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Obsolete to Useful to Obsolete Once Again: A History of Section 507 of the Food, Drug, and Cosmetic Act

GEORGE MALIHA*

ABSTRACT

Section 507 of the FDCA regulated antibiotic approval and production for decades. This paper explores the history of Section 507 and places it into the context of the history of antibiotic development. The paper also addresses the central paradox of Section 507. On one hand, Section 507 was one of FDA's first forays into regulating effectiveness, and it helped foster acceptance of broader pharmaceutical regulation. On the other, advances in medicine and science rendered the enactment anachronistic. In fact, FDA repurposed the program to facilitate generic development and drug testing, potentially delaying the provision's eventual repeal in 1997.

INTRODUCTION

In April 2012, ViroPharma sued FDA to enjoin it from granting approval to generic forms of the antibiotic vancomycin.[1] Vancomycin was first developed in 1947,[2] and the last core patent expired in 1996.[3] As a result, ViroPharma was forced to rely upon the extended exclusivity protection granted by the Hatch-Waxman Act, which was one of the few ways to keep generics off the market.[4] The case would have been easy had the drug been approved under the classic new drug approval pathway, Section 505[5] of the Food, Drug, and Cosmetic Act (FDCA). However, the drug was not approved

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1 ViroPharma, Inc. v. Hamburg, 898 F. Supp. 2d 1, 15–16 (D.D.C. 2012).

2 WALTER SNEADER, DRUG DISCOVERY: A HISTORY 303 (2005).

3 *ViroPharma*, 898 F. Supp. 2d at 10.

4 *Id.* The Hatch-Waxman Act, Pub. L. No. 98–417, 98 Stat. 1585 (1984), provides exclusivity to the developer of a compound by preventing FDA from approving a generic drug application (or declaring the effective date of an approval) for a period as well as granting patent-term extensions. *See* Marc S. Gross et al., *Generic Drug Approval Process, Post-1984: Hatch-Waxman Reform*, *in* THE PHARMACEUTICAL REGULATORY PROCESS 107, 108–10 (Ira R. Berry ed., 2005).

5 21 U.S.C. § 355 (2012). Section 505 provides the "classic" drug approval pathway that subjects new drugs to safety and effectiveness testing. Michael P. Peskoe, *The New Drug-Approval Process—Before and After 1962*, *in* PHARMACEUTICAL REGULATORY PROCESS, *supra* note 4, at 47, 53–58. Nearly all new small-molecule compounds go through this pathway today. *Id.*

under Section 505. Instead, vancomycin was approved under Section 507,[6] another provision of the FDCA that had since been repealed.[7] The Hatch-Waxman exclusivity provisions simply did not apply.[8]

The vancomycin suit is not a stand-alone incident. Several courts have had to deal with Section 507 in resolving patent disputes between generic and brand name pharmaceutical companies.[9] One exasperated judge declared "[i]t is unclear why the FDCA treated antibiotics differently than other drugs . . . ."[10]

This paper attempts to answer this judge's question. Section 507 has nothing to do with patent protection. Instead, Section 507 created a separate and—for a time—more rigorous regulatory framework for antibiotics, prescribing batch-by-batch certification of antibiotics, particular formulations for products, and more.[11] While the provision ceased to function as a separate regulatory device in 1982 and was repealed in 1997,[12] the story of Section 507 intertwines the history of medicine and the development of FDA into a robust regulatory agency. Its continued relevance to and complication of current disputes serves as a cautionary tale that an agency whose task is to regulate the cutting edge of medicine and science can easily fall behind the times. Nonetheless, when FDA commissioned[13] a set of illustrations to celebrate the thirtieth anniversary of the 1938 FDCA,[14] it chose to commemorate Section 507—alongside identification

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6 21 U.S.C. § 357 (1994), *repealed by* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, § 125, 111 Stat. 2296, 2325 (codified over various portions of Title 21 of the U.S. Code).

7 *ViroPharma*, 898 F. Supp. 2d at 7–8.

8 *Id.* at 21. While the case was at the preliminary injunction stage, *id.* at 5, ViroPharma also lost after a bench trial, *see generally* ViroPharma, Inc. v. Hamburg, 916 F. Supp. 2d 76 (D.D.C. 2013).

9 First, courts permitted FDA to keep antibiotics out of the Hatch-Waxman exclusivity provisions, so generic antibiotics could be marketed upon patent expiration. *See, e.g.*, Glaxo, Inc. v. Bowen, 640 F. Supp. 933, 936–38 (E.D.N.C. 1986). Second, courts permitted generic manufacturers to file abbreviated new drug applications (ANDAs)—a prerequisite to generic drug approval—without including a certification on patent infringement (typical ANDAs need to include such a certification to provide notice to the patent holder of the application). *See, e.g.*, Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339, 1350–51 (Fed. Cir. 2004). *See generally* Bayer Healthcare LLC v. Norbrook Labs., Ltd., No. 08-C-0953, 2009 WL 6337911, at *8 (E.D. Wis. Sept. 24, 2009) (attempting to sort through this same problem in the context of animal antibiotics, a slightly different statutory scheme that is not the focus of the paper).

10 Glaxo Grp. Ltd. v. Apotex, Inc., 272 F. Supp. 2d 772, 777 (N.D. Ill. 2003). *But see* Allergan, Inc. v. Crawford, 398 F. Supp. 2d 13, 17–18 (D.D.C. 2005) (beginning to discuss the history).

11 *See* 21 U.S.C. § 357(a) (1994); *see, e.g.*, 21 C.F.R. § 446 (1975) (describing the requirements for certification of tetracyclines).

12 *See* Exemption of Antibiotic Drugs and Antibiotic Susceptibility Medical Devices From Certification, 47 Fed. Reg. 39155 (1982) (all antibiotics); Exemption of Dermatologic and Vaginal Antibiotic Drug Products From Certification, 45 Fed. Reg. 71354 (1980); *see also Antibiotic Certification to End*, FDA CONSUMER, Feb. 1982, at 3, 3–4.

13 *30 Years of Scientific Achievement*, FDA PAPERS, Jun. 1968, at 17, 17 [hereinafter *Commemoration*].

14 Federal Food, Drug, and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938) (codified over various portions of Title 21 of the U.S. Code).

of unknowns,[15] synthetic hormone detection,[16] and natural poison assays.[17] The antibiotic certification commemorative print is reproduced at the end of this paper.[18]

To explore the history of and abstract the lessons from Section 507,[19] this paper proceeds in three parts: Part I will consider the period before the 1962 FDA Amendments, tracing the history of the human antibiotic certification program[20] from its birth in the mid-1940s. This section will argue that FDA pushed to expand the program, despite arguing that it would only be temporary. Part II will focus on the debates that bubbled over into the 1950s on the justification of the program. This section will posit that the program became unmoored from the policy goals it was supposed to serve as it formed a rhetorical basis for FDA's more aggressive efforts to police the pharmaceutical industry. Part III will consider the period after the 1962 Amendments and will discuss how the program became obsolete. This section will argue—counterintuitively—that the program's obsolescence might have contributed to the program's perpetuation.

I. Growing up with the science: the development of antibiotics and the certification program

Congress enacted the antibiotic batch certification program piecemeal. As some of the most revolutionary drugs of the twentieth century came onto the market, Congress and FDA lost sight of the origins of the program and its fundamental purpose. Although legal reasoning depends vitally on analogy, the reasoning technique has a different role for science and its regulatory apparatus.[21] As a result, what began as a useful program to ensure the quality of the nation's antibiotic supply evolved into something quite different.

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15 *Commemoration*, *supra* note 13, at 18, 20.

16 *Id.* at 18, 19.

17 *Id.* at 26, 28. The other items celebrated were analytical entomology, assays of multicomponent pills, and pesticide assays. *See generally id.*

18 *Id.* at 24.

19 For a brief review of the entire program, see generally Irving L. Wiesen, *FDA Antibiotic Regulatory Scheme: Then and Now*, *in* PHARMACEUTICAL REGULATORY PROCESS, *supra* note 4, at 241.

20 Although beyond the scope of this paper, certain animal antibiotics were certified as well. *See* 21 U.S.C. § 360b(n)(1) (1982) ("The Secretary . . . shall provide for the certification of batches of a new animal drug composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin, or any derivative thereof."); *see also* Animal Drug Amendments of 1968, sec. 101, Pub. L. No. 90–399, 82 Stat. 342, 350–51. This provision was repealed in 1988. Generic Animal Drug and Patent Term Restoration Act, § 107(a), Pub. L. No. 100–670, 102 Stat. 3971, 3984 (1988). Discussion of the special treatment of antibiotic exports, which do not have to comply with as many conditions as typical drugs, is also omitted. *See* 21 U.S.C. § 382(i) (2012) ("[A]ntibiotic drugs may be exported without regard to the requirements in this section if the insulin and antibiotic drugs meet the requirements of section 381(e)(1) of this title.").

21 *Cf.* Scott Brewer, *Exemplary Reasoning: Semantics, Pragmatics, and the Rational Force of Legal Argument by Analogy*, 109 HARV. L. REV. 923, 926 (1996) ("On the one hand, the methods associated with the natural and demonstrative sciences (deduction, induction, and abduction) also play a vital role in legal argument. On the other hand, theorists and practitioners in all intellectual disciplines, scientific and nonscientific alike, routinely rely on analogical reasoning.").

A. Penicillin

Penicillin was neither the first antibiotic nor the first effective treatment against infectious disease.[22] Nonetheless, it was one of the most revolutionary treatments of the twentieth century.[23] Yet, its discovery was fortuitous. The odd—and highly unlikely—circumstances surrounding the discovery of the compound in 1928[24] by Alexander Fleming[25] hinted at the fragility of the compound that made its manufacture so difficult initially:

> Firstly, on the floor beneath Fleming's laboratory, a colleague worked with moulds required for the production of vaccines to treat allergies, and it seems likely that one of these was wafted through the air into Fleming's laboratory to settle on a petri dish covered with a layer of agar impregnated with staphylococci. Secondly, this mould was a rare strain of *Penicillium notatum* that produced significant amounts of penicillin. Thirdly, Fleming left his culture plate on his work bench instead of placing it in an incubator at body temperature to ensure bacterial growth. Fourthly, an exceptionally cool spell followed when Fleming went on holiday at the end of July, which favoured growth of the mould in preference to that of the staphylococci. Fifthly, the climatic conditions changed later in the month, by which time the mould had produced sufficient penicillin to kill bacteria in its vicinity. The rise in temperature allowed colonies of staphylococci to grow elsewhere on the culture plate, thus enabling Fleming to observe a zone of inhibition of staphylococcal growth when he returned to the laboratory on 3 September.[26]

In yet another stroke of fate, because of previous work on another antibacterial, Fleming was uniquely positioned to study the properties of his new discovery.[27]

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[22] *See* SNEADER, *supra* note 2, at 287 (describing the process of extracting and studying Pyocynase); Lorenzo Zaffiri, Jared Gardner, & Louis H. Toledo-Pereyra, *History of Antibiotics. From Salvarsan to Cephalosporins*, 25 J. INVESTIGATIVE SURGERY 67, 67–69 (2012) [hereinafter Zaffiri et al.] (describing the discovery and development of the Sulfa and organoarsenic class of drugs); *see also* HELMUTH M. BÖTTCHER, MIRACLE DRUGS: A HISTORY OF ANTIBIOTICS 19–123 (Einhart Kawerau, trans., 1963) (1959) (describing antibiotic "remedies" in the pre-modern science era).

[23] *See, e.g.*, GLADYS L. HOBBY, PENICILLIN: MEETING THE CHALLENGE xvii (1985) ("The discovery of penicillin ranks among the most significant discoveries of mankind.").

[24] SNEADER, *supra* note 2, at 289.

[25] Other scientists had stumbled on fungi in the genus *Penicillium* producing a form of penicillin. For instance, the French physician Ernest Duchesne had briefly studied the antibiotic properties of the mold. However, the observations were not widely disseminated at the time. *See* BÖTTCHER, *supra* note 22, at 140–42. *But see* HOBBY, *supra* note 23, at 4–5 (noting that Duchesne never "actually demonstrated a substance with antibacterial properties").

[26] SNEADER, *supra* note 2, at 289.

[27] *Id.* at 289–90; *see also* HOBBY, *supra* note 23, at 15.

Although Fleming never progressed to human trials,[28] others, such as Howard Florey and Ernst Chain,[29] did.[30]

The first human trials of penicillin foreshadowed the issues Congress considered when attempting to regulate penicillin production—how to ensure pure extractions of the antibiotic and how to produce enough to treat people. Purification of the broth surrounding the mold was imperfect. In around 1940, at a time with few human subject research protections, Florey administered penicillin to a terminal breast cancer patient to determine suitability for further human trials.[31] The impurities in the mold broth caused a severe allergic-type reaction.[32] American tests on two patients conducted in late 1940 and early 1941 noted similar reactions even though the antibiotic produced a dramatic clinical effect on infectious disease.[33] The trials demonstrated that penicillin could be revolutionary if enough pure substance could be produced.[34] Indeed, Florey would resort to purifying penicillin from treated patients' urine and confine his studies to children (who required lower doses) to maintain and preserve his limited supply.[35]

Penicillin was a fragile and difficult-to-produce molecule partly because of its mechanism of action against bacteria.[36] Initial preparations were attempts to step up small-scale, petri dish fermentation. For instance, when Chain found that metal fermentation vessels destroyed penicillin, British scientists resorted to enamel-coated bedpans to begin to make more.[37] An American researcher described her predicament circa 1941:

> Our own facilities for producing the substance were little better than Fleming's. Within a few weeks after starting work on penicillin, it was clear that large volumes of fermentation liquor would be needed if sufficient drug was to be available for clinical use. Soon hundreds of two-liter flasks with *Penicillium notatum* growing on a modified [culture] medium lined *every classroom laboratory bench at the Columbia University Medical School*. We had no adequately large incubator and no

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[28] *See* HOBBY, *supra* note 23, at 12 ("Many have questioned why Fleming never tested the systemic chemotherapeutic activity of penicillin.").

[29] There were many investigators in the early days of penicillin and who-exactly-did-what and what country deserves the credit remain a topic of dispute. *See* Edward Abraham, *Foreword* to JOHN C. SHEEHAN, THE ENCHANTED RING: THE UNTOLD STORY OF PENICILLIN vii, vii–x (1982) (describing how previous accounts ignore the American perspective in the research project). This dispute is beyond the concern of this paper.

[30] As there are many histories of the discovery of penicillin and its clinical development, I do not wish to extensively rehash well-trodden ground. *See* SNEADER, *supra* note 2, at 290–92; *see also* HOBBY, *supra* note 23, at 48–68 (describing early trials in animals); Abraham, *supra* note 29, at 27–32.

[31] Abraham, *supra* note 29, at 32–33.

[32] *Id.* at 33. Interestingly, Florey "held doggedly to the conviction that the problem was not with the penicillin itself but with the impurities still present in the fermentation broth." *Id.*

[33] HOBBY, *supra* note 23, at 72.

[34] *Id.* at 73 ("From January 1941 on, it had been clear that if properly purified and available in sufficient quantity, penicillin could be used . . . probably effectively in the treatment of infections due to susceptible microorganisms.").

[35] *See* Abraham, *supra* note 29, at 33–34.

[36] Penicillin works by chemically attacking certain molecules on the bacterial cell wall. *See* Zaffiri et al., *supra* note 22, at 70.

[37] BÖTTCHER, *supra* note 22, at 168–69.

> space in our own small laboratory for such large numbers of flasks, but moved in and out of classrooms as the students moved out and in.[38]

Research began to increase yields. Through an accident of New Deal agricultural policy, a government lab discovered that corn derivatives stimulated *Penicillium*.[39]

The outbreak of the Second World War increased purification and supply problems, but it also encouraged the federal government to wade into the penicillin problem.[40] The federal government began to coordinate and fund scientific research for the war effort through the Office of Scientific Research and Development (OSRD).[41] For instance, one OSRD project was assisting commercial manufacturers in trials to industrialize the fermentation of penicillin.[42] Ultimately, the government was successful in industrializing the fermentation of penicillin,[43] although Washington still chose to ration civilian supplies of the antibiotic.[44]

The question of regulation first arose with increased antibiotic production. Although antibiotic regulation eventually became subject to FDA regulation, the Public Health Service (PHS) initially took regulatory initiative. First, the PHS regulated arsenicals, which were one of the first effective classes of antibiotics and used widely in the First World War.[45] Second, the PHS regulated products made by harnessing living organisms through a system of factory inspection and certification of product samples.[46] However, the service was reluctant to assume regulatory duties, which lead

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38 HOBBY, *supra* note 23, at 75 (emphasis added).

39 The now-famous Northern Regional Research Laboratory was not initially meant as a biomedical research lab—but a way to stimulate demand for American agriculture. *See* HOBBY, *supra* note 23, at 87, 90.

40 *See* Roswell Quinn, *Rethinking Antibiotic Research and Development: World War II and the Penicillin Collaborative*, 103 AM. J. PUB. HEALTH 426, 427 (2013) ("At the onset of World War II, *Penicillium notatum*, the mold made famous by Alexander Fleming in 1928, was well recognized for its ability to inhibit the growth of certain bacteria in laboratory experiments. The pharmaceutical popularly known as penicillin, however, did not exist. Although several American pharmaceutical firms had examined Fleming's widely distributed mold, none had continued to develop its potential, and it remained a curiosity. American officials only began to take the compound's potential seriously in the summer of 1941, after a visit by Oxford scientists Howard Florey and Norman Heatley." (footnote removed)); *id.* at 427–28 ("Extensive coordination by government agencies made this collaboration possible. The Office of Scientific Research and Development initiated US involvement with penicillin and oversaw most of the scientific work prior to 1943.").

41 *See* HOBBY, *supra* note 23, at 92.

42 *See* THE ENCHANTED RING, *supra* note 29, at 69–71. Interestingly, while the government encouraged private efforts at fermentation, it kept control of research into the chemical synthesis of penicillin. *Id.* at 49. The rational organic chemical synthesis would not be first worked out until 1957. *See id.* at 157–60.

43 *Id.* at 78; *see also* James Robert Dean, *FDA at War: Securing the Food That Secured Victory*, 53 FOOD & DRUG L.J. 453, 497 (1998).

44 *See generally* DAVID P. ADAMS, "THE GREATEST GOOD TO THE GREATEST NUMBER": PENICILLIN RATIONING ON THE AMERICAN HOME FRONT, 1940–1945 (1991).

45 *See, e.g.*, Dale Cooper, *The Licensing of German Drug Patents Confiscated During World War I: Federal and Private Efforts to Maintain Control, Promote Production, and Protect Public Health*, 54 PHARMACY HIS. 3, 4–7 (2012). That authority would be codified in a 1944 revision of the PHS statute. *See* Terry S. Coleman, *Early Developments in the Regulation of Biologics*, 71 FOOD & DRUG L.J. 544, 588 (2016).

46 Coleman, *supra* note 45, at 559–63, 567–72.

it to narrowly interpret its regulatory purview in some areas.[47] For instance, the agency essentially abdicated regulation of so-called "glandular products"—such as insulin—to FDA.[48] Further, FDA had taken interest in antiseptic products used to disinfect objects or wounds.[49]

FDA filled the regulatory void left by the PHS.[50] In September 1943, even under erstwhile military control, FDA began to informally request New Drug Applications (NDAs) and 25,000-unit[51] samples of each batch of penicillin produced.[52] The military helped enforce FDA requirements by mandating FDA inspection in purchasing specifications.[53] Thus, FDA prepared to take over oversight of the nation's penicillin producers and supplies.[54]

Against this backdrop, in 1945, FDA went to Congress to formalize its program to regulate a drug "produced by a biological process occasionally attended by unexplainable mishaps."[55] The New Deal had already fostered American acceptance of a more regulatory state. Regulation was especially welcome in the drug industry,

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[47] *See id.* at 573 ("In the early decades of the 1902 Act, there were drugs on the market that were arguably subject to licensing—even under the narrow interpretations that PHS had ascribed to the statutory classes—but that PHS nevertheless concluded were outside its jurisdiction. Those decisions were driven in large part by a view that the products were probably ineffective and declaring them to be outside the Act avoid licensing any more ineffective products than necessary. The decisions may also have been based in part on conclusions that the products were probably safe and that the inspection and licensing mechanism of the 1902 Act were unnecessary to protect the public."). *But see id.* at 582 ("This section describes product classes that were not obviously subject to licensure but that PHS reached out to regulate.").

[48] *See id.* at 601–03. Indeed, FDA had been working on hormone or glandular products since at least the late 1920s. *See, e.g.*, REPORT OF THE FOOD, DRUG, AND INSECTICIDE ADMINISTRATION 8 (1928) ("Because of the need for the standardization of glandular products, detailed studies were begun on the anterior lobe of the pituitary body, with a view to elaborating a method of assay.").

[49] *See generally* U.S. DEP'T OF AGRIC., FOOD, DRUG, AND INSECTICIDE ADMIN., FAKE ANTISEPTICS AND THE LAW (1930).

[50] *See* Coleman, *supra* note 45, at 604 ("The precedent established by the insulin legislation was followed a few years later when penicillin, which is arguably a biologic, was introduced and required lot-release testing. Congress placed the authority over penicillin in the FDCA." (footnote removed)). See note 68 and accompanying text for the insulin story. Indeed, even though the NIH certified biologics facilities, it did not do so for antibiotics. *See generally* U.S. DEP'T OF HEALTH, EDUC., & WELFARE, PUB. HEALTH SERV., BIOLOGICAL PRODUCTS: ESTABLISHMENTS LICENSED FOR THE PREPARATION AND SALE OF VIRUSES, SERUMS, TOXINS AND ANALOGOUS PRODUCTS, AND THE TRIVALENT ARSENIC COMPOUNDS (1966).

[51] A unit of penicillin is a quantity of penicillin that produces a certain antibacterial activity. Its definition has been altered slightly over time. *See generally* J.H. Humphrey, M.V. Mussett, & W.L.M. Perry, *The Second International Standard for Penicillin*, 9 BULL. WORLD HEALTH ORG. 15 (1953).

[52] FDA, ANNUAL REPORT, FEDERAL SECURITY AGENCY, 1945, at 3 (1945) [hereinafter 1945 REPORT]; HOBBY, *supra* note 23, at 187 ("In this informal manner, the Food and Drug Administration initiated a program that later became time consuming, costly, and unwieldy, but generally effective in controlling the safety and efficacy of all penicillin manufactured in the United States for clinical use."); *see also* FDA, FEDERAL SECURITY AGENCY, FOOD AND DRUG ADMINISTRATION, ANNUAL REPORT, 1944, at 3 (1944).

[53] Walton Van Winkle, *Drug Certification*, *in* DRUG RESEARCH AND DEVELOPMENT 398, 399 (Austin Smith & Arthur D. Herrick eds., 1948).

[54] *See* Dean, *supra* note 43, at 498–99.

[55] 1945 REPORT, *supra* note 52, at 11. One set of litigants proposed claimed to have unearthed unpublished documents that evince a legislative intent to promote equal competition among penicillin manufacturers. This argument was rejected. *See* Barr Labs., Inc. v. Harris, 482 F. Supp. 1183, 1185 n.* (D.D.C. 1980).

where policymakers perceived a market failure.[56] Although the motivation is unclear,[57] even the pharmaceutical industry supported formalizing the batch certification program at first.[58] Drug manufacturers conditioned their support on three conditions: first, antibiotic certification was not a backdoor to general pharmaceutical regulation;[59] second, the regulation was temporary and would be relieved as manufacturing techniques improved;[60] and third, FDA would expedite certification processes to prevent unnecessary delay.[61] All the conditions were arguably broken in the forty-year history of the program. Nonetheless, the second condition for drug manufacturer support—that the measure was temporary—deserves full reproduction since it highlights some of the early problems of penicillin production and the idea that FDA would step out of the way once problems were resolved:

Certification of penicillin is not expected to be a permanent procedure. It is offered as an extra measure of protection for a limited period of time due to uncertainties which have appeared to exist in the assay of penicillin and the possibility that there may be initial uncertainties attendant upon the assay of new penicillin preparations, particularly in the case of companies who have not previously worked with penicillin. Penicillin is a chemical produced by a fermentation process. *It is to be expected that within a reasonable period of time tests and assays for this drug will become sufficiently satisfactory to warrant regulations terminating certification requirements as is contemplated in section 507 (c)* [of the 1938 FDCA].[62]

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[56] *Cf.* PETER TEMIN, TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES 54–55 (1980) ("As a result of the Depression, policymakers in the federal government lost faith in the ability of the market economy to protect people from a variety of economic and noneconomic ills, and the New Deal moved in to substitute regulatory protection. The FDA's regulation . . . was simply a logical extension of this view."). *But see* DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 10 (2010) ("Nor does the power of American government in pharmaceutical regulation stand as a simple reflection of a democratic 'popular will' or a straightforward response to a 'market failure.' While FDA's power in pharmaceutical regulation has depended heavily upon broad popular support for its governing role, numerous facets of that power—authority over drug production and medical research, conceptual influence in science, and the many uses of gatekeeping—were shaped much more by regulatory officials themselves.").

[57] *See* TEMIN, *supra* note 56, at 57 ("The drug manufacturers did not object to government control over the quality of antibiotic drugs . . . They did not record their motives . . . Quality control . . . may have increased the costs of new and small firms more than those of established manufacturers and functioned as a partial barrier to entry.").

[58] *See, e.g.*, H.R. REP. NO. 79–702, at 13–15 (1945) (letters of the American Drug Manufacturers Association & Proprietary Association of America); *see also* John J. Powers, *Some Aspects of Certification of Antibiotics Under the Federal Food, Drug, and Cosmetic Act*, 4 FOOD DRUG COSM. L.Q. 337, 341 (1949) (A pharmaceutical company's general counsel states "[w]hen the penicillin legislation was first proposed, all interested parties were invited by the Food and Drug Commissioner, Dr. Paul B. Dunbar to meet with him to discuss the many problems inherent in that unique situation. Under the circumstances . . . he received the full cooperation and approval of the drug industry . . .").

[59] H.R. REP. NO. 79–702, at 14 ("The assurance from the Food and Drug Administration that pretesting and certification of penicillin is not a method of drug control to be generally extended.").

[60] *Id.*

[61] *Id.* ("The Food and Drug Administration plans to arrange for the running of tests and assays to provide the most rapid certification and thus assist in making this critical drug available to the public with the least delay.").

[62] *Id.* (emphasis added).

The Acting Administrator of the Federal Security Agency, an independent agency that housed FDA in the 1940s and early 1950s,[63] concurred that the regulation was specific to penicillin and that technological developments might make the certification unnecessary.[64] However, within a year, the Administrator noted that certification could apply to new, non-antibiotic drugs.[65] In any case, both houses of Congress approved the amendment on voice vote alone,[66] and FDA was mandated to check every batch of penicillin produced in the United States for human consumption.[67]

Congress analogized the certification program to other effectiveness-based FDA programs of the time, such as batch-by-batch certification of insulin[68] and "coal tar"[69] colors, and enacted a self-sustaining batch certification program[70] supported by user fees.[71] FDA was to promulgate regulations, develop standards for batches, and set expiration dates for the batches.[72] Individuals could petition FDA to change its regulations[73] (presumably to end certification), but Congress mandated that only drugs intended for research or internal manufacturing use be exempted from the certification program.[74] Importantly for the Hatch-Waxman issues discussed in the introduction,

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63 Mariano-Florentino Cuéllar, *"Securing" the Nation: Law, Politics, and Organization at the Federal Security Agency, 1939–1953*, 76 U. CHI. L. REV. 587, 601 & n.35, 614–15 (2009).

64 H.R. REP. NO. 79–702, at 11 ("It is recognized that control measures of this character are essential only in such special cases as insulin and penicillin products. Because of the newness of penicillin and the possibility of developments in manufacturing technology and otherwise that may obviate the need for special control the suggested amendment provides for the termination of certification requirements with respect to any penicillin product whenever the facts warrant.").

65 *See* Van Winkle, *supra* note 53, at 411–12 (discussing a letter between an industry representative and the Administrator).

66 91 CONG. REC. 6289–90 (1945) (House of Representatives); *id.* at 7113 (Senate).

67 Act of July 6, 1945, ch. 281, 59 Stat. 463.

68 Section 506 of the FDCA, the insulin regulation, was prompted by the loss of patent protection on the product. Through patent exclusivity, the Insulin Committee of the University of Toronto had regulated and standardized production. Congress mandated batch-by-batch certification in order to take the place of this standardization organization. *See* H.R. REP. NO. 77–1542, at 1 (1941); *see also* MICHAEL BLISS, THE DISCOVERY OF INSULIN 133 (25th Anniversary Ed., 2007) (Patenting "was to be a purely defensive manoeuvre, one which would never stop anyone else from making the extract. In fact the point was to stop anyone from ever being in a position to stop anyone else . . . ."). The law was passed by voice votes. Act of December 22, 1941, ch. 613, 55 Stat. 851 (codified before repeal in 1997 at 21 U.S.C. § 356 (1994)); 87 CONG. REC. 9988–89 (1941) (House of Representatives); *id.* at 10,017 (Senate). For more information on the program, see generally Annabel Hecht, *Insulin Standards: Precision With A Purpose*, FDA CONSUMER, Apr. 1977, at 12. Ironically, commercial insulin on the American market has never been free of patent protection. *See generally* Jeremy A. Greene & Kevin R. Riggs, *Why Is There No Generic Insulin? Historical Origins of a Modern Problem*, 372 NEW ENG. J. MED. 1171 (2015).

69 "Coal tar" color certification is another potential analog, though the program was based on safety alone. Section 504 of the FDCA. 21 U.S.C. § 354 (1946). The program continues today at Section 721 of the FDCA. *See* 21 U.S.C. § 379e(c) (2012) ("The Secretary shall further, by regulation, provide (1) for the certification, with safe diluents or without diluents, of batches of color additives . . . ."). The program had its origins in the enforcement of the Food and Drugs Act of 1906. *See* Van Winkle, *supra* note 53, at 399. *See generally* G. Robert Clark, *Certification of Coal-Tar Colors*, 71 PUB. HEALTH REP. 581 (1956).

70 21 U.S.C. § 357(a) (1946).

71 *See id.* § 357(b) ("such fees . . . as are necessary to provide, equip, and maintain an adequate certification service.").

72 See *id.*

73 *See id.* § 357(f).

74 *See id.* § 357(d).

penicillin was exempted from the new drug provisions of Section 505 of the FDCA, and certification entailed some proof of effectiveness.[75]

FDA spelled out its certification process more explicitly in a congressional hearing for expansion of the certification authority:

> In order to test the effectiveness of the drug against bacteria, there is a standard procedure by which we establish the zone of bacterial inhibition. Plates of this general type with culture mediums, flat plates, culture places, are prepared.
>
> . . . .
>
> In addition to that, we have to determine certain toxicity factors. One of those factors is pyrogenicity. That is the presence of impurities that cause elevated temperatures in patients. That is done by using rabbits as test animals. The injections are made in the ear of the rabbit, which is kept in a fixed position by a series of stocks. As a matter of fact, these rabbits live for years. They are getting doses of penicillin continuously and they are perfectly comfortable and happy.
>
> After a certain period of time, the rectal temperature of the rabbit is determined in order to find whether there has been any elevation of temperature due to the administration of this drug.
>
> Then there are certain other toxicity tests. We use white mice for acute toxicity tests; certain determinations of moisture are also made. That is about the list of them.[76]

Nearly 20 years later, a 1968 article in *FDA Papers* described some additional tests for purity and sterility and also described similar bacterial inhibition and pyrogen testing (rabbits and all).[77]

The post-war pharmaceutical and research boom soon forced Congress and FDA to revisit their handiwork with a revolutionary new antibiotic that could treat tuberculosis.

B. Streptomycin

As a student in 1915, Selman Waksman and his professor isolated an organism from soil, which became known as *Streptomyces grisesus*.[78] In 1943, while working on the organism he helped isolate at the beginning of his career, Waksman found what

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[75] *See id.* § 357(e); Van Winkle, *supra* note 53, at 420.

[76] *To Amend The Federal Food, Drug and Cosmetic Act: Hearings on H.R. 3151, H.R. 562, & H.R. 160 Before a Subcomm. of the H. Comm. on Interstate and Foreign Commerce*, 81st Cong. 7–8 (1949) (testimony of Dr. P.B. Dunbar, Comm'r of Food & Drugs) [hereinafter *Aureomycin, Chloramphenicol, & Bacitracin Hearings*].

[77] William W. Wright & Amiel Kirshbaum, *Testing and Certifying Antibiotic*, FDA PAPERS, May 1968, at 21, 23–24.

[78] SELMAN A. WAKSMAN, THE CONQUEST OF TUBERCULOSIS 117 (1964). Although Selman did not come to the antibiotic problem until the late 1930s, he would isolate many compounds from soil fungi. *See* SNEADER, *supra* note 2, at 300; SELMAN A. WAKSMAN, THE ANTIBIOTIC ERA: A HISTORY OF THE ANTIBIOTICS AND OF THEIR ROLE IN THE CONQUEST OF INFECTIOUS DISEASES AND IN OTHER FIELDS OF HUMAN ENDEAVOR 11 (1975) [hereinafter THE ANTIBIOTIC ERA]. Some of these compounds would become immunosuppressants or laboratory antibiotics. SNEADER, *supra* note 2, at 300.

became streptomycin.[79] Streptomycin could treat diseases that penicillin could not, including tuberculosis.[80] As with penicillin, the U.S. military initially controlled supplies of streptomycin[81] However, even as late as 1949, a researcher remarked:

> While penicillin is now a veteran antibiotic, which has behind it a well-established reputation and several hundred thousand case histories, streptomycin still has to achieve full recognition. Relatively, it is a new drug, for it has been clinically tested for only four years. The supply of streptomycin is still insufficient, the production slow and costly.[82]

Although informal testing had already begun,[83] in early 1947, FDA returned to Congress to request formal authority to batch test streptomycin.[84] FDA drew many parallels to the penicillin legislation that had been passed two years before, noting that "[s]treptomycin, like penicillin, is a biological product and its manufacture and testing are subject to the same kind of unexplained vagaries that characterize the production of penicillin."[85] In fact, FDA grouped streptomycin with penicillin and insulin:

> All three of these drugs—streptomycin, penicillin, and insulin—present problems of a common pattern in the importance of their need for effective control in the interest of public health. They are all highly efficacious for one or more serious disease; they all present unusual difficulties in the process of manufacturer and the methods of testing finished lots, and for this reason are prone to depart from standards of identity, quality, and purity appropriate to insure safety and efficacy of use.[86]

The agency noted that streptomycin displayed some dose-related side effects that could be more debilitating than those of penicillin, further supporting the need for Congressional action.[87] Once again, FDA stressed the temporary nature of the measure, positing that "[i]t is probable that as improved techniques in manufacture and better methods of testing are developed, the need for pretesting and certification of streptomycin may no longer exist."[88] Though no letter from the pharmaceutical

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79 THE ANTIBIOTIC ERA, *supra* note 78, at 119.

80 BORIS SOKOLOFF, THE MIRACLE DRUGS 192 (1949). Though a bit of an exaggeration, "[b]y happy coincidence, streptomycin is effective where penicillin is powerless." *Id.* at 193.

81 FDA, ANNUAL REPORT, FEDERAL SECURITY AGENCY, 1947, at 547 (1947) [hereinafter 1947 REPORT].

82 SOKOLOFF, *supra* note 80, at 192. *See generally* Max Tishler, *Production and Isolation of Streptomycin*, *in* STREPTOMYCIN: NATURE AND PRACTICAL APPLICATIONS 32 (Selman A. Waksman ed., 1949).

83 *See* 1947 REPORT, *supra* note 81, at 547; *see also* S. REP. NO. 80–45, at 1 ("At the present time samples from each batch of streptomycin produced are being tested by the Food and Drug Administration before they are released for distribution. This service is being carried on through cooperative arrangements with the War and Navy Departments, who have been purchasing most of the output, and under an order by the Civilian Production Administration, operating through the authority of temporary legislation.").

84 H.R. REP. NO. 80–75, at 1 (1947).

85 *Id.* at 2.

86 *Id.*

87 *Id.*

88 *Id.*

manufacturers appeared in the record,[89] according to FDA, the pharmaceutical industry concurred.[90] After confirming industry acceptance—or at least acquiescence—the bill passed on voice votes.[91]

The accelerated development of antibiotics would bring FDA to Congress within a few years.

C. Aureomycin/Chlortetracycline,[92] Chloramphenicol, & Bacitracin

The next antibiotics were discovered in rapid succession through the 1940s. An accomplished University of Wisconsin plant botanist, Benjamin Duggar, joined Lederle Laboratories to investigate antibiotics.[93] One of his initial projects was to improve fermentation yields of streptomycin.[94] To do so, he enlisted a global soil collection campaign by Lederle employees and labs to search for more strains of *Streptomyces* and other antibiotic-producing soil organisms.[95] In 1948, after three years of analysis and thousands of experiments, he found something new: aureomycin.[96] Aureomycin, like streptomycin, arose from a species of *Streptomyces*, in this case the red-gold-colored *Streptomyces aureofaciens*.[97] Although not used in humans today, Aureomycin formed the basis of the tetracycline-class of antibiotics.[98]

Similarly, chloramphenicol arose from a global soil survey coordinated by Yale botanist Paul Burckholder and funded by Parke, Davis, & Co.[99] This time, a Venezuelan soil organism, *Streptomyces venezuelae*, provided the compound.[100] Chloramphenicol was first used to treat twenty-two Venezuelan patients suffering

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89 This fact is telling according to the general counsels of two pharmaceutical companies. *See* Frank A. Duckworth, *Antibiotic Certification—A Reappraisal After 16 Years' Experience*, 17 FOOD DRUG COSM. L.J. 229, 232 (1962) ("Considerable opposition was expressed to this proposal. First, the standards were expressed in such generalities that little protection would be afforded against arbitrary interpretations. Only a short time before, spokesmen for the Administration had stated on numerous occasions that they would not seek the extension of this special type of control to drugs generally, and that they did not have in mind 'the extension of the principle of pretesting to any other product or group of products.'"); Powers, *supra* note 58, at 344.

90 *See* H.R. REP. NO. 80–75, at 3; *see also To Amend the Federal Food, Drug, and Cosmetic Act of June 25, 1938, as Amended: Hearing on H. R. 2045 Before the H. Comm. on Interstate and Foreign Commerce*, 80th Cong. 9 (1947) (statement of Chairman Rep. Charles A. Wolverton) ("The letter [from the Administrator of the Federal Security Agency] is very complete. It indicates that the matter has already been taken up with the interested industry, and there is no opposition to is part.").

91 Act of March 10, 1947, ch. 16, 61 Stat. 11; 93 CONG. REC. 1628 (1947) (House); *id.* at 1704 (Senate).

92 Aureomycin is a trade name, not a generic/chemical name. Congress would alter the term to the generic in the legislation. *See* Act of August 5, 1953, Pub. L. No. 83–334, 67 Stat. 389.

93 BÖTTCHER, *supra* note 22, at 178–79.

94 *Id.* at 180.

95 *Id.*

96 *See id.* at 182.

97 SOKOLOFF, THE MIRACLE DRUGS, *supra* note 80, at 220.

98 SNEADER, *supra* note 2, at 303–04.

99 *Id.* at 302.

100 *Id.* at 303.

under a typhoid outbreak.[101] All were cured.[102] By 1949, Parke-Davis worked out a synthesis and began to mass-produce the antibiotic.[103] The compound helped make the firm the largest pharmaceutical company in the world by the early 1950s.[104]

Bacitracin broke the mode of soil-survey-and-antibiotic-development. Frank Meleney,[105] a professor of surgery and head of a bacteriological laboratory at Columbia University Medical School,[106] was one of many tinkering with the idea that different strains of bacteria can inhibit one another.[107] He was able to isolate a bacterium—*Bacillus subtilis*—from the debrided tissue of one of his patient's legs.[108] The organism produced Bacitracin,[109] a substance that can inhibit some types of bacterial growth.[110]

In 1949, FDA returned to Congress. In now familiar language, FDA argued that the production of antibiotics was "subject to the same kind of unexplained vagaries that characterize the production of all biological products."[111] Indeed, the agency echoed the arguments for incorporating streptomycin into the regulatory scheme, for "in some instances at least, the need for predistribution checking is even greater [with bacitracin[112]] than with penicillin."[113] Again, FDA declared that once "improved techniques" were developed, the certification program would likely no longer be needed.[114] Industry also concurred,[115] though not universally.[116] Some industry representatives were outright opposed, with one commenting that "the inclusion of all three of these last antibiotics within the purview of Section 507 does violence at least to his own previous conceived notions as to the type of product properly belonging

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101 *Id.*

102 *Id.*

103 *Id.*

104 *Id.*

105 Other groups have claimed that they identified the antibiotic first, but it appears that these previous discoveries did not lead to commercialization and wide-spread use in medicine. *See* SOKOLOFF, THE MIRACLE DRUGS, *supra* note 80, at 214–15.

106 William R. Sandusky, *Frank L. Meleney: Pioneer Surgeon-Bacteriologist*, 118 ARCHIVES SURGERY 151, 151–54 (1983).

107 SOKOLOFF, THE MIRACLE DRUGS, *supra* note 80, at 211.

108 *Id.* at 212–13.

109 The name comes from *Bacillus* + Tracey, the surname of the patient from whom the bacteria was isolated. *Bacitracin Reports*, Archives & Special Collections, COLUM. U. HEALTH SCIS. LIBR. (1943-1949), http://library-archives.cumc.columbia.edu/finding-aid/bacitracin-reports-1943-1949 [https://perma.cc/76ZU-JENL].

110 SOKOLOFF, THE MIRACLE DRUGS, *supra* note 80, at 212-13.

111 S. REP. NO. 81–600, at 3 (1949).

112 Interestingly, the other antibiotics were not mentioned.

113 *Id.*

114 *Id.*

115 *Id.*

116 *See Aureomycin, Chloramphenicol, & Bacitracin Hearings*, *supra* note 76, at 9 (testimony of Dr. Dunbar) ("I state that requests for certification legislation on these three antibiotics have been made by the manufacturers. That is true in the case of Lederle Laboratories and Commercial Solvents. I was wrong in stating that Upjohn had requested this amendment. However, they have agreed to it; and Parke-Davis, also.").

under that section."[117] Indeed, FDA could not get the pharmaceutical industry to agree to just apply Section 507 to all antibiotics, although that was the policy that FDA likely favored.[118] Yet, though hinting a future change of position, FDA continued to confirm that this program was to be temporary and not the norm going forward for all antibiotics:

> If the same conditions develop in the case of newly developed antibiotics that exist here—that is to say, biological tests with resulting vagaries—if the articles developed are of such value as a therapeutic agent as are the present ones, it would be my notion that it would be necessary or desirable to have similar amendments to cover the new ones.
>
> *On the other hand, I think the time will come—in fact, it probably is here now—when the expertness of the manufacturers has reached a point where they can develop a uniform and very potent product which will not vary materially from day to day.* That situation has already been reached in the case of crystalline penicillin G and tomorrow's Register[[119]] will publish a proposed announcement for decertification of penicillin G.[120]

As discussed in Part III, few other antibiotics types would be exempted until the 1980s.[121]

The third and final 1940s expansion to the antibiotic certification law once again passed on voice votes.[122] However, industry opposition and discomfort with the

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117 Powers, *Some Aspects of Certification*, *supra* note 58, at 346–47.

118 *See id.* at 10 ("[T]here have been certain drafting difficulties presented in the formulation of a general antibiotic amendment . . . . We have been considering it very seriously. We have in fact attempted and are still attempting with a committee from the industry to draft such an amendment in general terms which would be acceptable to everybody. We have not yet reached that point, however, where there is a meeting of the minds sufficiently for us to feel that we should come before the committee and ask for that kind of an amendment. But we are working on it. In the meantime, the pressure for these three makes it highly desirable to have them put under the statute.").

119 *See* 14 Fed. Reg. 1770 (1949) (codified at 21 C.F.R. § 146a.25(f) (1955)). No reason for exemption—beyond a perfunctory declaration that certification was no longer needed—was given in the federal register notice. *See id.*

120 *Aureomycin, Chloramphenicol, & Bacitracin Hearings*, *supra* note 76, at 10 (testimony of Dr. Dunbar) (emphasis added).

121 *See* note 12 and accompanying text. There would be three exemptions granted to antibiotic *formulations* as opposed to manufactures or antibiotic class, namely Crystalline Penicillin G, Buffered Crystalline Penicillin, and Bacitracin Ointment/Zinc Bacitracin Ointment. *See* Steven Strauss, *Legal Aspects of Antibiotic Certification*, DRUG & COSM. INDUSTRY, Mar. 1982, at 41, 42. Citing "accumulated data showing that some batches of penicillin currently exempt from certification have been found to be non-sterile [and the fact that] . . . . many batches of bacitracin ointment . . . have been found to be subpotent," 36 Fed. Reg. 14477, 14477 (1971) (proposed rule), FDA revoked the three exemptions in 1972, *see* 37 Fed. Reg. 3426, 3426–27 (1972). However, FDA annual report for 1971 does not note any particular change in quality, declaring that 0.75% of the 15,500 total antibiotic batches failed. *See* FDA, ANNUAL REPORT 1950–1974 ON THE ADMINISTRATION OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND RELATED LAWS 771 (1976) [hereinafter COLLECTED ANNUAL REPORTS]. Nonetheless, industry was not particularly pleased with the few exemptions granted. *See* Paul Gerden, *A Further Review of the Antibiotic Law*, 9 FOOD DRUG COSM. L.J. 710, 715 (1954) [hereinafter Gerden, *Further Review*] ("[M]any of the exemptions granted are inconsequential when related to products still certifiable. Several of those decertified are in specified forms only, for which testing and the requisite fee are still required prior to distribution in certain dosage forms.").

122 95 CONG. REC. 6252 (1949) (House); *id.* at 8927 (Senate); *see also* Act of July 13, 1949, ch. 305, 63 Stat. 409.

regulatory scheme built in the 1950s as the program became enmeshed in a larger debate on reforming the nation's drug regulatory system.

II. A program that finds its way again: antibiotic certification in the 1950s and its role in expanding FDA authority

Industry and FDA continued discourse on the antibiotic certification program into the 1950s. The program became important to both sides as Congress began deliberating on the 1962 FDCA Amendments.

A. The Antibiotic Certification Program in the 1950s: A Prelude

In the 1950s, a peculiar dichotomy developed between the certified antibiotics—penicillin, streptomycin, chlortetracycline, chloramphenicol, and bacitracin—and antibiotics not specifically named by legislation. The former were subject to the batch-by-batch certification procedure described in Section I.A. The latter were merely subject to safety testing like other new drugs under the 1938 FDCA. This differential treatment was irrational. Especially as the batch-certified antibiotics became better established in industry and medicine, the contrast between the heavy-handed approach for old antibiotics compared to less-certain new ones became even more pronounced. The regulatory conundrum drove industry and FDA in different directions, however.

Industry made five main arguments to end the antibiotic certification program: 1) manufacturing techniques had progressed sufficiently to render certification superfluous;[123] 2) new antibiotics were coming onto the market through the "new drug" pathway without issue and any production issues could be dealt with through that regulatory scheme;[124] 3) FDA had broken its promise to the industry to create a temporary program;[125] 4) the testing was costly, duplicative, and not contributing to safety;[126] and 5) the standards for decertification were too vague.[127] Indeed, a 1955, Citizen's Advisory Committee appointed by the Secretary of Health, Education, and Welfare argued that decertification should begin for qualifying products.[128]

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123 *See* Gerden, *Further Review*, *supra* note 121, at 717 ("[S]cientific people in the industry consider the problems in the production of antibiotics as well settled, and as routine as the production of crystalline sodium chloride [table salt].").

124 *See id.* ("[B]ut to my knowledge no enforcement problem has arisen in this connection which the Food and Drug Administration has been unable to control."); *id.* at 719 ("These have been marketed under the provisions of the 'new drug' section without difficult, confusion or dire consequences, and without pretesting by the Food and Drug Administration.").

125 *See id.* at 713 ("[I]ndustry support was predicated on the principle that this was a temporary and not a permanent procedure, and that this type of drug control was not a method to be generally extended . . .The industry was later to learn that the term 'temporary' as used by the Food and Drug Administration . . . was apparently in its geologic sense.").

126 *See id.* at 716 ("[T]his appears to be a costly method of law enforcement, and perhaps the point of diminishing returns has been reached."). In the mid-1950s, the antibiotic certification program cost 0.07¢ per daily dose of antibiotic with 7 billion doses produced yearly. Henry Welch, *Certification of Antibiotics*, 71 PUB. HEALTH REP. 594, 598 (1956). This would translate to approximately $4.9 million in costs for a product worth $272 million. *Id.* at 596 tbl.2.

127 *See id.* at 718 ("While the standards set forth in the decertification provision are undoubtedly legally sufficient to support this delegation of authority, and in theory are adequate to protect those affected, in practice it would be extremely difficult to contest the exercise of the judgment of the Secretary, for these standards are not sufficiently precise to afford affected persons with any real remedy in the event of disagreement with an administrative determination.").

128 See *Reappraisal*, *supra* note 89, at 234.

FDA officials retorted that 1) antibiotics were so critical to sick people that special measures were required;[129] 2) decertification required *all* manufacturers of a particular product to reach an expert level;[130] 3) FDA could not ensure a safe and effective antibiotic supply without this power;[131] and 4) the conditions that led to the law's enactment were not the *exclusive* criteria for decertification.[132] By 1950, FDA, in fact, seemed to abandon the claim that the program was temporary: "[i]t is hoped that . . . Section 507 can be amended to preserve and strengthen its essential consumer protective features and to eliminate those features which are unnecessary or undesirable."[133]

Despite industry agreement that FDA had been fair in administering the program and had contributed greatly to developing antibiotic assays,[134] scandal rocked the antibiotic division at FDA and attracted Congressional scrutiny.[135] An exposé in a 1959 *Saturday Review* revealed that Dr. Henry Welch, the head of the FDA Antibiotics Division and a pioneer in penicillin development,[136] simultaneously held lucratively-paid posts on two antibiotics journals.[137] Many companies purchased advertising from the medical journal (a normal practice), but they also paid for reprints that languished in warehouses.[138] Upon learning the sum of money that Welch had accumulated—$250,000 over several years—the chairman of Merck was said to be "taken aback."[139] Although it was said that Dr. Welch could "fix up" issues that a manufacturer had,[140] a National Academy of Science (NAS) *ad hoc* committee would clear the decisions of the division of favoritism.[141]

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129 C.W. Crawford, *Legislative and Administrative Progress Under the Federal Food, Drug, and Cosmetic Act*, 5 FOOD DRUG COSM. L.J. 16, 24 (1950) ("While other drugs are highly important in certain disease and may be difficult to manufacture and control, the sum total of the values of these antibiotics to the sick is vastly greater than the sum total of these other drugs.").

130 *See id.* ("No matter how good a record an existing firm may have, certification may not be ended as to that firm so long as others in the same field have not demonstrated their ability to insure the safety and efficacy of the drug.").

131 *See id.* at 23 ("And the Administrator cannot ignore the possibility that after decertification persons will enter the field who are neither satisfactorily equipped nor sufficiently experienced to produce antibiotics that are safe and efficacious . . .").

132 *See id.* ("We do not believe that the statements describing the factual situation with respect to penicillin at the time of enactment necessarily constitute all of the factors the Administrator should consider at a future time. . .").

133 *Id.* at 24.

134 Gerden, *Further Review*, *supra* note 121, at 714.

135 *See generally* Richard E. McFadyen, *The FDA's Regulation and Control of Antibiotics in the 1950s: The Henry Welch Scandal, Félix Martí-Ibáñez, and Charles Pfizer & Co.*, 53 BULL. HIST. MED. 159 (1979).

136 *See* ROBERT BUD, PENICILLIN: TRIUMPH AND TRAGEDY 109 (2007).

137 John Lear, *The Certification of Antibiotics*, SATURDAY REV., Feb. 7, 1959, at 43, 46.

138 *See* BUD, PENICILLIN: TRIUMPH AND TRAGEDY 109.

139 *Id.* at 110; *see also* THE ANTIBIOTIC ERA: REFORM, RESISTANCE, AND THE PURSUIT OF A RATIONAL THERAPEUTICS 80 (2015) (describing Dr. Welch's impropriety in more detail).

140 BUD, PENICILLIN: TRIUMPH AND TRAGEDY 109 (internal quotations omitted).

141 *Drug Industry Antitrust Act: Hearing on S. 1552 Before the Subcomm. On Antitrust and Monopoly of the S. Comm. on the Judiciary*, 87th Cong. 459 (1961) [hereinafter *Kefauver Hearings*] (reprinting NAT'L ACAD. OF SCIENCES—NAT'L RES. COUNCIL, REPORT OF SPECIAL COMMITTEE ADVISORY TO THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE TO REVIEW THE POLICIES, PROCEDURES, AND

However, the scrutiny of the antibiotic certification program would be bundled with the general political pressure to expand FDA's authority in the early 1960s. The certification program would play several roles in this critical period.

B. Antibiotic Certification and 1962 Amendments

This section discusses how the antibiotic certification program became an argument for more general FDA powers and how the program was ultimately expanded in a compromise with the pharmaceutical industry. The story of the 1962 Amendments to the FDCA is often told as the story of the thalidomide tragedy[142] galvanizing public opinion and political processes to grant FDA the power to assess drug effectiveness.[143] The story may very well be true. However, as Congress and interest groups began to debate the proper role of FDA in the early 1960s, the parties had an example of a "more stringent"[144] FDA effectiveness program that had been running for over 15 years—antibiotic certification. As early as 1948, the uniqueness of the antibiotic program was recognized:

> Certification of a drug by any agency, particularly by the Government, carries with it the obvious implication of 'approval' of the product. At the risk of misleading the consumer, 'approval' of this nature cannot be given to one attribute or characteristic of the drug and not to all others. *Clearly, there would be little point in certifying the safety of a drug if the certification did not also extend to its usefulness and the claims made on its behalf.* Certification must deal, therefore, not only with safety but with identity, stability, efficacy[145] in treating or preventing disease, and claims made in the labeling and advertising.[146]

Every batch of the five antibiotics produced in the country was checked for contaminants as well as assessed for the ability to kill bacteria *in vitro*. The contaminants test was a safety check—no different from other drugs at the time. The *in vitro* assay was an effectiveness test—something unique for FDA testing at the time.

In fact, it was the pharmaceutical industry—looking for a way out of batch-by-batch certification—that proposed creating a modern new drug-like application pathway for

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DECISIONS OF THE DIVISION OF ANTIBIOTICS AND THE NEW DRUG BRANCH OF THE FOOD AND DRUG ADMINISTRATION (1960) [hereinafter NAS COMMITTEE]) ("Taking into account the limitations of the FDA's authority, funds, and scientific personnel, the Committee found the decisions it review acceptable, despite certain deficiencies in the quality and quantity of the data upon which they were based. It found no evidence of disregard for the public health, and noted that appropriate action had been taken when hazards were established by subsequent clinical experience.").

142 Briefly, FDA held approval of the anti-emetic for morning sickness while populations discovered that the drug was a potent teratogen. *See, e.g.*, James H. Kim & Anthony R. Scialli, *Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease,* 122 TOXICOLOGICAL SCI. 1, 1–2 (2011).

143 *See, e.g.*, REPUTATION & POWER, *supra* note 56, at 229 ("In the policy tragedy of thalidomide, a new image of the Administration crystallized in the public and legislative imagination.").

144 Pfizer, Inc. v. Richardson, 434 F.2d 536, 538 (2d Cir. 1970) (Friendly, J.) ("The net of all this was that while the standard antibiotics were not subject to the elaborate 'new drug' procedures of § 505 as such, they were under even more stringent regulation in two respects. Certification of batches of antibiotic drugs was required, and the drugs had to meet a standard of efficacy as well as of safety.").

145 The current term-of-art is effectiveness, but the original usage of efficacy is preserved in direct quotations throughout this paper.

146 *Drug Certification*, *supra* note 53, at 410–11.

all antibiotics. In 1950, the industry's proposed Section 507 would have FDA approve new antibiotic and formulations through

> (1) full reports of investigations which have been made to show whether or not such drug is safe and efficacious for use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full descriptions [sic] of methods used in, and the facilities and controls used for the manufacture, processing, and packing of such drugs; (5) such samples of such drug, and of the articles used as components thereof as are reasonably necessary for the Administrator to determine the ability of such person to manufacture the drug without risk to its safety or efficacy of use; and (6) specimens of the labeling proposed to be used for such drug.[147]

The proposal belies the discontent the industry felt towards the program as well as the premise that the antibiotic certification program was about more than quality control. It was about ensuring that antibiotics were safe *and effective*.

The NAS report provided a more influential push to expand certification and establish some framework for assessing drug effectiveness. Although the NAS committee was empaneled to examine the scandal at FDA's Antibiotic Division, many of its recommendations urged Congress to give FDA the ability to assess all drugs for effectiveness. As part of its more aggressive regulatory tenor, it also argued that the antibiotic program be dramatically expanded:

> The FDA should be given statutory authority to apply certification procedures to all antimicrobial agents used in the prophylaxis and treatment of infectious diseases. The Committee sees no reason for limiting certification to those antibiotic preparations which happen to have come on the market prior to 1950, and further believes that all agents employed for equally serious conditions should be subject to equivalent measures of control.[148]

Remarkably, FDA concurred with this recommendation.[149] FDA now declared that it wanted to certify more than the five antibiotics the agency was increasingly fighting the industry to regulate. This would include amphotericin, carbomycin, colistin, cycloserine, erythromycin, fumagillin, gramicidin, griseofulvin, kanamycin, neomycin, novobiocin, nystatin, oleandomycin, triacetyloleandomycin, oxytetracycline, paromomycin, polymomycin, polymyxin, risotcetin, tyrothricin, vancomycin, and viomycin.[150] To be fair, by the late 1950s and early 1960s, FDA had

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147 *Proposed Antibiotic Amendments*, 5 FOOD DRUG COSM. L.J. 442, 443 (1950); *see also Developments in the Law – the Federal Food, Drug, and Cosmetic Act*, 67 HARV. L. REV. 632, 679 (1954). *Cf.* 21 U.S.C. § 355(b)(1) (2012) (The New Drug Application) ("Such person shall submit to the Secretary as a part of the application (A) 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; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug . . .").

148 *Kefauver Hearings*, *supra* note 141, at 460 (reprinting NAS COMMITTEE, *supra* note 141).

149 *Id.* at 464.

150 *Reappraisal*, *supra* note 89, at 230–31 (quotations removed but list reproduced).

begun to test batches of antibiotics outside of the statutory five if they were marketed as combination products.[151] Yet, FDA's reversal likely surprised industry, as most of its discussions had focused on decertifying antibiotics. The key dispute—at least up until that time—had been whether manufacturers or whole formulations (i.e., penicillin G produced by Merck versus all penicillin G produced by all manufacturers) would be exempted from the certification requirements.[152]

However, more alarming for the industry were proposals to extend the certification program to non-antibiotics. Although commentators had been considering the idea since at least the late 1940s, it had been rejected as violating the congressional intent of the FDCA.[153] With FDCA amendments now pending, this statutory limitation became much less important. In fact, despite FDA assurances that the program would not extend even to other antibiotics, the importance of non-antibiotics was no longer an argument against treating antibiotics more stringently—but to regulate all drugs more strictly. A *New England Journal of Medicine* editorial crisply explained the position: extend "certification requirements to all antibiotics, *or for that matter, to all new drugs that are products of biologic processes* and in which the activity, purity and potency of the product has been found to vary significantly from batch to batch."[154] Even so, this resource-intensive proposal, as had been noted earlier,[155] was unlikely to gain traction absent a major increase in the resources available to FDA. Although included in the Department of Health, Education, and Welfare's proposed bill,[156] the proposal did not advance far.

The more dramatic effect of the antibiotic certification program, though, was in legitimizing FDA's role as an arbiter of both safety and effectiveness. In announcing the revolutionary new drug provisions, one congressional report noted that the effectiveness facet of the drug approval process was new—except for antibiotics.[157] One particular exchange between Senator Kefauver and a representative of the American Medical Association reveals how the antibiotic program became an argument for general, premarket effectiveness drug testing:

> [Senator KEFAUVER:] So there is a need for safety and efficacy, and the same principle applied to antibiotics applies to other drugs that are made synthetically.

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151 *See, e.g.*, COLLECTED ANNUAL REPORTS, *supra* note 121, at 208, 250 (1959 &1960 annual reports). Indeed, by the late 1940s, FDA also required certification of certain forms of streptomycin, namely dihydrostreptomycin. *See Production and Isolation*, *supra* note 82, at 51.

152 *Reappraisal*, *supra* note 89, at 232–33.

153 *Drug Certification*, *supra* note 53, at 409–10.

154 Editorial, *Ethical Drugs—Certification of Antibiotics*, 265 NEW ENG. J. MED. 858, 859 (1961) (emphasis added).

155 *See Drug Certification*, *supra* note 53, at 416.

156 *Reappraisal*, *supra* note 89, at 235–36.

157 H.R. REP. NO. 87–2464, at 2 (1962) ("Except in the case of those drugs for which the Federal Food, Drug, and Cosmetic Act requires premarketing clearance (i.e., new drugs, certain antibiotics, and insulin) . . . nothing can be done under the present act if these essential requirements demanded by good manufacturing practice are not met, until a particular shipment of drugs is marketed and the Food and Drug Administration can prove that the drug itself is deficient. This is not adequate assurance of consumer protection. People with inadequate experience, equipment, and technical competence can, and do, enter the business of making drugs.").

> Dr. HUSSEY[:] The antibiotics that are now made synthetically and can be tested for their potency, for their dosage reliability, by other means than formerly had to be used, these can be judged on the basis of safety without reference to efficacy.
>
> Senator KEFAUVER[:] You are not in favor of a useless antibiotic being put on the market, are you?
>
> Dr. HUSSEY[:] No.
>
> On the contrary, I would —
>
> Senator KEFAUVER[:] Then, if you can put a useless antibiotic on the market, it would take the place of one which would be useful; would it not?
>
> Dr. HUSSEY[:] I would not favor the arrival on the market of any useless drug, least of all an antibiotic.
>
> Senator KEFAUVER[:] I cannot understand why you did not oppose the writing of the word 'efficacy' in these two laws, and why you still think it might be a good idea when we do not know what kind of drugs may be developed in the future . . . .
>
> . . . So why should you not have the same rules apply to these new drugs that are going to be coming along which might be in the same category or just as important as those earlier ones?[158]

In essence, even as industry protested that the certification program was duplicative of industry controls,[159] Senator Kefauver supported what FDA wanted. He turned the antibiotic certification program into a general precedent for adding effectiveness testing, neutralizing opposition that objected to such testing by the federal government.

In the end, Congress compromised. In the now-famous 1962 amendments, all new drugs became subject to effectiveness testing—but not certification.[160] FDA's more modest proposal to extend certification over all antibiotics received more support. The arguments for and against the expansion simply rehashed the 1950s debate.[161] However, on the threat of compulsory licensing and patent reform tying patentability to effectiveness,[162] the industry dropped organized resistance to expanding the

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158 *Kefauver Hearings*, *supra* note 141, at 61–62 (statement of Dr. Hugh H. Hussey, Chairman, Bd. of Trs. of the Am. Med. Ass'n).

159 *Id.* at 2022–23 (statement of Eugene N. Beesley, Pres. Eli Lilly & Co) ("It would be a duplication of the tests manufacturers run.").

160 Drug Amendments of 1962, § 102, Pub. L. No. 87–781, 76 Stat. 780, 781–82 (codified over various portions of Title 21 of the U.S. Code) (adding effectiveness to the criteria for approving a new drug).

161 *See, e.g.*, *Kefauver Hearings*, *supra* note 141, at 293–94, 345, 438–39, 841–42, 2001–02, 2033–35 (opinions and discussions of the antibiotic certification program from various stakeholders).

162 *See id.* at 2005–06 (statement of Mr. Beesley) ("Finally, gentleman, of all the provisions in the bill the most far reaching is the proposal to reduce the period of the exclusive patent of medicines from 17 years to 3 years. This proposal obviously strikes directly and crucially at the industry's capacity and incentive for discovery of new and improved medicines, and we vigorously oppose it. If enacted, it would inevitably retard the scientific research which has enabled our industry to make its greatest contributions to the public health."); *see also* Editorial, *Ethical Drugs—To Assure Efficacy and Safety*, 265 NEW ENG. J. MED. 705, 705 (1961) ("The bill would also amend the United States Code relating to patentability of inventions and grants of patents so far as it applies to prescription drugs that are molecular or other modifications of any available drug, whether patented or not, and for combinations of such drugs. It would

certification program.[163] Antibiotic certification would now apply to all antibiotics marketed in the United States, so FDA would not need to return to Congress to add new antibiotics to the program like in the 1940s.[164] New antibiotics would be subject to safety and effectiveness testing (like other new drugs) before being eligible for certification.[165] Antibiotics approved under the safety-only regime in the 1950s were transferred to the certification regime, allowing FDA to require further studies of effectiveness as a condition for certification.[166] Congress further clarified the decertification procedures,[167] but industry would still not be satisfied with the sluggish pace.[168] Nonetheless, the all-antibiotic certification program embodied in Section 507 was born.

It would not be the first time that the certification program would provide benefits to FDA beyond its statutory purpose. The next section details how the antibiotic certification program affected far more than the batches of antibiotics inspected.

III. New purposes for an obsolete program: repurposing and the end of the certification program

The certification program was quickly—once again—condemned as an unnecessary and duplicative government regulation.[169] Yet again, FDA attempted to

require the Secretary of Health, Education, and Welfare to determine, before a patent is issued, that the therapeutic effect of any such modification or combination is significantly greater than that of the original drug so modified or combined.").

163 *See* Editorial, *Antibiotic Certification—An Anachronism*, 71 J. PHARMACEUTICAL SCI. 727, 727 (1982) ("However, drug industry opposition suddenly evaporated, apparently as the result of a closed-door political compromise in which the industry agreed to accept antibiotic certification as a trade-off for having Congress not disturb the exclusivity of drug patents.").

164 Drug Amendments of 1962, § 105(a)–(c), 76 Stat. 780, 785 (codified at 21 U.S.C. § 357(a) (1994)).

165 Wiesen, *supra* note 4, at 241, 246–47.

166 *See, e.g.*, Pfizer, Inc. v. Richardson, 434 F.2d 536, 539 (2d Cir. 1970) (Friendly, J.) ("To implement this agreement with respect to antibiotics and to facilitate the task of the Council in determining whether any certification or release should be rescinded or any regulation under 507 should be amended or repealed, the FDA, three months later, issued an order requiring each manufacturer to furnish specified information about the antibiotics in question. This included a 'list of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, package insert, or brochure' accompanying its sale and 'unpublished articles or other data pertinent to an evaluation of the claims.'").

167 *See* Drug Amendments of 1962, § 105(d), 76 Stat. 780, 786 (codified at 21 U.S.C. § 357(d) (1994)) ("In deciding whether an antibiotic drug, or class of antibiotic drugs, is to be exempted from the requirement of certification the Secretary shall give consideration, among other relevant factors, to—(1) whether such drug or class of drugs is manufactured by a person who has, or hereafter shall have, produced fifty consecutive batches of such drug or class of drugs in compliance with the regulations for the certification thereof within a period of not more than eighteen calendar months . . . or (2) whether such drug or class of drugs is manufactured by any person who has otherwise demonstrated such consistency in the production of such drug or class of drugs, in compliance with the regulations for the certification thereof, as in the judgment of the Secretary is adequate to insure the safety and efficacy of use thereof.").

168 *See generally* Rodney R. Munsey, *Antibiotic Certification and the APA*, 21 ADMIN. L. REV. 397 (1968–69) (detailing complaints that FDA was not following the APA in regards to decertifying antibiotics).

169 *See, e.g.*, *Drug Regulation Reform Act of 1978, Hearings on H.R. 11611 Before Subcomm. On Health and the Env't of the H. Comm. On Interstate and Foreign Commerce*, 95th Cong. 1395 (1978) [hereinafter *Reform Hearings*] (statement of Eli Lilly & Co.) ("Certification requirements for insulin and antibiotics were imposed many years ago. Long experience with these regulations has led Lilly to conclude that lot-by-lot certification is not a sound policy and involves duplicative, nonproductive, costly, and time-

enact an even broader certification program.[170] Nonetheless, because of the relatively low cost and risk of antagonizing the agency over such minor issues, opposition to antibiotic certification did not rise to an industry priority.[171] The special statutory scheme and obsolescence allowed the program to become useful for other purposes.

One purpose, mentioned in the introduction, was the facilitation of generic drugs. To see how antibiotic certification promoted generics, it becomes necessary to discuss another facet of the certification program: monographs. Once an antibiotic entered the certification program, FDA, not United States Pharmacopeia, defined standards for the product through a monograph in the Code of Federal Regulations.[172] Once the relevant patents for the antibiotic expired, *any* company could submit a batch of antibiotics for certification, provided it met the guidelines outlined in the FDA monograph.[173] Some criticized this system as disseminating pharmaceutical company's data publicly and facilitating freeriding[174] (a key issue that Hatch-Waxman would solve for non-antibiotic drugs), but the system remained in place for decades until antibiotic regulation was transferred to the new drug provisions of FDCA Section 505.

The other main benefit of the antibiotic program—and the focus of this section—is how the funds from certification program went to more than simply certification. In 1960, as the antibiotic certification program began to attract some Congressional attention, the Comptroller General (the head of what is now called the U.S. Government Accountability Office (GAO)) documented a seemingly odd occurrence: nearly $1 million accumulated in unspent certification fees.[175] When the investigation probed deeper into the reason for the buildup of cash, FDA responded that it was attempting to save funds to purchase new certification equipment since its old assays could not be moved to a new location.[176] While the purpose of the cash build up ended

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consuming procedures. Also the conditions which prompted adoption of certification requirements no longer exist.").

170 *Id.* at 1379 ("The bill permits FDA to expand its batch certification requirements to include drugs other than antibiotics, insulin, and biologics even though available information indicates that present batch certification requirements are obsolete, unproductive, unnecessary, and should be eliminated."). *See generally* Robert J. Temple, *The Effect of the Drug Regulation Reform Act of 1978 on Clinical Research, Drug Availability, and The Public Health*, 368 ANNALS N.Y. ACAD. SCI. 175 (1981).

171 George H. Schneller, *Antibiotic Batch Certification: A Regulatory Device That Has Outlived Its Usefulness*, PHARMACEUTICAL TECH., Nov. 1979, at 47, 54 [hereinafter Schneller, *Antibiotic Batch Certification*]. *Cf.* REPUTATION & POWER, *supra* note 56, at 271 ("The organizational legitimacy of the Administration was such that courts and national politicians deferred consistently to its interpretations, actions, and decisions.").

172 *Compare* 21 C.F.R. § 453 (1975) (defining the standards for lincomycin, i.e. a monograph) *with* THE UNITED STATES PHARMACOPEIA, TWENTIETH EDITION & THE NATIONAL FORMULARY, FIFTEENTH EDITION 450 (1980) ("Lincomycin Hydrochloride conforms to the regulations of [FDA] concerning antibiotic . . .").

173 Wiesen, *supra* note 4, at 241, 243.

174 *See, e.g.*, *Reform Hearings*, *supra* note 169, at 2080 (statement of Dr. Earl B. Herr, Pres. Lilly Research Laboratory Res. Lab.) ("In terms of one of our products which we have a patent for. There has been a monograph issued. Another company has filed a so-called form 6 on this compound which was approved by the FDA. They are currently on the market in this country.").

175 DEP'T OF HEALTH, EDUC., AND WELFARE, COMPTROLLER GEN. OF THE U.S., REPORT TO THE CONGRESS OF THE UNITED STATES: REVIEW OF ENFORCEMENT AND CERTIFICATION ACTIVITIES OF THE FOOD AND DRUG ADMINISTRATION 29 (1960).

176 *Id.* at 29–30.

up being benign, it began at least the documentation of a tradition of using funds for more than strictly certification.

Twenty years later, the GAO found that industry was still being overcharged for certification. However, the funds were not going towards buying new equipment, but some were being spent for a general regulatory program. While arguably this violated the Congressional command to enact "such fees . . . as are necessary to provide, equip, and maintain an adequate certification service,"[177] one FDA official interpreted the statute to allow funds to be spent on all antibiotic regulation. Indeed, FDA adopted a wide interpretation of "certification": "Agency studies and other documents describe antibiotic certification as consisting of reviewing drug applications, developing standards, testing batch samples, developing new test methods, monitoring marketed products, and other activities."[178] The Office of Management and Budget (OMB) agreed.[179] The FDA oral history, indeed, confirms that the money was well spent in a sense, considering that the antibiotic division "developed methods through the years . . . ."[180]

The antibiotic division of FDA was bolstered and protected by this steady stream of income. Indeed, this diversion of funds from narrowly-defined antibiotic certification may have led FDA to vigorously fight to maintain its authority to batch certify antibiotics—and attempt to expand its domain into other drug classes. In fact, FDA maintained an informal batch certification program over digitalis and its derivatives after quality control problems rocked that segment of the drug market.[181] Yet, Congress began to consider bills that would pare down antibiotic certification or pressure FDA to certify drugs of all classes that met specified criteria.[182] Even FDA began to move slowly to decertification, granting a manufacturer's petition to decertify an oral formulation.[183] But, FDA did not advance further initially.[184] However, by the

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177 21 U.S.C. § 357(b)(5) (1994).

178 U.S. GEN. ACCOUNTING OFFICE , REPORT TO THE SECRETARY OF HEALTH AND HUMAN SERVICES: FDA SHOULD REDUCE EXPENSIVE ANTIBIOTIC TESTING AND CHARGE FEES WHICH MORE CLOSELY REFLECT COST OF CERTIFICATION 22 (1981) [hereinafter GAO REPORT].

179 *Id.*

180 HISTORY OF THE U. S. FOOD AND DRUG ADMINISTRATION: MEETING FOR THE PURPOSE OF DISCUSSION THE HISTORY OF FDA SCIENCE WITH RETIRED FDA SCIENTISTS, JUNE 29, 1978, at 107–08 (1978), https://web.archive.org/web/20170304093618/http://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/OralHistories/SelectedOralHistoryTranscripts/UCM266370.pdf [https://perma.cc/3Q2M-F3LH].

181 Schneller, *Antibiotic Batch Certification*, *supra* note 171, at 54.

182 *See, e.g.*, *Drug Regulation Reform Act of 1979, Hearings on S. 1075, Before the Subcomm. On Health and Sci. Res. of the S. Comm. On Labor and Human Res.*, 96th Cong. 894 (1979) (explanation of the proposed bill) ("The Act repeals existing batch certification provisions that apply only to insulin and antibiotics and substitutes a batch certification provisions that applies to all drugs. Under current law, however, the act limits FDA authority to require that individual drug batches be approved by the agency. Only if there is reason to believe that batches will fail to meet pharmacopeial standards, and that such failure poses a public health risk, can FDA take action. The Act limits any batch certification requirement to three years, but the requirement may be renewed. Finally, the Act explicitly permits the FDA to exempt a particular facility or manufacturer from the general requirement.").

183 Schneller, *Antibiotic Batch Certification*, *supra* note 171, at 53. There were also criteria to decertify topical or local antibiotic formulations, *see* 21 C.F.R. § 144.1 (1973), but that is a small segment of the antibiotic market, *see* Schneller, *Antibiotic Batch Certification*, *supra* note 171, at 51.

184 Schneller, *Antibiotic Batch Certification*, *supra* note 171, at 51–53.

late 1970s, backlogs began to build up at the certification program.[185] Eventually, critics of the program and the advent of the deregulatory environment of the late 1970s and early 1980s[186] shut down certification for topical products in 1980[187] and all antibiotics in 1982.[188]

Congress would repeal Section 507 in 1997.[189] The statute transferred pending and approved antibiotic NDAs to the traditional Section 505 drug approval and regulatory pathway.[190] Although Congress did not explicitly address new antibiotic NDAs (those not filed before Section 507 repeal), FDA indicated that firms should use Section 505.[191] However, some antibiotics—especially members of new classes—could arguably be regulated as biologics.[192] In fact, Congress continues to take an interest in

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185 *See* John D. Harrison, *Antibiotic Application Requirements*, 4 CLINICAL RES. PRACS. & DRUG REG. AFF. 265, 267 (1986) ("The regulated industry's demands on the agency's testing service increased year by year as the market grew larger and larger. The agency's testing services became slower and slower due to personnel and facilities limitations imposed by the Office of Management Budget [sic]. As a result, during the late 1970's large quantities of antibiotic products were being held in quarantine for many weeks by industry while waiting for FDA's clearance at a time when interest rates were at an all time high.").

186 *See, e.g.*, *id.* at 47–48. *See generally* GAO REPORT, *supra* note 178.

187 Exemption of Dermatologic and Vaginal Antibiotic Drug Products From Certification, 45 Fed. Reg. 71354 (Oct. 28, 1980) (final rule); Antibiotics for Human Use; Exemption of Dermatologic and Vaginal Antibiotic Drug Products From Certification, 44 Fed. Reg. 39469 (July 6, 1979) (proposed rule).

188 Exemption of Antibiotic Drugs and Antibiotic Susceptibility Medical Devices From Certification, 47 Fed. Reg. 39155 (Sept. 7, 1982) (final rule); Antibiotic Drugs and Antibiotic Susceptibility Medical Devices; Interim Certification Procedures, 47 Fed. Reg. 20186 (May 11, 1982) (notice).

189 Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, § 125(b)(1), 111 Stat. 2296, 2325 (codified over various portions of Title 21 of the U.S. Code).

190 *See id.* § 125(d)(1), 111 Stat. at 2326–27.

191 *See* CTR. FOR DRUG, EVALUATION, AND RESEARCH, U.S. FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY AND REVIEWERS: REPEAL OF SECTION 507 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 2 (1998), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078754.pdf [https://perma.cc/EA5G-MZUQ]. This continuation with the 505/NDA pathway also conforms to historic FDA guidance to use the same regulatory scheme for natural products and their analogs from recombinant DNA production. *See* Statement of Policy for Regulating Biotechnology Products, 51 Fed. Reg. 23309, 23309–10 (June 26, 1986); *see also* Krista Hessler Carver, Jeffrey Elikan & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 685 (2010) ("FDA made the decision that recombinant versions of previously marketed naturally derived proteins would be regulated as new products under the same statute as their naturally derived predecessors.").

192 Some antibiotics are collections of several amino acids (e.g., vancomycin). SNEADER, *supra* note 2, at 309–10. Nearly all are produced by some sort of microorganism-driven process. *See generally* GENETICS AND BIOCHEMISTRY OF ANTIBIOTIC PRODUCTION (Leo C. Vining & Colin Studdard eds., 1995). However, FDA does not consider a peptide of less than 40 amino acids as a biologic, *see* U.S. FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY ON BIOSIMILARS: Q & AS REGARDING IMPLEMENTATION OF THE BPCI ACT OF 2009: QUESTIONS AND ANSWERS PART II (2012), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ [https://perma.cc/CVX2-J36P], and tends to regulate products according to precedent and tradition, *see* note 191 and accompanying text. Further, since antibiotics work by killing cells or slowing bacterial growth, antibiotics could be analogous to a "toxin"—another type of biological product—as they facilitate immune responses. *See* United States v. Loran Med. Sys., Inc., 25 F. Supp. 2d 1082 (C.D. Cal. 1997) (holding that a treatment that attempts to dodge the immune system qualifies as a toxin or its analog – and thus a biological product); *see also* 42 U.S.C. § 262(a) (2012); 21 C.F.R. § 600.3(h)(5)(iii) (2016) (A product is analogous to a toxin "if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.").

antibiotics,[193] demonstrating that however FDA regulates this drug class, antibiotics continue to be an area of special focus of policy and law.

CONCLUSION

A general counsel of one of the nation's leading pharmaceutical firms expressed well the fundamental flaw with the antibiotic certification program:

> With each successive step in the enactment of predistribution controls, precedents for additional controls are established, and it becomes increasingly difficult to oppose further extension thereof or to place limitations on such additions beyond those contained in the previous enactments, and so it was with the law providing for certification of penicillin.[194]

Although the certification program arguably had a vital and important purpose at its genesis in 1945, Congress and FDA lost sight of the conditions that prompted the creation of the program. It grew because of FDA pressure and pharmaceutical companies' willingness to horse trade the expansion of the program for greater benefits. Decades passed before a program that had outlived its usefulness finally ended.

For its longevity, it is a cautionary tale. FDA regulates at the cutting edge of medicine and science. Penicillin was that cutting edge in the 1940s, and FDA crafted a program to ensure that the new drug was not beset by quality-control issues and could be disseminated to the troops—and eventually to all. But, once antibiotic synthesis, fermentation, and manufacturing moved on, FDA did not. The program was not implemented to evolve with the science. Legal analogy became the focus of the analysis, so if penicillin is an antibiotic and benefits from this program, streptomycin must as well—and then tetracycline, chloramphenicol, bacitracin, ampicillin, cephalothin, cloxacillin, gentamicin, doxycycline, cephaloridine, dicloxacillin, carbenicillin, clindamycin, capreomycin, cephalexin, rifamycin, spectinomycin, and on and on and on. As FDA considers how to deal with new technologies, treatments, and all else that falls under its jurisdiction, it should consider an exit strategy contingent on scientific and medical advancement to best use its limited regulatory bandwidth and resources.

FDA was not stupid. It realized that the program had greater utility than a 1940s-system to check safety and effectiveness. With funds accumulated from the program, FDA deployed resources that helped the field of antibiotic testing and safety development. But, it took time for it to proceed to the next logical step and alter its regulatory priorities. Some of the delay was likely because a statutory mandate stood in the way, but Congress has amended the FDCA numerous times since the 1940s—sometimes with the specific intent of improving drug regulation. Yet, industry still could not prevail upon Congress to remove the burdensome requirement. In fact, the funds from certification might have incentivized FDA to prolong the status quo.

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193 *See, e.g.*, Food and Drug Administration Safety and Innovation Act, Title VIII—Generating Antibiotic Incentive Now, §§ 801–06, P.L. No. 112–144, 126 Stat. 993, 1077–82 (2012) (codified over various portions of Title 21 of the U.S. Code).

194 Gerden, *Further Review*, *supra* note 121, at 712.

Nonetheless, antibiotic product development moved at a glacial pace compared to the innovations in the pipeline today. While FDA certainly has a role in many of these emerging technologies, it should not fall into the trap that beset the antibiotic certification program.

APPENDIX: THE COMMEMORATIVE PRINT