin’s harmful side effects were too dangerous to permit a poorly supported indication for breast cancer. Emily P. Walker, *FDA Votes To Yank Avastin’s Breast Cancer Indication*, MED PAGE TODAY (June 29, 2011), <http://www.medpagetoday.com/PublicHealthPolicy/FDAGeneral/27537> (last visited Oct. 31, 2012).

to evaluate outside of the human body, clinical trials are the agency's most valuable source of data.<sup>14</sup>

Clinical trials require that product sponsors submit statistically significant data demonstrating the safety and efficacy of their drug in human subjects.<sup>15</sup> This process invariably costs millions of dollars and can last years.<sup>16</sup> Clinical trials themselves are also heavily regulated for bioethical reasons, to promote data quality, and to prevent fraud.<sup>17</sup> Despite these costs, the reasons for stringent data requirements are not especially controversial. The edifice of drug regulation is built upon the notion that drugs are not standard consumer products. Their properties are largely undetectable in the marketplace, so a consumer who purchases a defective, dangerous, or useless drug will probably remain unaware of its shortcomings until it is too late. At best, the consumer will have wasted money on an ineffective drug. At worst,

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<sup>14</sup> Clinical trials involve yet another balancing test. On the one hand, extensive clinical trials produce extensive data. On the other hand, well-conducted clinical trials require placebo and experimental treatments, either of which may pose risks to trial subjects. These considerations have led to extensive regulation of the clinical trial process, primarily focused on ensuring informed consent of the patients that volunteer to be trial subjects. See *infra* note 17 (discussing such regulations).

<sup>15</sup> See 21 U.S.C. § 355(b)(1)(A) (2006) (stating that applications for regulatory review must include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use"); *id.* § 355(b)(5)(B)–(C) (discussing the procedure for establishing the design of "clinical trials intended to form the primary basis of an effectiveness claim").

<sup>16</sup> See PHARM. RESEARCH & MFRS. OF AM. (PHRMA), DRUG DISCOVERY AND DEVELOPMENT: UNDERSTANDING THE R&D PROCESS 1 (2007) [hereinafter PHRMA], available at [http://www.innovation.org/drug\\_discovery/objects/pdf/RD\\_Brochure.pdf](http://www.innovation.org/drug_discovery/objects/pdf/RD_Brochure.pdf) ("It takes about 10–15 years to develop one new medicine from the time it is discovered to when it is available for treating patients. The average cost to research and develop each successful drug is estimated to be \$800 million to \$1 billion.").

<sup>17</sup> See, e.g., Phases of an Investigation, 21 C.F.R. § 312.21 (2012) (detailing characteristics, including the number of subjects, for Phases 1 through 3 of clinical investigations); Adequate and Well-Controlled Studies, *id.* § 314.126 (discussing design criteria "recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation"). In fulfilling the mandate of 21 U.S.C. § 355(b)(5), the FDA created the Investigational New Drug (IND) application process, by which "[a] sponsor shall submit an IND . . . if the sponsor intends to conduct a clinical investigation." 21 C.F.R. § 312.20(a) (2012). INDs serve as sub-applications, governed by 21 C.F.R. § 312, which require detailed assessments of clinical trial plans before such trials proceed. In turn, the conduct of approved clinical trials is subject to further guidelines promulgated by the FDA and the National Institutes of Health. See *Regulations*, FDA.GOV, <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713> (last visited Oct. 31, 2012) (listing twenty-one separate codified regulations and forty-four Federal Register notices regarding the conduct of clinical trials); see also Protection of Human Subjects, 45 C.F.R. § 46 (2011) (regulating the treatment of human subjects in clinical research); NAT'L INSTS. OF HEALTH, GUIDELINES FOR THE CONDUCT OF RESEARCH INVOLVING HUMAN SUBJECTS AT THE NATIONAL INSTITUTES OF HEALTH (5th prtng. 2004), available at [http://www.nccamwatch.org/research/human\\_guidelines.pdf](http://www.nccamwatch.org/research/human_guidelines.pdf) (providing background and guidelines for research involving human subjects).

she will develop an adverse reaction to the substance and be permanently injured or die. This risk calls for substantial premarket controls on drug development, production, and marketing.

### B. *The Hatch-Waxman Act*

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, better known as the Hatch-Waxman Act.<sup>18</sup> Hatch-Waxman created a modified regulatory framework for the development of generic drugs. As with much bipartisan legislation, the law struck a compromise between private and public interests: In exchange for extensions of patent exclusivity for innovator companies, the Act established investigational licenses and an accelerated approval process for generic competitors to increase the availability and affordability of drugs to the public.<sup>19</sup>

Before Hatch-Waxman, the pace of the FDA approval process often cut deeply into the term of patent exclusivity for new products.<sup>20</sup> It could take years for a drug to satisfy all of the agency's regulatory requirements and enter the market, and by the time a drug began making money for its innovator company, competitors soon would

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<sup>18</sup> Pub. L. No. 98-417, 98 Stat. 1585 (1984) (relevant sections codified as amended within 21 U.S.C. § 355 (2006) as “New drugs” and 35 U.S.C. § 156 (2006) as “Extension of patent term”).

<sup>19</sup> Rudimentary knowledge of the patent system is necessary to understand the incentive structure of Hatch-Waxman. A patent is a federally granted right to exclude others from making, using, marketing, or selling an invention for a specified period. In 2012, the patent term is set at twenty years. 35 U.S.C. § 154(a)(2) (2006). When the patent expires on a consumer product, then the design of that product becomes part of the public domain and competitors can enter the market with their own generic copies, bringing down the price of the product and revenues for the innovator. For products subject to few regulatory standards, these competitors may appear almost immediately. See *General Information Concerning Patents*, U.S. PATENT & TRADEMARK OFFICE, [www.uspto.gov/patents/resources/general\\_info\\_concerning\\_patents.jsp](http://www.uspto.gov/patents/resources/general_info_concerning_patents.jsp) (last visited Oct. 31, 2012) (“After the patent has expired anyone may make, use, offer for sale, or sell or import the invention without permission of the patentee, provided that matter covered by other unexpired patents is not used.”).

<sup>20</sup> It takes ten to fifteen years from drug development to FDA approval. See PHRMA, *supra* note 16, at 1. That leaves only five to ten years to recoup costs under the drug's existing patent term. See 35 U.S.C. § 154(a)(2) (2006) (explaining that a patent term is twenty years). A sponsor must include information on valid patent coverage with any application for regulatory review of a new drug. 21 U.S.C. § 355(b)(1)(G) (2006). Ideally, this information is simply “the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application.” *Id.* However, there are ways to challenge patent rights concurrently with an application for regulatory review. See *id.* § 355(b)(2)–(3) (detailing such a procedure). In any case, investing in regulatory review for a novel product for which a company cannot easily secure patent rights would leave the company vulnerable to losing both its investment and its ability to market the product if someone else patents the product.

appear.<sup>21</sup> This was an arguably unjust and innovation-chilling situation given the degree of investment required for drug development.<sup>22</sup> To adjust this dynamic in favor of innovators, Hatch-Waxman allowed sponsor companies to apply for an “[e]xtension of patent term,” by which “[t]he term of a [drug] patent . . . shall be extended by the time equal to the regulatory review period for the approved product.”<sup>23</sup> This provision removed the revenue penalty associated with FDA review, granting innovators the same period of market exclusivity that they would enjoy if their product were less heavily regulated.

In return for this benefit to innovators, Hatch-Waxman established investigational licenses and an abbreviated approval process for competitor drugs so that when extended patent terms on pioneer drugs finally did end, cheaper generic copies would immediately become available to the public.<sup>24</sup> The Act also amended 35 U.S.C. § 271, which covers patent infringement, to state that “[i]t shall not be an act of [patent] infringement to make, use, offer to sell, or sell . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.”<sup>25</sup> This provision established a license for generic drug developers to use patented material in preparing their products (i.e., copies of said patented material) for regulatory approval. In addition, the Act added subsection (j) to 21 U.S.C. § 355, creating an “abbreviated” pathway for generic drug approval that, among other things, contains no clinical trial requirement.<sup>26</sup>

The abbreviated new drug application (ANDA) process demonstrates that the principal goal of Hatch-Waxman is to lower the initial cost of generic development. ANDAs do not require clinical trials, so they demand significantly less time and investment than standard new drug applications (NDAs).<sup>27</sup> However, shortened approval times without patent-term extensions would anger and disincentivize innovators, since ANDAs reduce the burden of development for generic competitors on the strength of innovator clinical trial data. Therefore, under the Hatch-Waxman scheme, patent-term extensions allow innovators to maintain and even gain patent exclusivity, while a reduced regulatory burden entices generics to enter the market once patents

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<sup>21</sup> See *supra* notes 15–17, 19 (discussing regulatory requirements and patent dynamics).

<sup>22</sup> See PHRMA, *supra* note 16, at 1 (discussing the costs of drug development).

<sup>23</sup> 35 U.S.C. § 156(c) (2006).

<sup>24</sup> 21 U.S.C. § 355(j) (2006).

<sup>25</sup> 35 U.S.C. § 271(e)(1) (2006).

<sup>26</sup> 21 U.S.C. § 355(j) (2006).

<sup>27</sup> See *supra* note 17 (discussing the burden of conducting clinical trials).

expire. From one perspective, Hatch-Waxman simply moves the regulatory approval time that a generic competitor's drug would require at the end of an innovator's patent term (during which the innovator would maintain de facto market exclusivity) to the front of the patent term (during which the innovator enjoys premarket approval "bonus time").

The concept that enables waiver of clinical trial data for ANDAs is bioequivalence. ANDAs require a showing "that the new drug is bioequivalent to [a] listed drug," where "listed" drugs are previously approved products.<sup>28</sup> If drugs were less complicated consumer products, then the bioequivalence standard would be unnecessary—a regulator tasked with premarket approval of a generic could simply examine an approved drug and the proposed copy and proclaim them, for all intents and purposes, the same. Unfortunately, drugs are essentially impossible to examine for safety and effectiveness without observing their activity in human subjects.<sup>29</sup> Even if a drug's molecular structure is familiar, different formulations, dosage forms, and drug-drug interactions can produce unpredictable physiological effects.<sup>30</sup> To accommodate this complexity without requiring a full course of clinical trials, Hatch-Waxman grounds bioequivalence in a determination of "bioavailability," or, "the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action."<sup>31</sup>

In 1992, the FDA promulgated regulations for determining bioavailability.<sup>32</sup> For products not otherwise subject to a waiver,

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<sup>28</sup> 21 U.S.C. § 355(j)(2)(A)(i), (iv) (2006). Paragraph (6) of Hatch-Waxman requires that "the Secretary . . . publish and make available to the public . . . a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness." *Id.* § 355(j)(7)(A)(i). Congress mandated that this list be updated every thirty days. *Id.* § 355(j)(7)(A)(ii). In the industry, this list came to be known as the "Orange Book," and is available online via the Center for Drug Evaluation and Research. See *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*, FDA.GOV, <http://www.fda.gov/Drugs/InformationOnDrugs/ucm129662> (last visited Oct. 31, 2012). These approved drugs can also be found through an FDA online database. See *Drugs@FDA Database*, FDA.GOV, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda> (last visited Oct. 31, 2012).

<sup>29</sup> See *supra* notes 13–17 and accompanying text (explaining this dilemma and the need for clinical trials); see also *supra* Part I.A (discussing premarket regulation as a solution to this problem).

<sup>30</sup> See Dan M. Roden, *Principles of Clinical Pharmacology*, in HARRISON'S PRINCIPLES OF INTERNAL MEDICINE 33–49 (Dan L. Longo et al. eds., 18th ed. 2012) (discussing the many variables at play in drug action, and stating that "it is well recognized among physicians and the lay community that the outcome of drug therapy varies widely among individuals").

<sup>31</sup> 21 U.S.C. § 335(j)(8)(A)(i) (2006).

<sup>32</sup> Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,998 (Apr. 28, 1992) (codified at 21 C.F.R. § 320 (2012)). These regulations replaced similar provisions at the

generic sponsors must perform *in vivo* (i.e., human subject) studies in healthy volunteers to demonstrate that “the product’s rate and extent of absorption, as determined by comparison of measured parameters, e.g., concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects” is not significantly different from the rate and extent of absorption of the approved “reference” drug.<sup>33</sup> For products in certain dosage forms—for example, injectables, inhalants, and oral, nasal, or topical solutions—*in vivo* studies may be waived if the generic drug contains the same active ingredient in the same dosage form, with no confounding inactive ingredients, as an approved drug.<sup>34</sup>

Tests for establishing bioequivalence are listed “in descending order of accuracy, sensitivity, and reproducibility” in the regulations: (1) “An *in vivo* test in humans in which the concentration of the active ingredient . . . in blood . . . or other appropriate biological fluid is measured as a function of time,” or “an *in vitro* [i.e., outside of a living organism] test that has been correlated with and is predictive of human *in vivo* bioavailability data;” (2) an *in vivo* urinalysis; (3) an *in vivo* measurement of “an appropriate acute pharmacological effect;” (4) clinical trials; (5) a “currently available *in vitro* test acceptable to FDA;” and (6) “[a]ny other approach deemed adequate by FDA.”<sup>35</sup>

### C. Implementing the Bioequivalence Standard

Even though the regulations for determining bioequivalence construct precise requirements for *in vivo* studies and waivers, ambiguities abound. For example, the FDA may waive *in vivo* studies “for good cause . . . if waiver is compatible with the protection of the public health.”<sup>36</sup> Certain clauses also permit *in vitro* studies to substitute for *in vivo* data if the “drug product is . . . shown to meet an *in vitro* test that has been correlated with *in vivo* data.”<sup>37</sup> “Correlation” of *in vivo* and *in vitro* data is left undefined. Finally, the regulations appear to

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same location in the C.F.R. that applied to bioequivalence determinations for the Kefauver-Harris Drug Efficacy Study (DES) of pre-1962 drugs. See Daniel Carpenter & Dominique A. Tobbell, *Bioequivalence: The Regulatory Career of a Pharmaceutical Concept*, 85 BULL. HIST. MED. 93, 109–13 (2011) (discussing the DES as a precursor to the Hatch-Waxman regime).

<sup>33</sup> Basis for Measuring *In Vivo* Bioavailability or Demonstrating Bioequivalence, 21 C.F.R. § 320.23(a)(1) (2012).

<sup>34</sup> Criteria for Waiver of Evidence of *In Vivo* Bioavailability or Bioequivalence, 21 C.F.R. § 320.22 (2012).

<sup>35</sup> Types of Evidence To Measure Bioavailability or Establish Bioequivalence, 21 C.F.R. § 320.24 (2012).

<sup>36</sup> *Id.* § 320.22(e).

<sup>37</sup> *Id.* § 320.22(d)(3).

provide the agency with a trump card: “Any other approach deemed adequate by FDA” may be used to demonstrate bioavailability.<sup>38</sup>

For both innovator and generic drug companies, these regulations did little to chart a course through the wilds of Hatch-Waxman, and innovator companies took advantage of regulatory vagueness to mount legal challenges against bioequivalence determinations that would lead to approval of competitor generics.<sup>39</sup> Therefore, in the years following the 1992 regulations, the FDA began providing guidance “when asked for assistance by individual applicants.”<sup>40</sup> From 1992 through 2000, the FDA Office of Generic Drugs “responded to individual requests for information on [bioequivalence] studies in letter format after specific recommendations were prepared within the Center for Drug Evaluation and Research.”<sup>41</sup> As a result, “information about [bioequivalence] studies was only being provided to those specifically requesting such information.”<sup>42</sup> And as might be expected, this practice not only stimulated litigation,<sup>43</sup> but also “bec[a]me extremely time-consuming for the Agency.”<sup>44</sup>

In 2003, the FDA finalized a guidance document first proposed in 2000 of “General Considerations” for bioequivalence determinations for “orally administered drug products.”<sup>45</sup> This document provided a technical restatement of the regulatory requirements outlined above, with specific guidelines for conducting bioequivalence determinations for different dosage forms and types of drugs.<sup>46</sup> However, this guidance did not cover non-orally administered drugs and provided only a short discussion of crucial issues such as “narrow therapeutic range” drugs—drugs that are only safe and effective within very precise

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<sup>38</sup> *Id.* § 320.24(b)(6).

<sup>39</sup> *See infra* Part II (recounting court battles over bioequivalence).

<sup>40</sup> CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOEQUIVALENCE RECOMMENDATIONS FOR SPECIFIC PRODUCTS 2 (2010) [hereinafter BIOEQUIVALENCE RECOMMENDATIONS], available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072872.pdf>.

<sup>41</sup> *Id.*

<sup>42</sup> *Id.*

<sup>43</sup> *See, e.g., ViroPharma v. Hamburg*, 777 F. Supp. 2d 140, 142 (D.D.C. 2011) (examining whether the FDA failed to conduct notice-and-comment rulemaking prior to changing bioequivalence standards).

<sup>44</sup> BIOEQUIVALENCE RECOMMENDATIONS, *supra* note 40, at 2.

<sup>45</sup> U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS—GENERAL CONSIDERATIONS 1 (2003), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory-Information/Guidances/ucm070124.pdf>.

<sup>46</sup> *Id.*

dosage parameters—and locally acting drugs—drugs that are meant to act only within the gastrointestinal tract.<sup>47</sup>

In 2010, the FDA issued another guidance document that, in some sense, acknowledged the overwhelming difficulty of regulating bioequivalence.<sup>48</sup> It announced the agency's current practice of developing "[p]roduct-specific [bioequivalence] recommendations" and posting them online.<sup>49</sup> Nearly one thousand separate product-specific recommendations are now posted on the FDA website.<sup>50</sup> These documents do not "create or confer any rights for or on any person and [do] not operate to bind FDA or the public."<sup>51</sup> Rather, they are posted in part to "provide a meaningful opportunity for the public to consider and comment on [bioequivalence] study recommendations."<sup>52</sup>

## II

### BIOEQUIVALENCE CHALLENGED

The foregoing discussion highlighted the complexity of federal drug regulation, the detail with which generic drugs are regulated under Hatch-Waxman, and the ambiguities that remain in the regulatory regime. Currently, the FDA interprets these ambiguities through an ad hoc guidance process for determining bioequivalence for every proposed drug. The agency's ability to proceed in this manner is the result of a line of D.C. District and Circuit Court decisions that extended considerable deference to the FDA's interpretation of Hatch-Waxman and its choice of policymaking form. Before discussing these decisions, it may be useful to review the analytical approach courts have established to evaluate agency decisionmaking.

In contemporary administrative law, courts extend deference to agencies according to the framework established in *Chevron v. Natural Resources Defense Council*.<sup>53</sup> In *Chevron*, Justice Stevens

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<sup>47</sup> See *id.* at 20 (discussing narrow therapeutic range and locally acting drugs). In regard to narrow therapeutic range drugs, the guidance "recommend[ed] that sponsors consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs." *Id.* In regard to locally acting gastrointestinal drugs, the guidance allowed for "suitably designed and validated in vitro studies." *Id.*

<sup>48</sup> See BIOEQUIVALENCE RECOMMENDATIONS, *supra* note 40.

<sup>49</sup> *Id.* at 3.

<sup>50</sup> *Bioequivalence Recommendations for Specific Products*, FDA.GOV, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207> (last visited Oct. 31, 2012).

<sup>51</sup> *E.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE ON CARBAMAZEPINE (2008), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm083288.pdf>.

<sup>52</sup> BIOEQUIVALENCE RECOMMENDATIONS, *supra* note 40, at 1.

<sup>53</sup> 467 U.S. 837 (1984).

developed a two-step test for determining when judicial deference is merited. First, the court must assess whether “Congress has directly spoken to the precise question at issue.”<sup>54</sup> If so, then the matter is resolved and “the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress.”<sup>55</sup> However, if the statute is silent or ambiguous on the question at issue, then the court must consider whether the agency’s interpretation is based on “a permissible construction of the statute.”<sup>56</sup>

Standards codified in the APA largely define the boundaries of permissibility.<sup>57</sup> In cases where Congress expressly delegates interpretive power to an agency, the agency’s actions are subject to invalidation if they are “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law” or “unsupported by substantial evidence.”<sup>58</sup> If the delegation is implicit, then “a court may not substitute its own construction of a statutory provis[i]on for a reasonable interpretation made by the administrator of an agency.”<sup>59</sup>

The scope of *Chevron* deference and the nuances of judicial review in the case of express or implied deference have been refined since the Supreme Court’s initial announcement of the doctrine.<sup>60</sup> In addition, a “*Chevron* Step Zero” has emerged for determining the types of agency action that should be accorded full deference.<sup>61</sup> Under this step, the Court will accord deference “only, or mostly, when agency decisions have followed procedures that guarantee deliberation and reflectiveness.”<sup>62</sup> For example, in *United States v. Mead Corp.*, the Supreme Court declined to defer to an agency’s advisory letter because it was not promulgated according to “rules carrying the

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<sup>54</sup> *Id.* at 842.

<sup>55</sup> *Id.* at 842–43.

<sup>56</sup> *Id.* at 843.

<sup>57</sup> See Administrative Procedure Act, Pub. L. No. 79-404, 60 Stat. 237 (1946) (codified as amended at 5 U.S.C. §§ 500–504, 551–559, 701–706 (2006)) (describing, in part, standards and procedures for administrative decisionmaking and judicial review of agency decisions).

<sup>58</sup> 5 U.S.C. § 706 (2006).

<sup>59</sup> *Chevron*, 467 U.S. at 844.

<sup>60</sup> See, e.g., *Household Credit Servs. v. Pfennig*, 541 U.S. 232, 244–45 (2004) (stating that agency action pursuant to express delegation should stand if it is “rational” and “clear, easy to apply (and easy to enforce)”; *Chem. Mfrs. Ass’n v. Natural Res. Def. Council*, 470 U.S. 116, 125 (1985) (stating that agency actions pursuant to implicit delegation will stand if they are “sufficiently rational . . . to preclude a court from substituting its judgment”).

<sup>61</sup> See Cass R. Sunstein, *Chevron Step Zero*, 92 VA. L. REV. 187, 190–91 (2006) (describing “the addition of several epicycles to the *Chevron* framework,” most importantly “*Chevron* Step Zero—the initial inquiry into whether the *Chevron* framework applies at all”).

<sup>62</sup> *Id.* at 193.

force of law,”<sup>63</sup> a phrase that courts have interpreted to mean procedures that approximate those detailed in the APA.<sup>64</sup>

Despite recent Supreme Court decisions applying the “Step Zero” inquiry under *Mead*,<sup>65</sup> the approach is controversial.<sup>66</sup> In particular, Justice Scalia has argued that imposing deliberative requirements on agencies unjustifiably revives *Skidmore* deference, a pre-*Chevron* doctrine by which courts uphold agency determinations according to “the degree of the agency’s care, its consistency, formality, and relative expertness, and . . . the persuasiveness of the agency’s position.”<sup>67</sup> Still, *Mead* remains good law, and the Court has steadily trended toward requiring some degree of procedural formality before affording deference to agencies.<sup>68</sup> Courts have applied *Mead*’s limitations sparingly in FDA bioequivalence challenges,<sup>69</sup>

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<sup>63</sup> United States v. *Mead Corp.*, 533 U.S. 218, 227 (2001).

<sup>64</sup> The Supreme Court recently applied *Mead* to uphold a Treasury Department rulemaking, observing that “[t]he Department issued the . . . rule only after notice-and-comment procedures . . . a consideration identified in our precedents as a ‘significant’ sign that a rule merits *Chevron* deference.” *Mayo Found. for Med. Educ. & Research v. United States*, 131 S. Ct. 704, 714 (2011).

<sup>65</sup> See, e.g., *id.*; *Fed. Express Corp. v. Holowecki*, 552 U.S. 389, 395–400 (2008) (holding that policy statements in the Equal Employment Opportunity Commission manual were entitled to deference under *Mead*).

<sup>66</sup> See, e.g., Lisa Schultz Bressman, *How Mead Has Muddled Judicial Review of Agency Action*, 58 VAND. L. REV. 1443, 1445 (2005) (“[W]e still lack a clear answer to the question when an agency is entitled to *Chevron* deference for procedures other than notice-and-comment rulemaking or formal adjudication.”); Sunstein, *supra* note 61, at 190 (stating that *Mead* has created a “significant increase in uncertainty about the appropriate approach” to adjudicating deference); Amy J. Wildermuth, *What Twombly and Mead Have in Common*, 102 NW. U. L. REV. COLLOQUY 276, 277 (2008) (acknowledging “the many uncertainties *Mead* has generated”).

<sup>67</sup> *Mead*, 533 U.S. at 241 (Scalia, J., dissenting) (internal quotation marks omitted); *id.* at 239 (“[W]hereas previously, when agency authority to resolve ambiguity did not exist the court was free to give the statute what it considered the best interpretation, henceforth the court must supposedly give the agency view some indeterminate amount of so-called *Skidmore* deference.” (citing *Skidmore v. Swift & Co.*, 323 U.S. 134, 139–40 (1944))). Scalia claims that “totality-of-the-circumstances *Skidmore* deference is a recipe for uncertainty, unpredictability, and endless litigation” due to courts’ relative lack of expertise in administrative subject matter. *Id.* at 250.

<sup>68</sup> See Sunstein, *supra* note 61, at 190 (“In the last fifteen years . . . the Court appears to have moved strongly in the direction of pre-*Chevron* law, in an evident attempt to reassert the primacy of the judiciary in statutory interpretation.”).

<sup>69</sup> The D.C. District Court has cited *Mead* twice in bioequivalence matters. In two memorandum opinions that came down on the same day, the court cited *Mead* for the proposition that an agency publication should be afforded deference if it acts with “care . . . consistency, formality, and relative expertness.” *Allergan, Inc. v. Crawford*, 398 F. Supp. 2d 13, 21 (D.D.C. 2005) (quoting *Mead*, 533 U.S. at 228) (internal quotation marks omitted); see also *CollaGenex Pharm., Inc. v. Thompson*, No. 03-1405, 2005 U.S. Dist. LEXIS 5543, at \*44–45 (D.D.C. Jan. 19, 2005) (citing *Mead* for the proposition that the “thoroughness, logic and expertness” of an agency publication entitle it to deference (internal quotation marks omitted)). Both cases extended deference to the FDA in bioequivalence-related

however, and the following cases form a strong baseline of *Chevron* deference that remains compelling today.<sup>70</sup>

### A. *Early Challenges: Courts Grant Chevron Deference*

During the first years of Hatch-Waxman implementation, innovator drug companies brought challenges that focused largely on the scope of the FDA's ability to interpret the statute and that addressed the validity of the agency's initial efforts to regulate bioequivalence. These cases demonstrate how courts have accorded substantial deference to the FDA's bioequivalence determinations.

#### 1. *Plain Language: Schering Corp. v. Sullivan (Schering I)*

In 1992, the D.C. District Court reviewed a challenge by Schering Corporation to an FDA determination that "a generic drug may satisfy the bioequivalence requirement even if it does not satisfy the precise standards set forth in Section 355(j)(7)(B) [now 355(j)(8)(B)]."<sup>71</sup> Schering produced a number of "nonsystemic" medications such as topical ointments and asthma inhalers.<sup>72</sup> Copley Pharmaceuticals, a generic competitor, had filed an ANDA under Hatch-Waxman for its version of one of Schering's drugs, and the FDA had granted approval.<sup>73</sup> Schering asked the court to enjoin the FDA's approval based on the plain text of Hatch-Waxman, which could be read to mandate that all generics be amenable to evaluations of "rate and extent of absorption."<sup>74</sup> Nonsystemic generics that are not absorbed into the bloodstream would not be amenable to standard tests of absorption, and so would be excluded from bioequivalence determinations.

By the time the district court addressed Schering's petition, the FDA had promulgated regulations that mooted the dispute.<sup>75</sup>

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matters—in these cases, regarding preliminary determinations of whether plaintiffs' drugs were subject to Hatch-Waxman. *Allergan*, 398 F. Supp. 2d at 26; *CollaGenex*, 2005 U.S. Dist. LEXIS 5543, at \*45.

<sup>70</sup> See *infra* Part II.B.1 (demonstrating continued *Chevron* deference under these cases).

<sup>71</sup> *Schering Corp. v. Sullivan (Schering I)* 782 F. Supp. 645, 646 (D.D.C. 1992). 21 U.S.C. § 355(j)(7)(B) (1988) is now § 355(j)(8)(B) (2006) due to the Food and Drug Administration Modernization Act of 1997. Pub. L. No. 105-115, 111 Stat. 2296 (adding, *inter alia*, paragraph 355(j)(3) and renumbering subsequent paragraphs).

<sup>72</sup> *Schering I*, 782 F. Supp. at 646.

<sup>73</sup> *Id.* at 646–47.

<sup>74</sup> *Id.* at 648–49 (quoting 21 U.S.C. § 355(j)(7)(B) (1988)).

<sup>75</sup> Schering brought its challenge based on a 1990 letter it received from the FDA in response to an administrative petition and request for stay of action regarding the agency's approval of Copley's products. *Id.* at 647. The FDA's "citizen petition" process is governed by 21 C.F.R. § 10.30, by which a party may "request [that] the Commissioner of Food and

Nonetheless, the court took the opportunity to explain that Hatch-Waxman granted the agency broad discretion in evaluations of bioequivalence and that the absorption provisions only created a “safe harbor” for the clearest evaluations.<sup>76</sup> The court based its reasoning on the “language, structure, and legislative history” of Hatch-Waxman, “all of which suggest that Congress permitted the FDA to retain its historically wide discretion in defining showings of ‘bioequivalence.’”<sup>77</sup> Furthermore, the court explained:

[E]ven if the statute had been ambiguous or silent on the issue, the Court nonetheless would be constrained to uphold the FDA’s interpretation as a reasonable one, given the agency’s established practice of accepting alternative showings of bioequivalence and the lack of any evidence that Congress intended to override that practice.<sup>78</sup>

*Schering I* was an early statement in a line of cases that broadly construed the FDA’s powers under Hatch-Waxman and demonstrated courts’ willingness to defer to agency methods for finding bioequivalence.

## 2. *Congressional Purpose: Fisons Corp. v. Shalala*

In 1994, the D.C. District Court reviewed a challenge under the APA to the FDA’s recently promulgated bioequivalence regulations.<sup>79</sup> Plaintiff drug company Fisons Corporation produced an inhalant for the treatment of asthma, Intal NebsoL, for which the patent had recently expired.<sup>80</sup> In keeping with the provisions of 21 C.F.R. § 320.22, which state that *in vivo* evidence of bioequivalence may be waived if the drug is “a solution for aerosolization or nebulization,”<sup>81</sup> the FDA had indicated to Fisons that the agency intended to waive such determinations for generic versions of Intal NebsoL.<sup>82</sup> Fisons challenged this action on the grounds that the FDA’s waiver provisions exceeded the statutory authority of Hatch-Waxman and were

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Drugs . . . issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action.” 21 C.F.R. § 10.30 (2012). The 1992 regulations, *see supra* notes 32–35 and accompanying text, did not change the substance of Schering’s complaint, but mooted the grounds by superseding the response letter.

<sup>76</sup> *Schering I*, 782 F. Supp. at 649.

<sup>77</sup> *Id.* at 648. This discretion was “historical” insofar as bioequivalence determinations were part of the DES. *See supra* note 32 (discussing the DES as a precursor to the Hatch-Waxman regime).

<sup>78</sup> *Schering I*, 782 F. Supp. at 648.

<sup>79</sup> *See* Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,998 (Apr. 28, 1992).

<sup>80</sup> *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994).

<sup>81</sup> 21 C.F.R. § 320.22(b)(3)(i) (2012).

<sup>82</sup> *Fisons*, 860 F. Supp. at 861.

“arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law.”<sup>83</sup>

In addressing Fisons’s challenge, the court found that it did not need to go beyond step one of the *Chevron* inquiry: Congress effectively had “directly spoken to the precise question at issue.”<sup>84</sup> In particular, the court adopted Judge Boudin’s earlier reasoning in *Schering I*, even though that case predated the 1992 regulations, finding that “[t]he FDA’s waiver provision is well within the scope of its broad discretion” and consistent with the legislative history and statutory structure of Hatch-Waxman.<sup>85</sup> The court in *Fisons* reinforced its deferential decision with reasoning from *United States v. Rutherford*,<sup>86</sup> another high point of judicial deference to the FDA.<sup>87</sup> The Supreme Court in *Rutherford* “infer[red] approval” of an FDA decision based on ensuing congressional silence,<sup>88</sup> despite “strong equitable and moral arguments” for questioning the agency’s actions.<sup>89</sup>

### 3. *Ambiguity and Deference: Schering Corp. v. FDA (Schering II)*

After the D.C. Circuit found Schering’s appeal from *Schering I* to be moot due to intervening regulations,<sup>90</sup> Schering brought the controversy over ANDA requirements for generic copies of its non-systemic medications back to the district court in the District of New Jersey,<sup>91</sup> and then to the Third Circuit.<sup>92</sup> As a threshold matter, the Third Circuit indirectly affirmed the D.C. District Court’s standing analysis in *Fisons*—innovator companies had both constitutional and prudential standing to sue, partly because “[t]hey possess the scientific

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<sup>83</sup> *Id.* at 860. Specifically, Fisons argued that 21 C.F.R. § 320.22 (1993), which governed the criteria for waiver of *in vivo* evidence, exceeded the authority of 21 U.S.C. § 355(j)(7)(B) (1988), which required determinations of “rate and extent of absorption.” *Id.* at 863; *see also infra* note 94 (providing the text of § 355(j)(7)(B) at the time).

<sup>84</sup> *Fisons*, 860 F. Supp. at 863 (quoting *Chevron v. Natural Res. Def. Council*, 467 U.S. 837, 842 (1984)).

<sup>85</sup> *Id.* at 866.

<sup>86</sup> 442 U.S. 544, 549–50, 559 (1979) (holding that the sale of an unapproved cancer drug could be enjoined on the strength of an FDA determination that the drug was subject to premarket approval).

<sup>87</sup> *See* James T. O’Reilly, *Losing Deference in the FDA’s Second Century: Judicial Review, Politics, and a Diminished Legacy of Expertise*, 93 CORNELL L. REV. 939, 943 (2008) (describing *Rutherford* as one of “[t]he five peaks of modern judicial deference to the FDA”).

<sup>88</sup> *Rutherford*, 442 U.S. at 554 n.10.

<sup>89</sup> O’Reilly, *supra* note 87, at 944.

<sup>90</sup> *Schering Corp. v. Shalala*, 995 F.2d 1103, 1105–06 (D.C. Cir. 1993); *see also supra* note 75 (explaining this procedural posture).

<sup>91</sup> *Schering Corp. v. FDA*, 866 F. Supp. 821 (D.N.J. 1994), *aff’d*, 51 F.3d 390 (3d Cir. 1995).

<sup>92</sup> *Schering Corp. v. FDA (Schering II)*, 51 F.3d 390 (3d Cir. 1995).

data to recognize when the FDA may stray from the legislatively mandated testing requirements that impact the safety and effectiveness of the generic drug.”<sup>93</sup>

The court then moved on to the question of *Chevron* deference, at which point it diverged markedly from the court in *Fisons*. Rather than stopping at the first step of *Chevron*, the circuit court found “bioequivalence” to be an ambiguous term in Hatch-Waxman. After looking to other statutory sources and expressing frustration with the litigants’ inability to explain the distinction between terms such as bioavailability and bioequivalence, the court held that 21 U.S.C. § 355(j)(7)(B), the operative section for defining bioequivalence, was ambiguous,<sup>94</sup> and moved on to *Chevron*’s second step: adjudicating the permissibility of the agency’s construction of the bioequivalence standard.<sup>95</sup> Echoing previous opinions on bioequivalence, the court in *Schering II* extended broad deference to the FDA, finding its decision to “determine bioequivalence on a case-by-case basis depending on the drug” reasonable in light of prior legislation and a lack of “evidence that Congress intended to limit the discretion of the FDA.”<sup>96</sup>

In *Schering I* and *Fisons*, courts inferred a broad grant of discretion from statutory structure and from ensuing congressional silence. In *Schering II*, an appellate court found that the statute was ambiguous, so any reasonable interpretation on the part of the agency would be permissible under *Chevron*. Other courts have followed the reasoning of *Schering II*, most notably the D.C. Circuit in *Serono Laboratories, Inc. v. Shalala*, which applied *Chevron* to extend a “high level of deference” to the FDA “within its area of expertise” (i.e., bioequivalence).<sup>97</sup>

There are good arguments for granting this degree of deference to the FDA. The appellate courts’ analyses in *Schering II* and *Serono*

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<sup>93</sup> *Id.* at 396.

<sup>94</sup> At that time, the text of § 355(j)(7)(B)(1988) stated:

“A drug shall be considered to be bioequivalent to a listed drug if . . . (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . . .”

*Id.* at 397. The court found that this was ambiguous since “it neither imposes nor forecloses the interpretation that it is an exclusive definition of bioequivalent.” *Id.*

<sup>95</sup> *Id.* at 398–99 (“Given our holding that section 355(j)(7)(B) is ambiguous, we must review the FDA’s interpretation of that section to determine whether it is a permissible construction of the Act.”).

<sup>96</sup> *Id.* at 399.

<sup>97</sup> *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)) (internal quotation marks omitted).

comports with *Chevron's* regime for matters of agency expertise—bioequivalence involves highly technical facts, and concern for judicial competence ordinarily suggests that courts not involve themselves in technical determinations that Congress has delegated to an agency.<sup>98</sup> However, as the Supreme Court has observed and as I argue below, it is possible to accord too much deference to an agency, especially when agency action does not follow standardized procedures.<sup>99</sup> The case-by-case determinations approved by the court in *Schering II* and perpetuated by the FDA's current practice of product-specific bioequivalence recommendations exemplify the type of regulation that should draw courts' scrutiny, but have received only the lightest review.

There is ample scholarly criticism of the FDA's status as a recipient of judicial deference. In a symposium held by the *Cornell Law Review* discussing decades of deference to the FDA, Lars Noah noted that "the FDA enjoys largely unreviewable discretion in deciding whether and how to exercise its enforcement powers."<sup>100</sup> Regarding drug approval, James T. O'Reilly observed that:

Unlike other federal agencies that must seek adjudication by the courts to set precedential policy decisions, the FDA has long enjoyed freedom from judicial interference with drug approval decisions. This freedom from close judicial scrutiny . . . had a liberating effect on the FDA's operations. The FDA assumed that it had absolute gatekeeper power and could determine the fate of privately sponsored drugs without serious risk of judicial reversal. . . . [F]ederal judges acquiesced to this independence by readily showing deference to the FDA's determinations of drug safety.<sup>101</sup>

This Note does not intend to wade into the debate over deference to the FDA as a whole. The agency is enormous, and its regulatory tasks are varied and complex. Still, the commentary of scholars like Noah and O'Reilly accords with the bioequivalence jurisprudence

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<sup>98</sup> See *Chevron v. Natural Res. Def. Council*, 467 U.S. 837, 865 (1984) ("[T]he Administrator's interpretation represents a reasonable accommodation of manifestly competing interests and is entitled to deference: the regulatory scheme is technical and complex, the agency considered the matter in a detailed and reasoned fashion . . . . Judges are not experts in the field . . .").

<sup>99</sup> See *supra* notes 61–69 and accompanying text (discussing the *Mead* doctrine and constraints on deference).

<sup>100</sup> Lars Noah, *The Little Agency that Could (Act with Indifference to Constitutional and Statutory Strictures)*, 93 CORNELL L. REV. 901, 902 (2008) ("Throughout its history . . . the FDA has had an enviable record of success in the courts because judges have shown tremendous deference to its expertise in implementing its public health mission. For this same reason, judges also have given the agency greater leeway than normal on questions of statutory interpretation . . .").

<sup>101</sup> O'Reilly, *supra* note 87, at 956 (footnotes omitted).

discussed above, and this backdrop of extraordinary deference should highlight the need for increased judicial attention to suspect regulatory practices.

*B. Recent Challenges: Courts Maintain Deference and Deploy Justiciability Doctrine*

In tandem with applying broad *Chevron* deference to the FDA in bioequivalence matters, courts have progressively restricted access to bioequivalence litigants by tightening justiciability requirements. Justiciability doctrine flows from the “cases” and “controversies” requirement of Article III.<sup>102</sup> Courts may only hear cases that are ripe for review,<sup>103</sup> not moot,<sup>104</sup> and brought by plaintiffs who have standing.<sup>105</sup>

Over the years, justiciability doctrine has become difficult to systematize.<sup>106</sup> Scholars acknowledge that the malleability of “cases” and “controversies” leaves ample room for courts to simply avoid hearing cases that they do not want to hear for prudential or political reasons.<sup>107</sup> Standing doctrine, in particular, has become a source of concern in administrative law since government actions often consist of generalized public policies that may only indirectly or prospectively

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<sup>102</sup> U.S. CONST. art. III, § 2 (“The judicial Power shall extend to all Cases, in Law and Equity, arising under this Constitution, the Laws of the United States, and Treaties made, or which shall be made, under their Authority; . . . to Controversies to which the United States shall be a Party . . . .”); see also Jonathan R. Siegel, *A Theory of Justiciability*, 86 TEX. L. REV. 73, 76 (2007) (“Although the Constitution does not define the terms ‘cases’ and ‘controversies,’ the courts have understood these words to impose a constellation of constraints known collectively as doctrines of justiciability.”).

<sup>103</sup> See, e.g., *Abbott Labs. v. Gardner*, 387 U.S. 136, 148–49 (1967) (“[The] basic rationale [of ripeness] is to prevent the courts, through avoidance of premature adjudication, from entangling themselves in abstract disagreements over administrative policies, and also to protect the agencies from judicial interference until an administrative decision has been formalized and its effects felt in a concrete way . . . .”).

<sup>104</sup> See, e.g., *DeFunis v. Odegaard*, 416 U.S. 312, 316–17 (1974) (noting that “federal courts are without power to decide questions that cannot affect the rights of litigants in the case before them,” as in this case where plaintiff challenged the denial of his admission to law school, was admitted pursuant to a lower court decision, and would graduate before the Supreme Court could rule on the matter (quoting *North Carolina v. Rice*, 404 U.S. 244, 246 (1971)) (internal quotation marks omitted)).

<sup>105</sup> See, e.g., *City of Los Angeles v. Lyons*, 461 U.S. 95, 105–10 (1983) (holding that to assert standing a plaintiff must face “a real and immediate threat”).

<sup>106</sup> See Siegel, *supra* note 102, at 78 (“[Justiciability does not] serve any apparent purpose. Certainly no one has yet proposed a theory of the purpose behind the justiciability constraints that has achieved general acceptance.”). Justice Harlan characterized standing doctrine as “a word game played by secret rules.” *Flast v. Cohen*, 392 U.S. 83, 129 (1968) (Harlan, J., dissenting).

<sup>107</sup> See Siegel, *supra* note 102, at 108–12 (“[P]erhaps the vital purpose of justiciability is to give the courts a mechanism by which to avoid awkward cases.”).

harm a potential plaintiff. *City of Los Angeles v. Lyons*<sup>108</sup> provides a graphic example of restrictive standing doctrine that remains good law. In *Lyons*, the plaintiff sought injunctive relief against the Los Angeles Police Department after officers subjected him to a departmentally sanctioned chokehold technique that had caused at least fifteen other deaths.<sup>109</sup> Nevertheless, the Court held that Lyons did not have standing to sue because he could not establish “a real and immediate threat” of future harm.<sup>110</sup>

The Court took another step toward tightening justiciability requirements for administrative law challenges in *Lujan v. Defenders of Wildlife*.<sup>111</sup> In *Lujan*, the Court held that a group of environmentalist organizations did not have standing to challenge a Department of the Interior rule limiting the Endangered Species Act<sup>112</sup> to actions within the United States because they could not demonstrate “concrete” and “imminent” “injury in fact” causally related to the policy and likely to be redressed by a judicial remedy.<sup>113</sup> The Court rejected plaintiffs’ theories that they were harmed by their inability to see increasingly endangered animals when travelling abroad, and that anyone involved in the “ecosystem” or care of endangered species should have standing based on this connection.<sup>114</sup> *Lujan* has been criticized for its foreclosure of environmental and public interest suits on procedural grounds.<sup>115</sup>

D.C. District and Circuit Court bioequivalence cases demonstrate similar judicial movement toward tighter standing requirements. At first, in *Fisons*, the D.C. District Court found that the inevitability of future lost profits from generic competitors was sufficient to provide standing for innovator companies under the “injury in fact” and “zone of interests” tests.<sup>116</sup> Even though the district court ruled against Fisons Corporation, it rejected the FDA’s contention that innovator companies’ loss of future profits to generic competitors is too speculative a harm to grant standing. To the contrary, in finding that pioneer drug companies like Fisons could prove “injury in fact” as well as

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<sup>108</sup> 461 U.S. 95 (1983).

<sup>109</sup> *Id.* at 97–100.

<sup>110</sup> *Id.* at 110.

<sup>111</sup> 504 U.S. 555 (1992).

<sup>112</sup> Endangered Species Act, 16 U.S.C. §§ 1531–1544 (2006).

<sup>113</sup> *Lujan*, 504 U.S. at 560–61.

<sup>114</sup> *Id.* at 563–67.

<sup>115</sup> See *infra* Part III.B.2 (describing objections to *Lujan*).

<sup>116</sup> *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 862 (D.D.C. 1994) (discussing the constitutional “injury in fact” test for standing from *Associated Gas Distribs. v. Fed. Energy Regulatory Comm’n*, 899 F.2d 1250 (D.C. Cir. 1990) and the prudential “zone of interests” test for standing from *Hazardous Waste Treatment Council v. Thomas*, 885 F.2d 918 (D.C. Cir. 1989)).

demonstrate a relationship to the “zone of interests” implicated by Hatch-Waxman,<sup>117</sup> the *Fisons* court left the door open to future challenges from innovators.

However, a year later, in *Bristol-Myers Squibb v. Shalala*,<sup>118</sup> the court effectively overruled its standing analysis in *Fisons* by finding an “actual or imminent” harm requirement.<sup>119</sup> According to the court, “[u]ntil a competitor enters the field, plaintiff faces nothing more than a potential for harm which will not become actual or imminent unless and until a competitor comes forward.”<sup>120</sup>

From one perspective, the court in *Bristol-Myers Squibb* was simply applying prevailing Supreme Court precedent from *Lujan*. From another viewpoint, the court took advantage of a malleable standing doctrine to avoid hearing a difficult and controversial set of cases. Heightened standing requirements give courts an additional avenue besides deference to eliminate challenges to FDA bioequivalence determinations. The following recent cases show how courts are employing both doctrines to limit adjudication on the merits of bioequivalence challenges, which have remained substantively consistent since the early 1990s.

### 1. *Deference*: Graceway Pharmaceuticals, LLC v. Sebelius

In this recent D.C. District Court case, Graceway sued to block approval of an ANDA for imiquimod, the active ingredient in its topical cream Aldara, used for the treatment of actinic keratosis, some types of skin cancer, and warts caused by human papillomavirus.<sup>121</sup> During initial approval, Graceway had been required to perform separate clinical trials for all three conditions.<sup>122</sup> However, the Office of

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<sup>117</sup> *Id.*

<sup>118</sup> 892 F. Supp. 295 (D.D.C. 1995).

<sup>119</sup> *Id.* at 297–98 (citing *Lujan*, 504 U.S. at 560).

<sup>120</sup> *Id.* at 298. In *Pfizer Inc. v. Shalala*, decided four years after *Bristol-Myers Squibb*, the D.C. Circuit handed down a similar justiciability decision based on ripeness—an innovator’s suit was not allowed to proceed before a competitor’s ANDA was fully approved, since “[t]he critical fact remains that the FDA may never approve [the competitor’s] application—whether [due to] . . . a lack of bioequivalence [or due to other grounds].” *Pfizer Inc. v. Shalala*, 182 F.3d 975, 978 (D.C. Cir. 1999). This reasoning derived from *Texas v. United States*, 523 U.S. 296 (1998), a Supreme Court decision that tightened ripeness requirements generally. See *Pfizer*, 182 F.3d at 978 (drawing upon *Texas v. United States* for an analysis of ripeness). Ripeness is technically a separate inquiry from standing, but its docket-shrinking effect is similar. While a thorough account of justiciability doctrine and its discontents is beyond the scope of this Note, tightening standards and their effects are further discussed *infra* Part III.B.2.

<sup>121</sup> *Graceway Pharm., LLC v. Sebelius*, 783 F. Supp. 2d 104, 107–08 (D.D.C. 2011). “Actinic keratoses are flat, scaly growths on the skin that usually form on parts of the body that are exposed to direct sunlight.” *Id.*

<sup>122</sup> *Id.* at 108.

Generic Drugs (OGD) told generic competitor companies that they would only be required to demonstrate bioequivalence in patients with actinic keratoses—this one determination was sufficient to find bioequivalence for all three conditions.<sup>123</sup>

Graceway argued that the agency acted arbitrarily and capriciously by approving nonsystemically acting generics without requiring site-specific efficacy tests.<sup>124</sup> In support of its case, it presented evidence of internal disagreement at the agency itself, between the OGD and the Dermatology Division within the Center for Drug Evaluation and Research (CDER).<sup>125</sup> A director of the CDER resolved this disagreement internally by affirming the single-test approach.<sup>126</sup>

The court granted summary judgment in favor of the FDA, citing *Serono* and *Schering II*.<sup>127</sup> Echoing those cases' deferential language, the court observed that "the FDA's evaluations of scientific data within its area of expertise are entitled to a high level of deference."<sup>128</sup> The court approvingly acknowledged the agency's "comprehensive response"<sup>129</sup> to Graceway's administrative inquiries<sup>130</sup> and noted that the response had been codified into a draft guidance document.<sup>131</sup>

In granting summary judgment to the FDA, the court necessarily opined that there was no genuine issue of material fact, although it also acknowledged the scientific distinctions between imiquimod's various indications as well as the internal agency dispute.<sup>132</sup> In

<sup>123</sup> *Id.* at 108–09.

<sup>124</sup> Before suing, Graceway had sought administrative relief via a citizen petition, arguing that "genital warts are completely unrelated to actinic keratoses and [skin cancer], both in terms of the cause and the nature of the conditions." *Id.* at 108. The FDA responded negatively to the petition, concluding that one study was sufficient to determine bioequivalence for all three indications. *Id.* at 109–10.

<sup>125</sup> The Dermatology Division had produced a memorandum effectively supporting Graceway's position that "[genital warts are] unrelated to and occur [ ] at different anatomical locations than actinic keratoses and [skin cancer]," and thus multiple trials would be appropriate. *Id.* at 109.

<sup>126</sup> *Id.*

<sup>127</sup> *Id.* at 111–12, 117.

<sup>128</sup> *Id.* at 110–11 (citing *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998)).

<sup>129</sup> *Id.* at 114–15 (quoting *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 20 (D.D.C. 2009)) (internal quotation marks omitted).

<sup>130</sup> *Id.* at 116 ("[W]as the FDA's denial of the plaintiff's Citizen Petition well-reasoned, sufficiently explained, and in line with the scientific evidence before it? After a thorough review of the FDA's Response, and the entire administrative record, the Court concludes the answer to this question is yes.").

<sup>131</sup> *Id.* at 108.

<sup>132</sup> *Id.* at 112–17.

discussing these controversies and then ruling them non-material,<sup>133</sup> the court's grant of summary judgment stymied judicial review of an administrative action that had not been subject to public comment and which arguably did concern an issue of fact: whether or not one test was sufficient to support drug approval for multiple usages. Instead of engaging in a full hearing on the matter, the court opted to fall back on precedent, extending a "high degree of deference . . . to the FDA's determinations regarding which methodologies it determines are needed to test the bioequivalency [sic] of a given generic."<sup>134</sup>

## 2. *Justiciability*: ViroPharma, Inc. v. Hamburg

In another recent D.C. District Court case, ViroPharma sued the FDA for procedural violations in producing guidance related to ViroPharma's drug Vancocin (vancomycin), an antibiotic capsule that releases its active ingredient in the gastrointestinal (GI) tract to treat local GI infections.<sup>135</sup> The FDA had issued a guidance document in 1996 recommending that generic versions of Vancocin be subject to *in vivo* bioequivalence testing, but in 2006 it revised this guidance to allow *in vitro* methods.<sup>136</sup> ViroPharma challenged the revision in 2006, but the agency did not respond with a final action. Meanwhile, the agency solidified its change of course by responding to a 2007 citizen petition by another company, Cobalt, regarding a similar locally acting GI drug, asserting its "discretion to accept *in vitro* studies for a non-systemically absorbed drug . . . when such studies are determined to be a scientifically valid method of determining bioequivalence" according to 21 C.F.R. § 320.24.<sup>137</sup>

ViroPharma's suit argued that permitting *in vitro* studies under 21 C.F.R. § 320.24 should first require a waiver of *in vivo* studies under 21 C.F.R. § 320.22.<sup>138</sup> By issuing guidance on *in vitro* tests for locally acting GI drugs without first determining whether or not the drugs fulfilled regulatory waiver requirements, the agency was essentially modifying its own regulations without engaging in notice-and-comment rulemaking. By finding primary regulatory authority in the evidence requirements of 21 C.F.R. § 320.24, the FDA arguably

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<sup>133</sup> In regard to the internal dispute, the court observed that "it is not the Dermatology Division's opinion that is afforded deference under the precedent of this Circuit." *Id.* at 116.

<sup>134</sup> *Id.* at 111 (quoting *Astellas*, 642 F. Supp. 2d at 19).

<sup>135</sup> *ViroPharma, Inc. v. Hamburg*, 777 F. Supp. 2d 140, 144 (D.D.C. 2011).

<sup>136</sup> *Id.*

<sup>137</sup> *Id.* (quoting the FDA response letter) (internal quotation marks omitted).

<sup>138</sup> *Id.* at 143.

converted the waiver provisions of 21 C.F.R. § 320.22 into surplus. The court, citing *Lujan* and *Pfizer, Inc. v. Shalala*,<sup>139</sup> dismissed for lack of standing based on future lost profits and ViroPharma's failure to demonstrate a concrete harm causally connected to the FDA's actions.<sup>140</sup>

*ViroPharma* is a bold illustration of the courts' justiciability limitations. Far from viewing private sector litigants as resources that "possess the scientific data to recognize when the FDA may stray,"<sup>141</sup> the court declined altogether to address ViroPharma's substantial allegation of regulatory inconsistency, further immuring the agency behind a wall of justiciability requirements.<sup>142</sup>

### III

#### REFORMING DEFERENCE AND JUSTICIABILITY

In this Part, I summarize the stakes of accurate bioequivalence determinations before proposing two reforms to ameliorate the lack of transparency and judicial review generated by unchecked deference and strict justiciability requirements. I devote the final section to normative and prospective reasons for reducing deference, concluding that the need for progressive codification of regulatory science and the reality of expanding frontiers in biotechnology justify a change.

##### A. *The Stakes of Bioequivalence*

This Note does not take a stance on the overall quality of generic drugs approved under Hatch-Waxman. There is no consistent evidence that approved generics are inherently inferior to innovator drugs, and claims to this effect are confounded by the medical background of particular patients, the variable usefulness of particular drugs, and the complexity and intractability of particular diseases.<sup>143</sup>

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<sup>139</sup> 182 F.3d 975 (D.C. Cir. 1999); *see also supra* note 120 (discussing *Pfizer*).

<sup>140</sup> *Id.* at 145–48.

<sup>141</sup> *Schering Corp. v. FDA (Schering II)*, 51 F.3d 390, 396 (3d Cir. 1995); *see also supra* note 93 and accompanying text.

<sup>142</sup> In March 2012, the D.C. Circuit affirmed the district court's decision in *ViroPharma* in a brief memorandum opinion. *ViroPharma Inc. v. Hamburg*, No. 11-5143, 2012 WL 1138803, at \*1 (D.C. Cir. Mar. 21, 2012). The court emphasized that ViroPharma could not claim standing based on the FDA's rejection of a third party's petition alone, even if that petition foreseeably would affect ViroPharma's own case. *See id.* at \*2 ("We have heretofore made it abundantly clear that 'mere precedential effect within an agency is not, alone, enough to create Article III standing, no matter how foreseeable the future litigation.'" (quoting *Sea-Land Serv., Inc. v. Dep't of Transp.*, 137 F.3d 640, 648 (D.C. Cir. 1998))).

<sup>143</sup> Compare Lesley Alderman, *A New Disquiet About Generic Drugs*, N.Y. TIMES, Dec. 19, 2009, at B6 ("[T]here is a gnawing concern among some doctors and researchers that certain prescription generic drugs may not work as well as their brand-name counterparts."), with *Generic Drugs: Questions and Answers*, FDA.GOV, <http://www.fda.gov/>

Still, as discussed in Part I, the regulatory process by which generic drugs reach the market is a sensitive one, and the scientific inquiry at its core is not entirely pure: Bioequivalence is, at best, a compromise between the need for regulatory accuracy and the value of public access to medicine.<sup>144</sup> Given the complexity of this process, the possibility that public harm could result from an inaccurate bioequivalence determination, and the long-term need to construct a regulatory system that works efficiently for all products, insulating the FDA from public comment and judicial review is counterproductive.<sup>145</sup>

The broad preemption regime that has developed regarding FDA regulations further enhances the stakes of reaching the right bioequivalence determinations.<sup>146</sup> Recently, the Supreme Court ruled in *Pliva v. Mensing* that FDA approval of innovator drug labeling preempts tort suits based on drug labeling against generic manufacturers.<sup>147</sup> In doing so, the Court expanded FDA preemption power

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Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100.htm (last updated Aug. 24, 2011) (discussing generic drug standards and assuring that “FDA approved generic drugs have met the same rigid standards as the innovator drug. To gain FDA approval, a generic drug must . . . be identical in strength . . . [and] meet the same batch requirements for . . . strength, purity, and quality”).

<sup>144</sup> Daniel Carpenter and Dominique Tobbell have dubbed bioequivalence a “joint regulatory and scientific creation,” the product of a political battle extending back to the earliest days of modern FDA regulation. Carpenter & Tobbell, *supra* note 32, at 94. They point out that some scientists and many drug companies have argued against equivalence determinations since the 1950s, when relaxed patent provisions and promotion of generic alternatives were first seriously proposed. *Id.* at 97. In the face of scientific and industry skepticism, the concept of bioavailability developed via the Drug Efficacy Study under Kefauver-Harris and strengthened the push for safe and effective generics. *Id.* at 104–08, 110–13. When the legislative negotiations that eventually led to Hatch-Waxman took place in the 1980s, “[t]he deal that had so long eluded members of Congress on generic drugs was able to be struck because the concepts were in place for a legislative bargain.” *Id.* at 128. The transformation of bioavailability into a legislative concept “was not the case of a purely ‘scientific’ development driving changes in regulation. Nor was it the case of a ‘regulatory development’ driving science.” *Id.* at 104.

<sup>145</sup> See *infra* Part III.B.1 (discussing the risks involved with policymaking form); *infra* Part III.C (discussing transubstantive product regulation). Nina Mendelson has spoken about the need to keep “regulatory beneficiaries” substantively involved in agency policymaking, especially “indirect regulatory beneficiaries” who do not traditionally have access to administrative procedure. Nina A. Mendelson, *Regulatory Beneficiaries and Informal Agency Policymaking*, 92 CORNELL L. REV. 397, 414–15 (2007). Excluding these beneficiaries via informal and ad hoc processes raises concerns for legitimacy and regulatory quality. See *id.* at 397 (“[W]hen an agency uses guidance documents rather than rulemaking to set policy, regulatory beneficiaries suffer significant losses to . . . means of accountability.”).

<sup>146</sup> See, e.g., *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 327–30 (2008) (holding that state tort claims against manufacturers of FDA-approved medical devices are preempted). The broad preemptive power of FDA approval is arguably problematic. See, e.g., Editorial, *No Recourse for the Injured*, N.Y. TIMES, Feb. 22, 2008, at A22 (arguing that *Riegel* is a threat to consumer rights).

<sup>147</sup> *Pliva, Inc. v. Mensing*, 131 S. Ct. 2567, 2577–78 (2011).

and entrenched an important aspect of the regulatory consensus on generic and innovator drug identity; tort claims to the contrary—based on claims that generic product labeling should be different—were legally foreclosed.<sup>148</sup> *Pliva* therefore increases the burden on the FDA to “get it right” during bioequivalence evaluations, since it decreases the chance that patients injured by non-equivalent generics will be adequately compensated in tort and prevents individual accounts of product inferiority from affecting the generic approval regime.

In addition, current guidance procedures “leave[ ] regulated entities guessing about their rights and obligations.”<sup>149</sup> And when regulated entities have questions about their rights, they go to court. The high cost of losing market share to generic competitors compounds the incentive to litigate. Given the large investment that innovator companies make when developing a product and the additional revenue that may result from even one extra month of market dominance, bringing suit over agency guidance is almost always an economically reasonable option. Lawsuits, however, take agency time and resources away from other important endeavors. Clearer ex ante administrative action could deter potential litigants and encourage affirmative compliance.<sup>150</sup>

Finally, when bioequivalence cases are decided under the status quo, they run the risk of making and perpetuating bad law. When reviewing courts are presented with complex, technical subject matter, they may contort procedural doctrines to avoid addressing the merits of a case.<sup>151</sup> This dynamic is apparent in the shift in standing and ripeness doctrine between *Fisons*, *Bristol-Myers Squibb*, and *Pfizer*.<sup>152</sup> Arguably, by the time the substantial regulatory issue in *ViroPharma* came before the D.C. District Court, it was too easy to dismiss the

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<sup>148</sup> See *id.* at 2574 (“A brand-name manufacturer seeking new drug approval is responsible for the accuracy and adequacy of its label. A manufacturer seeking generic drug approval, on the other hand, is responsible for ensuring that its warning label is the same as the brand name’s.” (internal citations omitted)). This duty of sameness preempts state tort claims that would require different labeling. *Id.* at 2577–78.

<sup>149</sup> Noah, *supra* note 100, at 905.

<sup>150</sup> See Jonathan Stroud, *The Illusion of Interchangeability: The Benefits and Dangers of Guidance-Plus Rulemaking in the FDA’s Biosimilar Approval Process*, 63 ADMIN. L. REV. 599, 637 (2011) (“[The FDA] should avoid case-by-case ad hoc approvals to prevent wasteful clinical research, reduce approval costs, and increase certainty, hence allowing more effective interchangeability determinations. This will encourage follow-on companies to submit narrowly tailored, detailed [data]. It will also cut down on the paperwork and bureaucratic delay.”). Stroud writes in reference to a proposed regulatory model for biosimilars. See *infra* note 155.

<sup>151</sup> See Siegel, *supra* note 102, at 108–12 (discussing justiciability as a vehicle for judicial avoidance).

<sup>152</sup> See *supra* Part II.B (discussing justiciability in bioequivalence cases).

case on justiciability grounds. By creating precedents that deem challenges to FDA bioequivalence determinations nonjusticiable, courts raise the chances that live matters of administrative law and policy will go unaddressed.<sup>153</sup>

### B. Proposals for Reform

This Section lays out how courts can work within deference and justiciability doctrine to promote reform—specifically, engagement by the FDA in notice-and-comment rulemaking or at least more substantial administrative procedures than are required for ad hoc guidance documents. By decreasing deference to policies that are not codified and by viewing a broader range of suits to be justiciable, courts can pressure the agency to engage in APA rulemaking more frequently and comprehensively.<sup>154</sup> I do not propose the exact form that new regulations might take, although existing frameworks from the 1992 regulations could serve as a template for future rulemakings. For example, regulations that address GI drugs as a class (pursuant to the *ViroPharma* dispute) need not be any more complicated than existing waiver regulations (e.g., for inhalants and topical medications). At present, no mention of GI drugs exists in the Code of Federal Regulations (C.F.R.). Instead, all bioequivalence determinations for these drugs have been based on guidance documents. Expanding the C.F.R. to accommodate additional drug classes is one practical suggestion for responding to the doctrinal recommendations I make below.<sup>155</sup>

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<sup>153</sup> See *infra* Part III.B.2 (discussing justiciability and bioequivalence); see also *infra* note 191 (discussing public interest challenges to FDA policy that were dismissed for lack of ripeness).

<sup>154</sup> See Mendelson, *supra* note 145, at 419–20 (“[W]hether regulatory beneficiaries can hold an agency accountable for implementing a particular statutory program will depend on the ability of beneficiaries to invoke external mechanisms of control. Courts are especially important, since they are likely to be more broadly accessible than congressional or presidential oversight processes.”).

<sup>155</sup> Jonathan Stroud suggests a similar solution for FDA regulation of biosimilars—a framework that the agency has yet to establish. See Stroud, *supra* note 150, at 636–37. He suggests:

[T]he FDA should provide detailed notice-and-comment rules that indicate clearly how and where each individual type of biologic will be classified. . . . [F]inal rules should be issued following the notice-and-comment rulemaking requirements of the APA and should be published in the *Code of Federal Regulations*, in addition to the *Federal Register*, to provide the biologics industry with a clear picture of the regulatory landscape, increase certainty in the market, and encourage generic manufacturers to apply for more licenses.

*Id.* (footnote omitted). Stroud’s suggestion is similar to the codification I envision, and supports the notion that the FDA should retrospectively clarify its approach to drug classes before biosimilars arrive to pose new and more complex problems.

### 1. *Courts Should Apply the Mead Doctrine to Guidance Documents and Agency Correspondence*

The FDA's reliance on guidance documents makes clear that the agency prefers to approach bioequivalence determinations in a flexible manner. Product-specific guidance documents and correspondence with industry allow the agency to promulgate informal "recommendations" without engaging in time-consuming, APA-mandated procedures.<sup>156</sup> However, the cases discussed above also make clear that courts treat FDA letters and guidance documents as more than mere recommendations. In *Graceway* and *ViroPharma*, bioequivalence determinations in draft guidance documents and citizen petition responses constituted authoritative agency action that effectively received deference from the D.C. District Court.

To be sure, the FDA's task is an extremely difficult one, and in general, agencies are free to choose the form in which they generate policy.<sup>157</sup> Arguably, issuing a new guidance document for every drug is an innovative approach to an intractable administrative problem, and, in any case, is a good faith attempt to advertise the details of agency decisionmaking. As stated in the 2010 Guidance on Bioequivalence Recommendations, the agency endeavors to "provide a meaningful opportunity for the public to consider and comment."<sup>158</sup> On the other hand, it is the APA that traditionally establishes what constitutes a meaningful opportunity for notice and comment, not agencies themselves. The role of the APA as a "constitution" for the administrative state<sup>159</sup> is to prevent agencies from accruing discretionary lawmaking power beyond the bounds of their enabling statutes and constitutional due process.<sup>160</sup> Since it is unclear by what

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<sup>156</sup> As stated at the top of every finalized bioequivalence recommendation: This guidance represents the [FDA's] current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

See, e.g., GUIDANCE ON CARBAMAZEPINE, *supra* note 51.

<sup>157</sup> See M. Elizabeth Magill, *Agency Choice of Policymaking Form*, 71 U. CHI. L. REV. 1383, 1383–84 (2004) ("[T]he typical administrative agency is authorized to use a range of distinct policymaking forms to effectuate its statutory mandate, and its choice about which tool to rely on appears, at first glance at least, to be unregulated by courts.").

<sup>158</sup> BIOEQUIVALENCE RECOMMENDATIONS, *supra* note 40, at 1.

<sup>159</sup> See, e.g., Steven P. Croley, *The Administrative Procedure Act and Regulatory Reform: A Reconciliation*, 10 ADMIN. L.J. AM. U. 35, 35 (1996) ("Like a constitution, the APA establishes a set of fundamental ground rules . . . according to which many particularized governmental decisions are made.").

<sup>160</sup> See, e.g., *Morton v. Ruiz*, 415 U.S. 199, 232 (1974) ("The [APA] was adopted to provide, *inter alia*, that administrative policies affecting individual rights and obligations be promulgated pursuant to certain stated procedures . . ."). The extent to which due process

principles the FDA incorporates extra-agency input on draft guidance,<sup>161</sup> the danger of self-oversight looms large.

Scholars have commented on the pitfalls of “regulation by guidance”—consistent use of guidance documents in place of more systematic and transparent APA procedures.<sup>162</sup> Outside of due process concerns, there is the risk that an agency may “coerce private parties to comply with [its] views without going through the effort to promulgate a legislative rule.”<sup>163</sup> Similarly, the brevity and expediency of guidance documents might simply lead to poorly formulated and insufficiently vetted policy.<sup>164</sup> In the specific context of the FDA, Lars Noah observes that FDA guidance documents “may operate as de facto rules but escape normal procedural safeguards for their promulgation or review. . . . [T]hey allow the FDA to take positions that do not even constrain agency officials, which leaves regulated entities guessing about their rights and obligations.”<sup>165</sup>

In 2007, the Office of Management and Budget (OMB) addressed these concerns across the executive branch as a whole with a “guidance document on guidance documents,” pursuant to the Data Quality Act,<sup>166</sup> recommending that “significant guidance documents”

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is implicated in bioequivalence determinations is debatable, since from one perspective they are meant to be purely scientific exercises and do not implicate individual legal rights. However, the inevitable link between bioequivalence and innovator property rights, summarized by Carpenter & Tobbell’s “joint regulatory and scientific” characterization, implies that due process is a relevant limit on bioequivalence determinations. *See supra* note 144. This link is complicated and attenuated by the fact that innovator “property” only amounts to market share at the time of ANDA approval (since the original patent will have expired).

<sup>161</sup> Mendelson, *supra* note 145, at 406, 410 (“The agency is not legally obligated to assemble a detailed record, disclose its data, prepare extensive analysis, or respond to significant comments. . . . Moreover, although they may participate informally to some degree, regulated entities generally lack the entitlement they would possess in rulemaking to participate in the guidance development process.” (footnote omitted)). *But see infra* notes 166–168 and accompanying text (discussing efforts to formalize procedures for producing guidance documents).

<sup>162</sup> *See, e.g.*, Magill, *supra* note 157, at 1441 (noting “the oft-repeated charge that agencies are ‘regulating by guidance’—that is, relying on interpretive rules or policy statements instead of legislative rules to effectuate their policy judgments”).

<sup>163</sup> *Id.* at 1438; *see also id.* at 1441 (discussing courts’ adaptation of deference principles to agencies’ regulation by guidance); Mendelson, *supra* note 145, at 407–08 (“Regulated entities often comply with the policies announced in guidance documents . . . to avoid FDA enforcement and the accompanying hassle and penalties. . . . [B]y issuing a guidance document, an agency can obtain a rule-like effect while minimizing political oversight and avoiding the procedural discipline, public participation, and judicial accountability required by the APA.”).

<sup>164</sup> *See* Magill, *supra* note 157, at 1438 (noting poor vetting as a potential concern for reviewing courts).

<sup>165</sup> Noah, *supra* note 100, at 905 (footnote omitted).

<sup>166</sup> Pub. L. 106-554 app. C § 515, 114 Stat. 2763A-153 (2000) (uncodified).

be subject to informal publicity and notice-and-comment procedures for the purpose of “maximizing [their] quality, utility, objectivity and integrity.”<sup>167</sup> The FDA had promulgated similar regulations for its own guidance practices seven years ahead of OMB, publicizing internal procedures for developing guidance documents and accepting comments.<sup>168</sup>

Still, guidance-on-guidance documents create a system of self-oversight that falls short on basic transparency and accountability.<sup>169</sup> And, as discussed above, *Mead* requires that agency actions be promulgated according to “rules carrying the force of law.”<sup>170</sup> Although *Mead* has been cited occasionally in bioequivalence cases,<sup>171</sup> courts generally have declined to require the level of transparency and structure that the “*Chevron* Step Zero” line of cases seems to require. I argue that courts *should* require this structure in the form of APA or APA-approximating procedures,<sup>172</sup> and if it is

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<sup>167</sup> OFFICE OF MGMT. & BUDGET, EXEC. OFFICE OF THE PRESIDENT, OMB BULL. NO. 07-02, FINAL BULLETIN FOR AGENCY GOOD GUIDANCE 1, 5 (2007) (internal quotation marks omitted), *available at* <http://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2007/m07-07.pdf>.

<sup>168</sup> Administrative Practices and Procedures; Good Guidance Practices, 65 Fed. Reg. 56,468 (Sept. 19, 2000) (codified in various parts of 21 C.F.R.).

<sup>169</sup> Nina Mendelson addresses the shortcomings of “guidance-plus” regulation that replaces APA standards with agency-specific notice-and-comment procedures. *See* Mendelson, *supra* note 145, at 420–33, 447–50. For example, “often . . . agencies do not solicit comment widely, but instead make ad hoc decisions regarding to whom a draft guidance document will be ‘floated.’ . . . Even among regulated entities affected by a proposed agency policy, there may be wide variation in involvement.” *Id.* at 427. Generally, participation in guidance-formulation may be “deemphasized” for all but the most clearly concerned and easily contacted entities. *See id.* at 429–33 (discussing reasons for low participation). Overall, “the opportunity to comment provided by agency self-regulation efforts is helpful. But without judicial review or some similar opportunity to hold agencies accountable for taking regulatory beneficiaries’ concerns into account, self-regulation, under the new OMB Bulletin or otherwise, is unlikely to fully address those concerns.” *Id.* at 450; *see also* Catherine Campbell Meshkin, *Unchecked Data: A Tool for Political Corruption?*, ENGAGE, Dec. 2010, at 45–49 (discussing the Data Quality Act, encouraging judicial review, and asserting that “[a]n agency cannot be held to police itself”).

<sup>170</sup> *See supra* notes 61–68 and accompanying text (discussing the *Mead* doctrine).

<sup>171</sup> *See supra* note 69 (discussing the application of *Mead* in *Allergan, Inc. v. Crawford*, 398 F. Supp. 2d 13 (D.D.C. 2005) and *CollaGenex Pharms., Inc. v. Thompson*, No. 03-1405, 2005 U.S. Dist. LEXIS 5543 (D.D.C. Jan. 19, 2005)).

<sup>172</sup> It should also be noted that the Hatch-Waxman Act itself requires that the FDA “promulgate . . . such regulations as may be necessary for the administration of [the Act]” in accordance with the APA. Pub. L. No. 98-417, § 105(a), 98 Stat. 1585, 1597 (1984) (codified as amended in 21 U.S.C. § 355 (2006)). Courts can regulate the quality and form of agency decisionmaking by affirmatively policing the boundaries of enabling statutes as well as enforcing the requirements of the APA. *See* Magill, *supra* note 157, at 1413 (“[T]he judicial gloss on the statutes—especially the APA—is as (if not more) important as the underlying requirements imposed by Congress.”).

absent, then courts should attempt to conduct an inquiry into the merits of the determination.<sup>173</sup>

The most salient counterargument to this approach is that courts must defer to agencies when the subject matter of a case is too technical for quality review, and that bioequivalence determinations exemplify this high degree of technicality.<sup>174</sup> However, courts regularly address remarkably technical subject matter, for example, in the realms of patent protection, financial markets, and environmental regulation, and the aura of non-addressability surrounding bioequivalence may be more a matter of historical and political privilege than actual complexity.<sup>175</sup> *In extremis*, Congress should consider assigning jurisdiction over bioequivalence matters to the Federal Circuit, since patent law is implicated and the Federal Circuit rules on highly technical controversies as a matter of course.

## 2. *Courts Reviewing Bioequivalence Determinations Should Incorporate Public Interest Concerns into Their Standing Analyses*

The contention that courts should incorporate public interest concerns into statutory analyses may seem counterintuitive to those with strong faith in the quality and usefulness of generic drugs. And, to reiterate, this Note does not pass judgment on the safety or efficacy of generic drugs in general. In fact, it seems manifestly clear that the generic pipeline Hatch-Waxman created has made a greater range of drugs available to a broader population of people, helping them manage a spectrum of medical conditions at a much lower cost.<sup>176</sup> Nevertheless, the generic approval process establishes a lower barrier to market entry than the new drug application process. And while this lower barrier may be justified by public health gains, it also raises public health concerns.<sup>177</sup> APA notice-and-comment procedures constitute the standard process by which public concerns are voiced, but

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<sup>173</sup> In the context of the *Graceway* decision, this would require that the D.C. District Court hear outside expert input on the “one test, multiple indications” approach before deferring to the agency’s internal expertise.

<sup>174</sup> See *Skidmore v. Swift & Co.*, 323 U.S. 134, 139 (1944) (granting deference when, among other things, a determination is “based upon more specialized experience and broader investigations and information than is likely to come to a judge in a particular case”).

<sup>175</sup> For a discussion of the history of bioequivalence as a legislative and regulatory concept, see generally Carpenter & Tobbell, *supra* note 32.

<sup>176</sup> See *supra* notes 1–3 and accompanying text (discussing widespread generic use and lowered medical costs).

<sup>177</sup> See, e.g., Alderman, *supra* note 143, at B6 (discussing an independent laboratory study in which a particular generic version of the antidepressant Wellbutrin was shown to behave differently than the brand-name product).

since courts have extended deference to the FDA in the absence of such procedures, the agency effectively may regulate without any external input. I already have recommended that courts reduce deference to the FDA in order to induce APA compliance and permit systematic public input. In addition, courts themselves should serve as fora for public interest claims. This would require a modification of the *ViroPharma* standing doctrine.

Heightened justiciability requirements may preclude meritorious claims about administrative and scientific procedure simply because a plaintiff cannot show concrete or inevitable harm. This result is problematic. To reach the merits of cases involving bioequivalence determinations, courts should apply the recommendations of many scholars in the wake of *Lujan* and other cases that closed off the ability of third-party activists to assert standing in court for public interest harms.<sup>178</sup> As mentioned above, justiciability doctrine is complex,<sup>179</sup> and tighter control over judicial dockets is often essential for a functioning court system. However, advocates of broader justiciability rules routinely argue that lighter dockets should not come at the expense of the public interest, and that “injury in fact” should be interpreted broadly.<sup>180</sup> Recommendations for reform often amount to greater recognition of plaintiffs who may have difficulty demonstrating a “distinctive concrete harm,”<sup>181</sup> but for whom Congress intended to create a cause of action against the government’s procedural failures.<sup>182</sup>

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<sup>178</sup> These recommendations argue, among other things, that the *Lujan* standard is unconstitutional or otherwise unworkable, and they attempt to restore standing to third-party activists via looser interpretations of “injury in fact,” or by administrative mechanisms that would create redressable harm in the case of administrative misfeasance. See, e.g., Harold Feld, *Saving the Citizen Suit: The Effect of Lujan v. Defenders of Wildlife and the Role of Citizen Suits in Environmental Enforcement*, 19 COLUM. J. ENVTL. L. 141, 142 (1994) (suggesting a system of mandatory cash bounties for valid regulatory complaints, the denial of which would create redressable harm); Gene R. Nichol, *The Impossibility of Lujan’s Project*, 11 DUKE ENVTL. L. & POL’Y F. 193, 198–200 (2001) (arguing that the *Lujan* standard is “illegitimate” and “impossible”); Cass R. Sunstein, *What’s Standing After Lujan? Of Citizen Suits, “Injuries,” and Article III*, 91 MICH. L. REV. 163, 224 (1992) (“Congress [should] expressly . . . create a property interest in the various regulatory ‘goods’ that it wants to authorize citizens to protect. It might, for example, say that citizens generally have a beneficial interest in certain endangered species . . .”).

<sup>179</sup> See *supra* Part II.B.

<sup>180</sup> See Nichol, *supra* note 178, at 201–04 (discussing the “injury in fact” standard).

<sup>181</sup> *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 577 (1992).

<sup>182</sup> See, e.g., Sunstein, *supra* note 178, at 225 (“It is almost always the case that procedural rights have only speculative consequences for a litigant. . . . [S]uppose that an administrator . . . violated the [APA] by promulgating a regulation without first publishing it for comment in the Federal Register. It is entirely speculative whether compliance would make any difference to the complainants.”).

In fact, the Supreme Court may have begun to take advantage of ambiguities in *Lujan* by opening the courts to suits with tenuous justiciability claims. In *Massachusetts v. EPA*, for example, the Court indicated that the “causation” and “redressability” prongs of *Lujan* are more flexible in the context of procedural rights.<sup>183</sup> Rather than perpetuating the skepticism that the *ViroPharma* court exhibited toward the causal link between agency action and future lost profits, the analysis in *Massachusetts v. EPA* implies that profits may be beside the point, and that courts should view the right to challenge bioequivalence determinations as a general procedural right under the APA.<sup>184</sup> While the D.C. District Court’s “actual or imminent” harm analysis in *ViroPharma* still would constitute a barrier to standing under *Lujan*,<sup>185</sup> courts also should consider the fact that generics are intended to be fungible with innovator drugs,<sup>186</sup> and the eventuality of generic market dominance and widespread use is all but assured due to the public perception of interchangeability as well as pressure from insurance companies to prescribe generics whenever they are available.<sup>187</sup> In this scenario, whatever harms might result from an arbitrary and capricious bioequivalence determination should be seen as “imminent” rather than merely speculative.<sup>188</sup>

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<sup>183</sup> *Massachusetts v. EPA*, 549 U.S. 497, 517–18 (2007); see also Devin McDougall, Note, *Reconciling Lujan v. Defenders of Wildlife and Massachusetts v. EPA on the Set of Procedural Rights Eligible for Relaxed Article III Standing*, 37 COLUM. J. ENVTL. L. 151, 175 (2012) (“*Massachusetts* simply expanded the types of claims that may qualify as procedural rights for the purposes of the *Lujan* procedural rights standing rule.”).

<sup>184</sup> “[A] litigant to whom Congress has ‘accorded a procedural right . . . can assert that right without meeting all the normal standards for redressability and immediacy’ . . . [and] has standing if there is some possibility that the requested relief will prompt the injury-causing party to reconsider the decision that allegedly harmed the litigant.” *Massachusetts*, 549 U.S. at 517–18 (citations omitted) (quoting *Lujan*, 504 U.S. at 572 n.7).

<sup>185</sup> See *ViroPharma, Inc. v. Hamburg*, 777 F. Supp. 2d 140, 145, 146 n.2 (D.D.C. 2011) (endorsing the “actual or imminent” harm requirement for standing).

<sup>186</sup> See *Generic Drugs: Questions and Answers*, *supra* note 143 (“FDA requires generic drugs have the same high quality, strength, purity and stability as brand-name drugs.”); see also *supra* notes 147–148 and accompanying text (discussing the Supreme Court’s ruling in *Pliva, Inc. v. Mensing*, 131 S. Ct. 2567 (2011), that tort suits seeking variations in generic product labeling are preempted by pioneer product labeling regulations).

<sup>187</sup> LEIGH PURVIS, AARP PUBLIC POLICY INST., STRATEGIES TO INCREASE GENERIC DRUG UTILIZATION AND ASSOCIATED SAVINGS 4 (2008), available at [http://www.aarp.org/health/drugs-supplements/info-12-2008/i16\\_generics.html](http://www.aarp.org/health/drugs-supplements/info-12-2008/i16_generics.html) (“Generic substitution policies require physicians to take affirmative steps before prescribing brand name drugs. One variation is mandatory generic substitution, under which the generic version of a drug must be dispensed when available.”).

<sup>188</sup> In the context of the *ViroPharma* decision, a reformed approach to standing would permit *ViroPharma* to bring its dispute pursuant to the broad harm of an ambiguous regulatory regime, as well as the potential for harm to patients if the regime is not clarified and the agency is permitted arbitrarily to waive *in vivo* studies.

One difficulty with arguing for public interest standing in the context of generic drug approval is that practically every plaintiff to challenge bioequivalence determinations has had a pecuniary interest in the matter—that is, the plaintiffs either are innovator drug companies aiming to sustain their market dominance or rival generic drug companies seeking to preempt their competitors' entry into the market. Such plaintiffs are a far cry from the storied environmentalist organizations that have battled for hearings against heavy industry and captured agencies.<sup>189</sup> Still, before *Bristol-Myers Squibb*, controlling precedent had acknowledged that, in this situation, regulated industry could be a key resource for policing regulatory quality.<sup>190</sup> While it may be naive to imagine that drug companies ever would value a stronger and more sustainable regulatory regime, it may be equally cynical to assume that a hearing on the merits and public interest ramifications of a drug company's claim would only benefit innovator companies and hurt the generic pipeline.<sup>191</sup>

### C. *The Need for Progressive Regulatory Science*

Finally, a prospective and normative case also may be made for progressively codifying guidelines for determining bioequivalence. Over the course of the twentieth century, the FDA took on an expanding series of statutory mandates that eventually led to our contemporary, comprehensive system of food and drug regulation.<sup>192</sup> The agency is proud of the statistic that it is responsible for regulating a

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<sup>189</sup> For example, organizations like Friends of the Earth, the Natural Resources Defense Council, Greenpeace, and the Sierra Club, all of which were parties to *Massachusetts v. EPA* and other impact litigation cases.

<sup>190</sup> As the court observed in *Schering II*, innovator drug companies may indeed “possess the scientific data to recognize when the FDA may stray from the legislatively mandated testing requirements that impact the safety and effectiveness of the generic drug.” *Schering Corp. v. FDA*, 51 F.3d 390, 396 (3d Cir. 1995).

<sup>191</sup> A number of nonprofit consumer rights groups also advocate for regulatory quality at the FDA, and there is some evidence that these groups suffer as well from heightened justiciability standards. In 2003, for example, Public Citizen and the Center for Science in the Public Interest brought suit against the FDA, requesting APA rulemaking on a decision to allow “qualified health claims” on food labeling. *Ctr. for Sci. in the Pub. Interest v. FDA*, No. 03-1962, 2004 U.S. Dist. LEXIS 18541, at \*5–7 (D.D.C. July 30, 2004). The D.C. District Court dismissed the plaintiffs as lacking standing and their claim as unripe for review, and the FDA was permitted to continue its course of action. *Id.* at \*19. It is difficult to determine the effect of justiciability doctrine on nonprofit food and drug advocacy (e.g., administrative petitions may be preferable given the strategies of these groups); however, it is reasonable to imagine that greater access to judicial review would serve interests besides those of for-profit corporations. *See also* Mendelson, *supra* note 145, at 417 (“We should see the interests of regulatory beneficiaries in the way an agency carries out its mandate as real interests, and ensure that beneficiaries too are among those that can hold an agency accountable.”).

<sup>192</sup> *See supra* Part I (discussing progressive amendments to the FDCA).

full twenty percent of the average American's household budget,<sup>193</sup> and it must increasingly “grapple with advances in science and technology that Congress could not have anticipated many decades earlier, including the advent of genetically modified foods, bioengineered drugs, nanotechnology, tissue engineering and regenerative medicine, gene therapy, and pharmacogenomics.”<sup>194</sup>

The scope and gravity of the agency's regulatory charge are unlikely to diminish any time soon, and indeed have expanded significantly in the past two years with the passage of the Patient Protection and Affordable Care Act (PPACA) in 2010<sup>195</sup> and the Food Safety Modernization Act (FSMA) in 2011.<sup>196</sup> PPACA establishes an Approval Pathway for Biosimilar Products that is modeled on the Hatch-Waxman bioequivalence determination but is intended to promote production of generic versions of more complex “biologic” products such as vaccines, antibodies, and blood products.<sup>197</sup> Section 7002 of PPACA, which outlines the new “biosimilar” approval pathway, clearly establishes a clinical trial requirement.<sup>198</sup> However, PPACA also aims to reduce the burden of development and approval for products that may be, from a scientific point of view, utterly unique.<sup>199</sup>

Biosimilarity is thus a scientific-legal concept par excellence—while based in scientific principles, it could not exist outside of the progressive history of food and drug regulation. Although the FDA

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<sup>193</sup> See U.S. FOOD & DRUG ADMIN., STRATEGIC PRIORITIES 2011–2015: RESPONDING TO THE PUBLIC HEALTH CHALLENGES OF THE 21ST CENTURY 1 (2011), available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM252092.pdf>.

<sup>194</sup> Noah, *supra* note 100, at 917 (footnotes omitted).

<sup>195</sup> Pub. L. No. 111-148, 124 Stat. 119 (2010) (to be codified as amended in scattered sections of 42 U.S.C.).

<sup>196</sup> Pub. L. No. 111-353, 124 Stat. 3885 (2011) (to be codified as amended in scattered sections of 21 U.S.C.).

<sup>197</sup> Patient Protection and Affordable Care Act § 7002; *What Are “Biologics” Questions and Answers*, FDA.GOV, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm> (last visited Oct. 31, 2012).

<sup>198</sup> Patient Protection and Affordable Care Act § 7002(k)(2)(A)(i)(I)(cc) (requiring “a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency”).

<sup>199</sup> For example, transplanted human cells are considered “biologics” under the current FDA regulatory scheme, but demonstrating identity between two human cells to the same degree as small-molecule drugs is, at present, practically impossible. Even if two cells are genetically identical, epigenetic phenomena and indeterminate subcellular processes can prevent scientists from determining functional identity. See, e.g., Cédric Blanpain et al., *Stem Cells Assessed*, 13 NATURE REV. MOLECULAR CELL BIOLOGY 471 (2012) (discussing epigenetic differences between induced pluripotent and embryonic stem cells as a challenge for medical applications); see also Stroud, *supra* note 150, at 606 (“[Some critics] argue it is a scientific impossibility to achieve interchangeability between some biologics (due to their variable nature as living organisms) . . .”).

has yet to take significant public steps toward implementing the biosimilarity mandate in PPACA, the biotechnology industry is abuzz with speculation on the direction that such regulation will take.<sup>200</sup> Not all of this buzz is positive. Skepticism abounds about the FDA's ability to comprehensively and equitably establish a regime for biosimilarity approval.<sup>201</sup> Therefore, a final argument in support of codifying a stable, transsubstantive bioequivalence regime may derive from the basic wisdom in finishing one battle before starting the next.

Depending upon one's view of the FDA's mission, this wisdom acquires a normative dimension beyond mere prudence. Serving the public interest in a rapidly accelerating biotechnological age requires both progressive regulation and accountable policymaking. While ad hoc guidance may be possible when the number of approvable generic drugs is in the hundreds, will agency resources last when products number in the thousands? Laying a detailed regulatory foundation now for approval of generic versions of future medical and pharmaceutical advances is essential for timely propagation of these advances to the public at large.

#### CONCLUSION

The FDA must balance a constellation of concerns when regulating drugs. During premarket approval, the agency must weigh the need for consumer safety against the need to transmit technological advances to the public. When evaluating clinical trials, the agency must weigh the empirical efficacy of a drug against its toxicity. When implementing patent modifications, the agency must balance innovation-spurring market exclusivity with the public good of low-cost and widely available drugs.

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<sup>200</sup> In November 2010, for example, the FDA held a two-day hearing that featured over fifty academics, activists, lawyers, regulators, and industry representatives all speaking on the future of biosimilars. See *Approval Pathway for Biosimilar and Interchangeable Biological Products Public Meeting*, FDA.GOV, <http://www.fda.gov/Drugs/NewsEvents/ucm221688> (last updated Jan. 25, 2012).

<sup>201</sup> As Stroud explains:

"Some critics argue that any new biologics pathway will be so restrictive that it will do little to improve price competition. Others argue it is a scientific impossibility to achieve interchangeability between some biologics (due to their variable nature as living organisms) and so the FDA's efforts are doomed. The traditional model for interchangeability under Hatch-Waxman (bioequivalence) is based on the assumption that a single-molecule drug may be chemically synthesized by another laboratory and will have the same effect. With biologics, however, protein folding, cellular mutation, and environmental factors . . . can all contribute to wildly unpredictable results in any given final product."

Stroud, *supra* note 150, at 606 (footnotes omitted).

The approval and regulation of generic drugs constitutes another balancing act for the FDA—one that incorporates the above concerns and also involves a broader negotiation between innovator and generic manufacturers. At the heart of this negotiation is a fundamental, yet fraught, scientific-legal concept: functional identity between two drug products, or bioequivalence. The parameters of bioequivalence define the fate of pharmaceutical product lines by determining their value to innovators and their amenability to generic reproduction. So far, Congress and the courts have permitted the FDA to define and redefine these parameters on a case-by-case basis without legal consequences, despite the potential for both private and public harms. However, as courts are compelled to scrutinize agency procedures more closely, and as biotechnological innovation demands increasing legal and regulatory attention, the FDA may find that its preference for administrative flexibility is unsustainable.