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THE FDA's REGULATION AND CONTROL OF ANTIBIOTICS IN THE 1950s

THE HENRY WELCH SCANDAL, FÉLIX MARTÍ-IBÁÑEZ, AND CHARLES PFIZER & CO.*

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The discovery and widespread production of antibiotics such as penicillin, tetracycline, streptomycin, and others mark a dramatic page in the history of modern medicine.[1] This rapid increase in the number of antibiotics pouring onto the American market after the Second World War put new responsibilities on the Food and Drug Administration to control and regulate these new antibiotics properly. In the more than a half century since the passage of the first Pure Food and Drugs Act, the Food and Drug Administration had never been tainted with an internal scandal. But in late 1959 and early 1960, a high official of the FDA, Dr. Henry Welch, was charged with serious instances of conflict of interest involving the regulation of antibiotics. The Welch scandal had a number of significant ramifications. Although the Welch case proved to be an isolated episode, it seriously damaged the reputation and morale of an agency that had had a long, proud history of consumer protection. The Welch scandal alerted the agency to the dangers of becoming too closely intertwined with the industry it was supposed to regulate. In addition, the Welch scandal, along with Senator Carey Estes Kefauver's investigation into the pharmaceutical industry and with the

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[1] For more on the history of antibiotics see Harry F. Dowling, *Fighting Infection: Conquests of the Twentieth Century* (Cambridge: Harvard University Press, 1977).

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thalidomide scare,[2] did much to awaken the agency to the need to revamp federal legislation regulating the booming antibiotics field.

At the beginning of the 1950s, Dr. Henry Welch found himself in a key position in the development of antibiotics. Welch, who held a Ph.D. in bacteriology from Western Reserve (he was not an M.D.), had joined the FDA in 1938. In 1943, at the request of the Army, the FDA, under the guidance of Dr. Welch, undertook the task of developing standards and tests to insure the safety and efficacy of each batch of penicillin. With the arrival of the commercial production of penicillin, the FDA was empowered to certify each batch of penicillin produced.[3] Welch became director of the Division of Penicillin Control and Immunology, later in 1951 renamed the Division of Antibiotics.[4] Rapidly within the next five years or so newly discovered antibiotics, such as streptomycin, tetracycline, bacitracin, and chloramphenicol, were added to the certification lists.[5]

In his position in the FDA, Dr. Welch by the early 1950s was on the cutting edge of new developments in antibiotics. He himself had published widely in the field and was well on the way to establishing himself as a major figure in this new and growing area.[6] Thus it was not surprising that in 1950 Dr. Welch was approached by Dr. Henry J. Klaunberg to edit a new journal dedicated to the growing field of antibiotics. At the same time, Klaunberg suggested that Welch, along with Dr. Charles Lewis, also of the FDA, might author a book on antibiotic therapy for the physician. Both the journal and the book were to be published by the Washington Institute of Medicine. Welch requested permission from his superiors to undertake these outside activities pointing out that he would receive an honorarium for editing the journal, if successful, and the usual author's percentage on the book. In due time, Welch received permission to proceed from the then commissioner of FDA, Dr. Paul B. Dunbar.[7]

By October 1950, the new journal, called *The Journal of Antibiotics,* made its first appearance. The journal boasted a distinguished editorial board in-

[2] For a more complete discussion of the thalidomide episode see Richard E. McFadyen, "Thalidomide in America: a Brush with Tragedy," *Clio Medica,* 1976, *11:* 79-93. See also *Suffer the Children: The Story of Thalidomide,* by the Insight Team of *The Sunday Times* of London (New York: Viking Press, 1979).

[3] In 1945 the Food, Drug, and Cosmetic Act was amended to require certification of penicillin. U.S. Congress, Senate. *Administered Prices Hearings before the Subcommittee on Antitrust and Monopoly of the Committee on the Judiciary,* 86th Cong. 2nd sess., Part 23, 13075-76; hereafter cited as Administered Prices.

[4] *Ibid.,* 12634.

[5] *Ibid.,* 13076. Under the Kefauver-Harris Amendments of 1962, all antibiotics were added to the certification list.

[6] For a list of Welch's publications see *ibid.,* 13081-93.

[7] *Ibid.,* Part 22, 11926-38; also for a chronology of Welch's outside activities see Part 23, 12949-52.

cluding five Nobel Prize winners and such stellar names in the history of antibiotics as Sir Howard W. Florey, Dr. Selman Waksman, and Sir Alexander Fleming. Work moved rapidly ahead on the book, *Antibiotic Therapy*, by Welch and Lewis which was published in 1953.[8] In the first two years of his editorial duties, Welch received only $150 for his efforts; by 1952, his endeavors were a little more lucrative, but the $3270.59[9] he received was within the limits of an honorarium. But by 1952, a series of events radically changed Welch's relationship with his publisher, setting him on the road to potential conflict of interest charges.

In 1952, Welch's publisher, the Washington Institute of Medicine, under Dr. Klaunberg, fell into bankruptcy. As a result, Klaunberg sold all rights to Welch's book to Welch and his new partner, Dr. Félix Martí-Ibáñez. The two men now set up a new corporation, Medical Encyclopedia, which was to publish the book as well as other monographs. Around the same time, Dr. Martí-Ibáñez also took over control of the Washington Institute of Medicine, which published Welch's journal. Although Welch was not an owner of the Washington Institute, he was now in a position to benefit greatly monetarily from its editorship.[10]

Welch and Martí-Ibáñez realized the vast commercial potential represented by the growing market for antibiotics. They now proceeded to exploit Welch's position and prestige in the field of antibiotics through their various publishing enterprises. Articles and editorials which dealt favorably with a company's drug products could potentially be sold as reprints to companies who would distribute them, along with advertising material, to doctors. In addition to the very lucrative reprint business, the journals (a second one was created in the mid-1950s) also carried advertisements from the drug companies. Rather rapidly Welch, the chief regulator of the antibiotics industry, found himself in the position of chief editor of "scientific papers" frequently sponsored by drug companies and which were to appear in his journals supported by the companies' own advertising and bulk purchases of reprints. Incredibly, this arrangement went on for almost a decade.

One venture envisioned by the two men was the publication of a series of monographs recounting the history and use of particular antibiotics to doctors. By 1958, MD Encyclopedia, Inc., was publishing over 10 different volumes edited by Welch on various antibiotics including penicillin, Ter-

[8] See *ibid.*, Part 23, 12260, 13078.
[9] For an account of Welch's earnings see *ibid.*, Part 23, 12323.
[10] See *ibid.*, 12261-86, also 12949-50.

ramycin, and aureomycin.[11] The publishers were not hesitant in sending unpublished manuscripts to drug companies to determine if they might be interested in sponsoring the publication of the volume by buying advance copies of the book. In one case, the advertising department of Charles Pfizer and Co. informed Martí-Ibáñez that they were not interested in buying reprints of a manuscript dealing with carbomycin because "the paper is extremely conservative" and besides not much emphasis was being put on the drug by the Pfizer sales planning group. A book on Terramycin might be more favorably received, however. The following year, a book on Terramycin was published by MD Encyclopedia.[12]

Martí-Ibáñez and Welch felt it necessary to keep a semblance of objectivity to their work, turning down a request by Pfizer to substitute their trade name "Terramycin" wherever the generic name "oxytetracycline" appeared in the monograph.[13] But the monograph did appear under Pfizer's trade name with its generic name in parenthesis, prompting a reviewer to comment: "The book tries to sell Terramycin rather than critically appraise it. . . ."[14]

The author of the monograph on Polymycin, another volume in the series, was upset by the commercialization of his manuscript at the hands of Welch as editor. He wrote Martí-Ibáñez: "I am quite unhappy about your repeated reference to Pfizer products—these were not in my manuscript. . . . They give the impression that the book is written for the benefit of Charles Pfizer and Co., rather than for physicians."[15]

By 1953, the first journal, now named *Antibiotics and Chemotherapy*, had become a financial success. Although the paid circulation of the journal was small (only 3,000 copies a month at the end of the decade),[16] Welch and Martí-Ibáñez had found other ways to make their journal profitable. The journal made money in three ways: (1) advertising revenues from drug companies, (2) the sale of reprints to companies, and (3) payments for the addition of extra pages.

Later investigation revealed that MD Publications realized a total of $309,898 from advertising revenues in its journals from 1953 to 1959. But surprisingly the sale of reprints was far more lucrative, bringing in total sales of $685,760. Obviously major drug companies found reprints published in a

[11] For a list of their books see *ibid.*, 13062.
[12] See letter, Chas. Pfizer & Co., Inc., to Martí-Ibáñez, Feb. 4, 1955, *ibid.*, 13156.
[13] Letter, Martí-Ibáñez to George E. Peabody, Feb. 15, 1956, *ibid.*, 12480.
[14] *Ibid.*, 13053. The review appeared in the *Archives of Internal Medicine*, Aug. 1957.
[15] See letter, Ernest Jawetz to Martí-Ibáñez, Feb. 7, 1956, *ibid.*, 13025.
[16] *Ibid.*, 12635.

journal edited by the FDA's top antibiotics regulator extremely valuable. The total revenue resulting from extra page charges amounted to $69,454.[17] Far from receiving just an honorarium, Dr. Welch was to receive 7½ percent of the net advertising revenues, and most interestingly, a 50 percent cut of net income from the sale of reprints as well as 25 percent of the extra page revenue.[18]

Welch, from 1953 to 1960, earned a total of $287,142.40 for his editorial efforts. Of this sum the largest part came from the journals, some $224,016.70. At this rate, he was averaging over $35,000 a year with his worst year at a little over $13,000 and his best at over $50,000.[19]

With the continued growth of their journal, Martí-Ibáñez decided that it would be desirable to start a second journal. *Antibiotics and Chemotherapy* would continue to focus on laboratory and *in vitro* reports, but a new journal was needed to bring papers of a more clinical nature directly to physicians. With this aim in mind, a second journal, first called *Antibiotic Medicine*, was created in 1954. But after a year of publication the second journal was having trouble establishing a readership. It was decided to change the name of the journal to *Antibiotic Medicine and Clinical Therapy* which would broaden the editorial content of the journal, therefore making the journal more attractive to a wider range of advertisers. The journal would also become a controlled circulation periodical sent free to 60,000 doctors on a trial basis for a year and a half, after which some 23,000 doctors opted to continue to receive the journal on a complimentary basis.[20] In October 1956, Martí-Ibáñez attempted to market a British edition of their second journal, *Antibiotic Medicine and Clinical Therapy*. After only one year of existence, the British edition was discontinued due to lack of advertising support or subscription revenue.[21]

The difficulties faced by Welch and Martí-Ibáñez in winning acceptance for their new magazine reveal the length to which the two would go to prejudice the journals' editorial content to satisfy the advertisers. Evidently some question was raised by at least one concerned person regarding the ability of the journal to maintain its objectivity. Dr. Harry Dowling of the University of Illinois Medical School, a member of the editorial board of both journals, questioned what effect transforming the journal into a controlled circulation periodical might have on its editorial policy. Martí-Ibáñez

[17] *Ibid.*, 12678-79.
[18] See *ibid.*, Part 22, 11937.
[19] *Ibid.*, Part 23, 12678.
[20] *Ibid.*, 12356-66, 12950.
[21] *Ibid.*, 12680.

assured Dowling, "We will carefully preserve the good scientific standing and the recognition that the journal has earned. . . . "[22] But Dowling's fears were very well founded.

Clearly the dependence of the journal on advertising and reprint revenues prejudiced the editorial policy, both in terms of article contents and editorial statements. Martí-Ibáñez clearly saw the American and British version of AM&CT as a forum in which manufacturers could publish clinical studies they had sponsored. In a letter to Welch, Martí-Ibáñez pointed out that the journal offered a sponsoring company "the opportunity to publish . . . any important clinical papers" as well as "important news about its products" in a special clinical newsletter section. Although he continued "it would be better for the sponsoring company not to announce to the readers that they are sending the journal . . . as this would somehow weaken the impact of their papers in the journal."[23]

In the American edition, Welch evidently made a practice of allowing advertisers to review editorials *before* they were published, soliciting their comments as well as reprint orders on upcoming editorials.[24] Likewise the scope of the journal was widened beyond antibiotics to include hormones, vitamins, and other chemotherapeutic agents in the hopes of attracting greater advertising.[25] One company promised increased advertising if the journal promised "that there will be articles on vitamins and nutrition."[26]

Invariably, critics noticed the declining scientific quality of the journal and questioned the rigor and objectivity of its content. One critic wrote, "I have been so disappointed with many of the articles . . . (T)here have been far too many with little or no scientific merit. This is not only my own opinion, but it seems to be shared by all with whom I have discussed the subject, and there have been a good many." The writer was particularly disturbed by an article discussing antibiotic-vitamin combinations.[27]

In addition to their book and journal publishing ventures, Welch and Martí-Ibáñez also arranged an annual antibiotics symposium to be jointly sponsored by Martí-Ibáñez's MD Publications and the Food and Drug Administration. From 1953 to 1957 the symposium, which was chaired by Dr. Welch, received the blessing of the FDA. The proceedings were then col-

[22] See letter, Martí-Ibáñez to Harry Dowling, June 15, 1959, *ibid.*, 12490-91.
[24] See letter, Martí-Ibáñez to Welch, April 13, 1956, *ibid.*, 12426.
[24] See letters, *ibid.*, 13166, 13174.
[25] *Ibid.*, 13172-73.
[26] *Ibid.*, 13172, also see 13179.
[27] See letter, William W. W. Kirby to Welch, July 13, 1956, *ibid.*, 13191-2; also see 13206-07 and 13250.

lected and published as the "Antibiotics Annual" by none other than Medical Encyclopedia, the firm in which Welch owned a half interest.[28]

As with their other endeavors, Martí-Ibáñez was not bashful at all regarding manipulating the symposium to the advantage of large drug companies, therefore boosting sales of the "Antibiotics Annual" and reprints from it. In a long letter to Welch, outlining plans for the second symposium, Martí-Ibáñez commented, ". . . we have a unique opportunity to slant the papers of the Symposium in whatever direction we feel will be most useful to the audience of our publications." Among his many plans for the symposium, Martí-Ibáñez envisioned an increased number of "official" cocktail parties hosted by large drug companies. No wonder that one doctor returning from a trip to Europe reported, "The Europeans have a strong feeling that our Antibiotics Symposium is little more than a parade of new products and testimonials . . . without first class scientific data. . . ."[29]

By the mid-1950s, elements within the drug industry itself were becoming concerned regarding Welch's outside financial activities. In June of 1956, John Connor, Chairman of the American Drug Manufacturers Association's committee on FDA-NIH Relationships, expressed concern to HEW secretary, Marion B. Folsom, and commissioner of the FDA, George Larrick. The following month Connor met with Welch and Dr. A. H. Holland, medical director of the FDA, to discuss the matter. Welch again assured all parties that he received only an honorarium for his editorial services and that he did not make any effort to encourage the industry to use his journals for advertising purposes.[30]

Welch evidently felt that he had convinced Connor. Connor, however, was far from satisfied; he thought that Welch had agreed to state in a letter what he had told Connor regarding his outside activities. Martí-Ibáñez and Welch exchanged letters outlining Welch's activities, but the letters were left in HEW files and not distributed publicly. Connor felt Welch had reneged on his promise to publish his letter of explanation. In a last effort to clear the air, Connor urged that the industry group place the matter before Secretary Folsom and Larrick for final action. Connor commented, "My own view is

[28] *Ibid.*, 12636-37.

[29] See letter, Martí-Ibáñez to Welch, March 10, 1954, *ibid.*, 13022-24 and letter, William P. Boger to Welch, June 3, 1959, *ibid.*, 13031-32.

[30] Chronological Summary A: Inquiry by Mr. John Connor, American Drug Manufacturers Association, Respecting Outside Activities of Dr. Welch and Responses of FDA Thereto. (Undated). National Archives, Washington, D.C.

that other committee members will be quite surprised and shocked at the growing extent of Henry Welch's personal profitable enterprises."[31]

The industry group, however, felt that they had done all they could to bring the problem to the attention of HEW-FDA authorities. Despite the industry efforts, FDA management apparently felt it unnecessary to press Welch on the matter any further ignoring Connor's warning that it was "unsound for an important government official in a position like Dr. Welch's to have outside business interests that depend for their success on the financial support and backing of the very industry members whose activities he regulates or controls to such an important extent."[32]

Later investigation was to reveal how far Welch would compromise his scientific standing to benefit himself financially. In the mid-1950s a debate was taking place concerning the so-called synergistic effect to be derived from the use of combination drugs. In his opening remarks at the 1956 Antibiotics Symposium, Welch threw his support behind the use of combination drugs marketed in fixed ratios, heralding the arrival of "a third era of antibiotic therapy." Welch's advocacy of combination drugs caused quite a controversy at the symposium, spilling over into the editorial pages of his journals. Welch reprinted his symposium endorsement of combination drugs as an editorial in *Antibiotic Medicine and Clinical Therapy*. This action prompted Dr. Maxwell Finland to continue criticism that he, as well as others, had raised regarding the use of antibiotics in fixed combination. In a strong editorial in a subsequent issue of Welch's journal, Finland charged that "much of the clinical information presented at the symposium had the sound of testimonials rather than carefully collected and adequately documented scientific data." He further warned that "scientific publications have the duty to protect the medical profession and the public against the abuse of preliminary scientific information. . . ."[33]

In the following year, Welch was so determined to back up his endorsement of combination drugs that he put the FDA's own antibiotic research team on the job of demonstrating the synergistic powers of certain antibiotic mixtures. The research team's results were presented at the next year's antibiotic symposium.[34]

[31] Letter, John Connor to Dr. Karl Bamback, Sept. 13, 1956, National Archives.

[32] Chronological Summary A. Op. cit.

[33] For a copy of Welch's opening remarks see Administered Prices, Part 23, 12844-45, for essentially the same statement in his journal, see pp. 12846-47. For Finland's editorial see, 12925-28.

[34] See *ibid.*, 12860-80. For the results see *ibid.*, 12881-92.

Subsequent investigations revealed at least one major reason for Welch's keen interest in combination drugs. Senator Estes Kefauver's investigation into the drug industry showed that Welch had allowed Charles Pfizer and Co. to edit his opening remarks to be delivered at the 1956 Symposium.

Members of Pfizer's advertising staff inserted into Welch's speech the phrase "a third era of antibiotic therapy" which the Pfizer staff had previously decided would be the theme of the upcoming campaign for their new combination drug, Sigmamycin (a combination of oleandomycin and tetracycline). Dr. Welch's opening remarks, including the reference to "a third era of antibiotic therapy," were delivered at the symposium and were included in that year's *Antibiotic Annual*. Subsequently Pfizer purchased over 260,000 copies of reprints of Dr. Welch's opening remarks from his company, Medical Encyclopedia, Inc., for distribution at home and abroad.[35]

Due to some questioning of the desirability of the FDA's jointly sponsoring the Antibiotics Symposium with a private company, the agency ended its sponsorship after 1957. Welch, however, was allowed to remain chairman of the symposium, and FDA personnel were authorized to participate.[36] FDA management remained oblivious to Welch's financial dealings. The agency continued to accept Welch's statement that he received only an honorarium, and no effort was made to determine if he profited from advertising or reprint revenue.

Finally, in February 1959, John Lear, science editor of the *Saturday Review*, broached the subject of the possibility of conflict of interest regarding Welch's dual roles as regulator and editor. In a private interview with Welch, Lear pressed Welch about his financial arrangements. Welch again claimed that he received only an honorarium for his efforts, and he did not intend giving up his editorial position.[37]

The Lear article brought the question of conflict of interest into the public eye. As a result of the article and a number of letters from interested congressmen as well as queries from the press, HEW Secretary Arthur Flemming began looking into the matter. In the spring and early summer the investigation was slowed when Dr. Welch suffered a heart attack. By May Flemming had determined that the matter could only be settled by writing new policy regarding outside activities. Top FDA-HEW officials now began studying whether honorariums, advertising revenues, and sales of reprints were common practice in scientific publishing. But still Welch was being

[35] *Ibid.*, Part 22, 11967-70, 11997, 12014-15.
[36] *Ibid.*, Part 23, 12561, 12585, 12951.
[37] John Lear, "The Certification of Antibiotics," *Saturday Review*, Feb. 7, 1959, 43-48.

treated with kid gloves. Top FDA management refused to ask Welch the really hard questions: namely, how much he actually received and what was the formula for his payments.[38]

As late as June 1, 1959, the FDA still had no clear understanding as to how the journals were financed. Larrick, on a speaking trip to Florida, stopped to visit Welch who was recuperating in Miami. Only then did Larrick learn that the *Journal of Antibiotic Medicine and Clinical Therapeutics* was a controlled circulation journal whose principal revenues came from advertising and reprints. But Larrick was misled by Welch's statement that the journal consistently lost money. Larrick, ever reluctant to push Welch, failed to determine that it was the first journal which was the really lucrative vehicle.[39]

By October 1959, Secretary Flemming had formulated new policies greatly tightening outside activities, and thus requiring Welch to resign his editorial position and sever all ties with Medical Encyclopedia. In his press conference announcing the changes, Flemming, however, complimented Welch for being "one of the outstanding scientists at the present time"; he further stated, "No one has intimated any actual conflict of interest."[40]

It took the Kefauver investigation into the Welch case in May and early June of 1960 to reveal finally the degree to which Welch had indebted himself to major drug manufacturers. In turn the Kefauver investigation clearly demonstrated the lengths to which Welch had gone to endorse combination drugs for the benefit of Pfizer.[41]

A week before the Kefauver committee released the real amount of Welch's "honorarium," Welch filed for retirement on grounds of disability. The day after the release of the Kefauver findings (May 18), Welch, under orders from Secretary Flemming and Larrick, resigned. There was no way to deny him his federal disability pension which had been granted before the disclosures were made.[42]

The Kefauver revelations alerted Flemming to the possibility of further cases of conflict of interest in the agency and to the need to revamp the agency's regulatory powers, especially regarding drugs.

Two outside committees were appointed to probe the workings of the FDA to evaluate the performance of the agency. A panel of distinguished

[38] Administered Prices, Part 23, 12951, 12959-63, for copies of congressional inquiries see 12969, 12975-82.

[39] Memo, George P. Larrick to Charles Miller, June 1, 1959, *ibid.*, 12964.

[40] *Ibid.*, 12952, 12966.

[41] The investigation into the Welch affair can be found in *ibid.*, Part 22, with a mass of supporting documents in Part 23.

[42] *Ibid.*, Part 22, 12086-88.

scientific experts reviewed the policies and procedures of Welch's Antibiotic Branch and the New Drug Branch generally giving them an acceptable rating. But the panel also pointed out that the agency needed to increase its statutory powers in areas concerning the regulation of drug advertising and the control over the proof of drug efficacy. Most importantly the agency needed the proper budgetary allowances to keep abreast of the most recent advances in its regulatory field.[43]

A second committee spent six months trying to locate other possible conflict of interest cases and determining if the agency worked too closely with the drug industry. A careful examination of key FDA employees revealed that no present employee of the FDA presented a potential conflict of interest problem. But the experience of being required to divulge one's personal finances and having to prove one's integrity had a damaging effect on morale in the agency. The second committee did find, however, that due to increased responsibilities and decreased resources, the FDA in the fifteen years since the end of the war had moved too close to the drug industry. The committee felt that the agency needed to depend less on industry self regulation and act more aggressively in the consumer's interest.[44]

In the end, the Welch scandal proved to be an isolated case. But the episode did force the agency to revitalize its regulation of drugs, leading to the most comprehensive revision of the food and drug law since 1938. Indeed in the aftermath of the passage of the Food and Drug Amendments of 1962 (the Kefauver-Harris Amendments) the agency has been accused of being overly cautious in its regulation and introduction of new drugs.

[43] For the full report of this investigation see: *National Academy of Sciences–National Research Council Report of Special Committee Advisory to the Secretary of Health, Education and Welfare to Review the Policies, Procedures, and Decisions of the division of Antibiotics and the New Drug Branch of the Food and Drug Administration.* U.S. Congress, Senate. *Drug Industry Antitrust Act Hearings before the Subcommittee on Antitrust and Monopoly of the Committee on the Judiciary on S. 1552,* 87th Cong., 1st and 2nd sess., (1961), Part 2, 459.

[44] For the second report see: "Report to the Secretary of Health, Education, and Welfare Concerning the Food and Drug Administration," *ibid.*, 471-72, 474.