

# Pharmaceutical Manufacturing in America: A Brief History

by Arthur Daemmrich\*

*Abstract:* This article reviews the history of drug manufacturing and changes in the compounding of drugs by pharmacies in the United States and outlines opportunities for new research into the making of medicines. The pharmaceutical industry has long been on the vanguard of globalization, and drug companies restructured their international manufacturing footprints frequently in the 19th and 20th centuries. Firms in the prescription drug sector were among the first to market products internationally, to build manufacturing plants around the world, and to integrate research from laboratories across multiple time zones. Yet, issues of quality and safety have arisen repeatedly and the industry has continued to produce its newest medicines in North America even as technological capabilities increased significantly in China, India, and elsewhere since the 1980s. Compounding pharmacies, by contrast, experienced a steady decline during the second half of the 20th century as medicines arrived from producers in final form. The emergence of individualized therapies, however, is now bringing a resurgence in business for biological labs acting in many ways as compounders. Broadly, as pharmaceutical firms turned to a business model built around research and intellectual property production, and as pharmacists shifted from producing medicines to repackaging them for patients, analysts likewise turned to regulation, pricing, and new product innovation as subjects of their research. As a consequence, pharmaceutical manufacturing is largely ignored in the recent historiography of medicine, pharmacy, and pharmaceuticals, an oversight that should be rectified.

## Introduction

Pharmaceutical firms known today for their new drug innovation and worldwide marketing largely grew out of nineteenth-century pharmacies and chemical manufacturers. On the leading edge of globalization, these companies expanded production around the world between the 1890s and 1910s, rebuilt in the interwar period, and then grew internationally again after World War II. By the 1990s, manufacturing was highly specialized and involved complex production chains that often spanned multiple countries. Small molecule chemicals, including both generics and active ingredients for branded drugs, were typically made in facilities in China, India, or other developing

countries, while biotech-based medicines were produced in the United States and Europe.

In the meantime, the majority of pharmacies experienced a sharp decline in the need for drug compounding even as they grew into national chains between the 1950s and early 2000s. The recent emergence of personalized medicine, typically involving treatments customized based on a patient's specific cancer or immunological disorder, is sparking new demand for the services of compounding pharmacies and biotechnology laboratories. Furthermore, a new wave of concern regarding product quality and counterfeit drugs suggests that writing an obituary for drug manufacturing in the United States is premature.

Published in 1965, Glenn Sonnedecker's "The Rise of Drug Manufacture in America" offers an intriguing snapshot against which to consider subsequent changes to pharmacies

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and the pharmaceutical industry.<sup>1</sup> In the article, Sonnedecker captured the sector's history from nineteenth-century apothecary to a modern industry, with manufacturing at the center of its identity. Written just three years after the major regulatory intervention of the 1962 Kefauver-Harris Drug Amendments, Sonnedecker's essay in retrospect marked the end of an era for compounding pharmacies and the beginning of a shift in the industry away from its manufacturing roots. While firms had established research laboratories starting in the early 1900s (and had chemistry labs to test compounds and occasionally synthesize new ones some decades before), they retained strong manufacturing identities through the 1950s.<sup>2</sup> Similarly, while chain pharmacies enjoyed tremendous growth after WWII thanks to sales of prescription drugs pre-supplied in pill or tablet form, compounding of medicines remained at the core of their business when Sonnedecker wrote his article.<sup>3</sup> Both would change significantly after the mid-1960s.<sup>4</sup>

Taking Sonnedecker's essay as a point of departure, this article advances a long-range history to the pharmaceutical industry's manufacturing function, with attention also to shifts in pharmacies as sites for compounding drugs. While critical of linear path innovation narratives, most recent scholarship nevertheless gives dominance to the laboratory and clinic while underplaying manufacturing. The production of medicines is not seen as a place of change over time or of strategic significance to the industry. Furthermore, few studies connect pharmacy and pharmaceuticals as historians like Sonnedecker and others had done for decades.<sup>5</sup>

Instead, historians and economists are examining success or failure with drug discovery, clinical trials, marketing, and mergers to explain the longevity or brevity of individual firms.<sup>6</sup> For the pharmaceutical industry writ large, scholars are tracking the industry's strategic shifts when examining knowledge production, information management, and advertising and marketing. As a result, manufacturing has been ignored as a potential contributor to innovation or as a source of competitive advantage. Even though the business of pharmaceutical firms has been aptly characterized as "the manufacture and processing of raw materials into medicines," historians of science, technology, and medicine have been

drawn instead to the arenas of medicinal innovation, human clinical trials, and marketing.<sup>7</sup>

This article begins with an overview of Sonnedecker's 1965 work and then brings the history up to the present by outlining changes in the manufacture of drugs in America. I find that the pharmaceutical industry offers a key locus for issues of interest to historians of science, technology, and medicine as well as to contemporary policy analysts regarding manufacturing more generally. The article concludes with thoughts concerning ongoing tensions in the ontological status of the pharmaceutical industry, an important issue raised somewhat cryptically at the end of Sonnedecker's article.

### **Origins and Growth of American Drug Manufacturing**

Sonnedecker begins his review with an intriguing observation concerning both individual and collective (i.e., public health) reliance on a "remote industrial complex" that produced drugs and medical supplies.<sup>8</sup> Treatments that were historically manufactured or compounded locally by a physician or pharmacist were produced and packaged at a distance by the mid-1960s. Sonnedecker suggests that discomfort with this distance was greater than for other industries; thus even though food was bought packaged from stores in the 1960s, consumers maintained some proximity to farms and could see the original source of what they were buying. The claim is an intriguing one; Americans had bought medicines from Europe and Asia since colonial times and national marketing of both patent drugs and legitimate medicines had separated consumers from the animal, plant, or mineral origins of therapeutics since at least the 1880s. But Sonnedecker was correct to observe that further distancing patients from where the ingredients in their prescription medicines were sourced, and who had compounded them, was impacting public trust.

From the early colonial period through the mid-nineteenth century, limited medical supplies and the vagaries of shipping constricted American pharmacy. Native therapies were adopted and adapted into folk treatments and Americans living and working on large farms in the south or on the frontier often had a medi-

cine chest with powdered and dried materials that they mixed themselves using recipes provided with the kit. A variety of texts supported home remedies, ranging from practical folk narrative to exotic suggestions. For urban residents, apothecaries grew up in the heart of cities like Boston, New York, and Philadelphia. Some, for example, Smith, Kline & French in Philadelphia, later grew from small community pharmacies into manufacturers of pills and then began doing research into new medicines in the early twentieth century.

The Revolutionary War impacted drug imports for several years and stimulated domestic production in larger pharmacies. The Continental Congress even set up a manufacturing laboratory under an Apothecary General. Medicine chests, a useful source for historians

seeking to understand both treatment practices and changes over time to therapeutics, reveal a rough balance among botanical medicines, chemical drugs, and preparations ready to use (tinctures and plasters). Superstitious remedies found in sixteenth-century and seventeenth-century medicine kits were no longer common by the 1770s. However, concerns about variation in kits, worries about the compounding of drugs on the American frontier, and the desire of pharmacists and the nascent pharmaceutical industry to demonstrate independence from Europe spurred the development of the first United States Pharmacopeia, published in 1820.<sup>9</sup>

Yet, while some pharmacies turned into manufacturing laboratories and later into multinational drug companies, mechanization slowly impacted their business. Thus, as the industrial



*A typical eighteenth-century medicine chest, which were sold widely for use at home and while traveling. Photograph courtesy of the Smithsonian National Museum of American History (M-06371).*

revolution unfolded in Britain in the eighteenth century and in the United States in the mid-nineteenth century, machine power had modest impact on the more “delicate and varied hand operations required to make drugs,” in pharmacies in Philadelphia, Boston, and elsewhere in the country.<sup>10</sup> Sonnedecker describes Ellis and Morris, a Philadelphia pharmacy, and the drug producer Squibb as gradually moving into factories and employing steam-driven stirring and grinding machines in the 1850s and 1860s. Drug manufacturers remained small operations, with only 20 to 30 employees.

The late nineteenth century brought more significant changes to pharmaceutical production. Handicraft methods for the extraction and concentration of active substances and their combination with inert materials into pills were replaced by new equipment. Interestingly, much of it was repurposed or modified from the baking industry (mixers), laundries (centrifugal machinery), confectionaries (sugar coatings), liquor producers (distillation) and the paint and pigment industry (tube-filling). Just as pin-making machines significantly increased output for an industry once characterized by craft skill, medicines production jumped from 5,000 pills per day when made by humans to two million per machine in a factory process.<sup>11</sup>

Even though U.S. firms started to hire scientists from the 1890s on, first in quality control and then to carry out research into new chemical therapies, German dominance in synthetic organic chemistry meant that both intermediates and so-called “finished medicinals” were largely imported.<sup>12</sup> World War I blockades forced American chemists to replicate German processes for producing drugs such as aspirin, the antimicrobial salvarsan, and barbitol, a powerful hypnotic useful in easing the pain of battle wounds, among others. American pharmaceutical manufacturing also benefitted tremendously from the expropriation of German patents. The U.S. Alien Property Custodian assigned German company held patents to a newly created “Chemical Foundation,” which in turn offered nonexclusive licenses to any firm qualified to produce the medicines.<sup>13</sup>

## World War II and Post-War Growth

The interwar period saw a gradual increase in international trade and steady growth for U.S. manufacturers, but as the economy endured the shock of the Great Depression, drug production also slowed. World War II, however, brought about a major transformation for the U.S. pharmaceutical industry, especially following innovations in deep tank fermentation for the production of antibiotics. A wartime project to test, mass-produce, and ultimately distribute penicillin to soldiers on the front featured collaboration among government officials, pharmaceutical firms, and academic researchers. Coordinated by the U.S. government, specifically the War Production Board, the initiative involved otherwise competing firms sharing production knowledge gained as they moved from petri dishes to shallow flasks to deep-tank fermentation.<sup>14</sup> As the price of penicillin dropped after WWII, companies developed accelerated research projects and found dozens of new medicines, produced through the same fermentation processes.

Beyond the booming postwar antibiotic market, a new generation of psycho-pharmaceuticals moved quickly from invention to mass-markets. The marketing of meproamate as *Miltown* by Wallace Laboratories (a division of Carter Products) and as *Equanil* by Wyeth starting in 1955 signaled the start of an era of treating less severe mental and emotional conditions among significantly larger patient populations. Medicines were newly available to treat not just major psychiatric disorders, but also for use by the general public with issues of anxiety and stress. Physicians drawing on the newly standardized terminology advanced by the American Psychiatric Association could differentiate between psychotic disorders (e.g., schizophrenia) and milder psychoneurotic disorders (e.g., anxiety).<sup>15</sup> *Miltown* quickly became iconic in American life; within months of its market introduction it was the best-selling drug in the country and by 1957, one-third of all prescriptions were for *Miltown* or *Equanil*.<sup>16</sup>

International opportunities for the industry became apparent gradually in the late 1940s



*Deep tank fermentation, seen here at Abbott Laboratories in the 1940s, revolutionized the manufacture of antibiotics. Photograph Courtesy of the Kremers Reference Files [P39(g)].*

and then in an accelerating fashion after the mid-1950s. Production capacity for both antibiotics (deep-tank fermentation processes) and synthetic organic chemicals (multi-stage industrial synthesis) and manufacturing know-how enabled firms to set up plants in Europe and newly independent nations across the developing world. Drug producers also could draw on a boom in academic chemistry and the ready availability of a new generation of chemical engineers, both in the United States and internationally.

Developments in pharmaceutical manufacturing and packaging meant that physicians could prescribe branded end dosage forms for most ailments by the early 1950s. The percentage of prescriptions that required compounding by pharmacists declined from 75 percent in 1930 to 25 percent in 1950 and fell further to only 4 percent by 1960.<sup>17</sup>

When pharmacists began to substitute generic drugs for branded prescriptions in the early 1950s in an effort to reduce inventory costs

and save customers money, state governments intervened with anti-substitution laws (44 states prohibited the practice by 1959).<sup>18</sup> Doctors' prescriptions were to be filled as written and physicians had sole authority over the choice of medicine. As a result, pharmaceutical firms were separated from direct contact with patients. Physicians acted as authoritative intermediaries, making the collection of data about patients' experiences with drugs, whether positive or negative, subject to their control and oversight.

### **Knowledge Management Firms**

From the mid-1960s on, business analysts and pharmaceutical industry leaders began to de-emphasize manufacturing. For example, after John J. Powers assumed the presidency of Pfizer in 1965, he invited the respected management consultant Peter Drucker to evaluate the company's structure and approach. Drucker concluded that "Pfizer acted like a classic manufacturer," and he advised the firm, "What you are making and selling is knowledge, and manufacturing is incidental."<sup>19</sup> Firms across the industry began to see themselves as in the drug discovery business.

At the same time, pharmaceutical research came to be understood as high risk, especially as new rules for clinical trials took hold in the late 1960s. One strategy followed by many firms involved diversification into a variety of consumer health products, including cosmetics, oral health, and others. When questioned, company leaders often suggested there were efficiencies of scale in manufacturing that would cut across prescription and non-prescription products, or that their expertise in core chemistry would pay dividends.<sup>20</sup> These approaches faded in the 1990s as firms found the prescription drug market significantly more profitable than commodity chemicals or over-the-counter products and little cross-fertilization occurred in either research or manufacturing.

Regulatory oversight of drug manufacturing intensified after the late 1970s. The U.S. Food and Drug Administration (FDA) had long overseen biologicals, largely through certification of antibiotics and certain other treatments. However, the introduction of Good Manufacturing Practices (GMPs) through rules governing drugs (and medical devices) in 1978 set new

standards across the industry.<sup>21</sup> Specifically, the regulations outlined methods for processing, packaging, storing, and shipping drugs that company employees were required to follow. Facilities were also regulated to specify standards for cleanliness, approaches to recordkeeping, and even the kinds of equipment that could be used to make medicines.<sup>22</sup>

One year after GMP rules were finalized, the FDA issued policies for Good Laboratory Practices (GLPs). The GLP rules initially targeted the production of medicines for experimental uses, but would eventually have an impact also on personalized (or “precision”) medicine when it emerged in the early 2000s. GLP rules specified recordkeeping methods, approaches to sterility and cleanliness, and other dimensions of laboratory work to ensure the safety of drugs manufactured in small batches, typically for clinical research studies. They also covered the production of food and color additives, animal food additives, medical devices for human use, and more recently, electronic products.<sup>23</sup>

Furthermore, the law provided for a system of pre- and post-market oversight, including FDA inspections, to ensure that companies follow GMPs, keep appropriate records on the design and manufacture of their products, and maintain systems for handling complaints. While designed with industry input, rules for Good Manufacturing Practices also locked in production to highly specified procedures and equipment. Unlike in other sectors, pharmaceutical firms committed to specific manufacturing approaches and changes, which, even if they saved money or reduced waste, involved additional regulatory review.

In October 1982, a tragic wave of seven deaths arose from criminal tampering with over-the-counter Extra-Strength Tylenol. Once the link was established, the manufacturer Johnson & Johnson announced a nationwide recall encompassing some 31 million bottles of the product, and halted all sales for over six months. The cost to the company was later estimated at over \$100 million for the recall and subsequent relaunch of the pain medication. When relaunched, the product featured three security layers, namely a glued box, a plastic seal over the neck of the bottle, and a foil seal over the bottle’s mouth. Regulatory responses included new FDA-issued tamper-resistant packaging

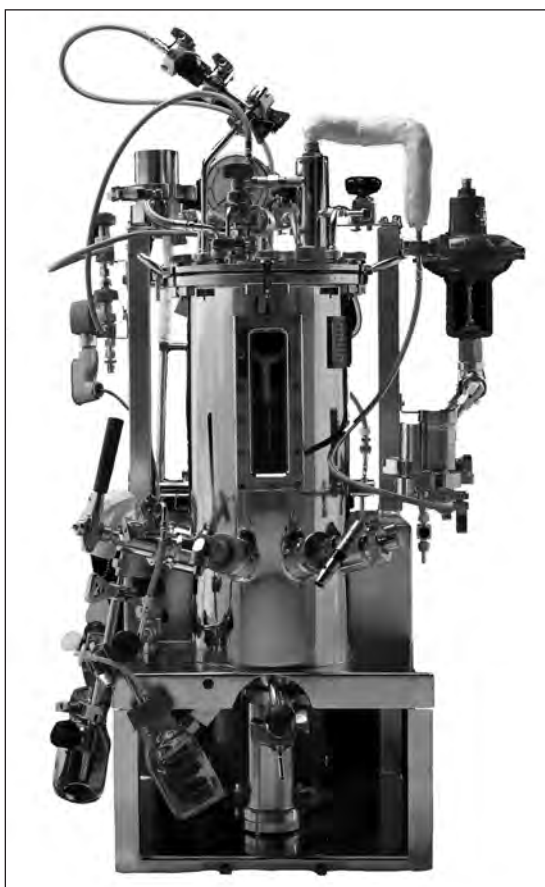
regulations for all over-the-counter human drug products (incorporated into GMPs). In addition, the U.S. Congress passed the Federal Anti-Tampering Act in 1983, making it a crime to tamper with packaged consumer products. Broadly, the acetaminophen tragedy had an impact across the pharmaceutical industry as capsules were replaced by tablets. Johnson & Johnson’s rapid response and strong public communication later became a case study in corporate communication and ethical management.<sup>24</sup>

In 1986, the heartburn and peptic ulcer drug cimetidine (Tagamet) was the first prescription drug to generate \$1 billion in sales in a single year. Labeled a “blockbuster,” it came at a time of rapid growth for the pharmaceutical industry as prescription drug prices and sales volumes increased rapidly year-on-year.<sup>25</sup> With the promised gains from portfolio diversification not materializing, pharmaceutical firms sold off their non-prescription drug businesses and engaged in a series of mergers during the 1990s and 2000s. Although challenging to quantify considering the large number of confounding variables, some economists found that the mergers contributed to an innovation decline across the industry, indicating that it was a self-defeating strategy.<sup>26</sup>

## **Biotechnology and Individualized Therapies Made in America**

The targeted creation of genetically modified organisms moved quickly from a laboratory technique in the mid-1970s to the basis for a wave of new biotechnology firms by the early 1980s. Promising not only cures for cancer and immune disorders, but also a new way of conducting research and manufacturing pharmaceuticals, first hundreds and eventually thousands of new biotechnology firms were started in the United States.<sup>27</sup> Interestingly, the industry eventually stabilized at between 350-450 publicly traded and approximately 2,000 private biotechnology companies in any given year from 2010-2016.

Even as biotech expanded the manufacturing portfolio of the pharmaceutical industry, firms took advantage of lowered trade tariffs and expanded technical capacity in India and China to import ever more active pharmaceu-



*This fermenter was used at Genentech during the early 1980s to grow recombinant bacteria from which proteins were extracted to be used in medicines. Photograph courtesy of the Smithsonian National Museum of American History (2012.0198.01).*

tical ingredients. As a result, the United States shifted from a net exporter to importer of pharmaceuticals in 1997.<sup>28</sup> Nevertheless, global biotech drug research and production remained centered in the United States, where investors continued to optimistically fund new firms and pricing remained unregulated.

Large pharmaceutical firms adopted diverse strategies in dealing with, or ignoring, the biotech industry. Some firms drew on their lineages in antibiotics and other biological-based research to develop new manufacturing capabilities.<sup>29</sup> For these firms, research alliances and joint ventures drew on new in-house expertise. Other large firms opted to wait for biotech com-

panies to advance new therapies through the clinical trial process before acquiring them.<sup>30</sup> In some cases, small biotech companies developed drugs that gained FDA approval and then built out manufacturing and marketing capabilities; in effect, joining the ranks of the more established pharmaceutical industry.

Although compounding pharmacies had all but disappeared from public or even regulatory awareness by the early 2010s, a tragic case of tainted medicines brought them back into the limelight. The owner and head pharmacist of the New England Compounding Center was later found responsible for fungal contamination of spinal steroid injections that were distributed to 75 facilities in 23 states. Out of 14,000 patients, there were 48 fatalities and some 720 persistent infections that needed lengthy treatment. Inspectors found an unclean and unsanitary facility with standing water and mold and bacteria on worker's gloves. Reporters covering the story were surprised to learn that compounding pharmacies were only subject to state licensing and inspections not to FDA regulation.<sup>31</sup>

Starting in the late 1990s, a new wave of entrepreneurs and scientists began to anticipate a future of personalized medicine, also termed precision medicine. Even as the definition of personalized medicine shifted rapidly in its early years, some critics warned it was overpromising and under-delivering. Yet, the first medicine widely hailed as a personalized therapy was approved by the FDA in May 2017. Merck's pembrolizumab (Keytruda) was approved for the treatment of tumors that express one of two biomarkers, regardless of where in the body the tumors are located. The decision marked the first time FDA approved a cancer drug based on the expression of specific biomarkers, rather than the tumor's location in the body.

Emerging personalized medicine treatments hold tremendous promise to target attacks on cancers or potentially heal the immune system. Their production, however, requires remarkably sophisticated controls, since any stray proteins or other contaminants, even at a part per million level, can cause fatal allergic reactions. As a result, GLP regulations have gained in salience in addition to the GMP rules; both were revised numerous times in the 1990s and 2000s. Yet personalized drugs fall under the umbrella of drug compounding, with

small-scale production of medicines by a small number of laboratory scientists and specialized pharmacists. In 2013, the Drug Quality and Security Act (H.R. 3204) moved oversight for compounding labs from the state level to the FDA in response to fatalities and other adverse reactions from contaminated compounded drugs. The FDA's proposed rules for oversight were available as "draft guidance" starting in January 2017. Yet, the costs of individualized or precision drugs are proving extremely challenging for health insurers and patients; the 50 "targeted" therapies holding FDA approval in 2017 were priced between \$70,000 and \$130,000 per treatment cycle.<sup>32</sup>

### Conclusion

The pharmaceutical industry, Sonnedecker notes, is a "complex industrial organism"; it serves a public purpose when inventing and manufacturing medicines, but does so in a quest for profits and financial returns. Its fundamental reason for existence, to Sonnedecker, is clear: "public health."<sup>33</sup> Whether it fulfills that purpose is a frequent topic of policy dispute in settings ranging from congressional hearings to street protests. When outcomes align, there are measurable gains in longevity and quality of life for millions of people. But incentives are also strong to convince physicians to write prescriptions by any means possible, to downplay or ignore adverse reactions, and to focus on diseases impacting wealthier people while ignoring those affecting people in poorer regions.

Under the innovation model that has held across the pharmaceutical industry for the past fifty years, manufacturing has become completely cut off from research and product development. Whereas pharmacists who made medicines in the nineteenth and early twentieth century and scientists who engaged in the pro-

duction of early antibiotics could iterate and innovate in manufacturing, a mix of regulations, standards, and strict separation of expertise changed this dynamic from the 1960s onward. Only after products were synthesized and had undergone testing to meet regulatory controls did management give consideration to manufacturing methods. Manufacturing expanded in the 1980s and 1990s to adopt new approaches to biotechnology. Analogous to deep-tank fermentation of antibiotics in the 1940s and 1950s (a method that continues to be used with modest changes), new bio-based molecules are now produced in pristine stainless-steel vats, with precise temperature and pressure controls. But emerging approaches to individualized therapies for certain forms of cancer—the leading edge of what may become a broader approach to personalized medicine—now involve a diverse set of research, laboratory, and manufacturing expertise in the production of a therapy.

Sonnedecker's final sentence in a bibliographic addendum noted the absence of a "systematic definitive history of drug manufacture in America."<sup>34</sup> While no such comprehensive volume has been written since, it would be an important undertaking, especially considering that the invention and manufacture of therapeutic drugs in the United States remains strong, even as many other industries shifted production and even new product research overseas. Sonnedecker concluded, almost wistfully, "A century ago... a drug manufacturer understood that his work was to manufacture, without becoming entangled with unpredictable, often unproductive, but always costly, scientific experiments."<sup>35</sup> Had the industry not become research-intensive it likely would not have survived. At the same time, building a firm around intellectual property has also proven a challenge, not least for the public policy implications.





*Sprawling manufacturing plants like this E. R. Squibb & Sons facility in New Brunswick, New Jersey (seen here in 1958), helped to supply mass-market pharmaceuticals after World War Two. Photograph courtesy of AIHP Drug Topics Collection.*

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