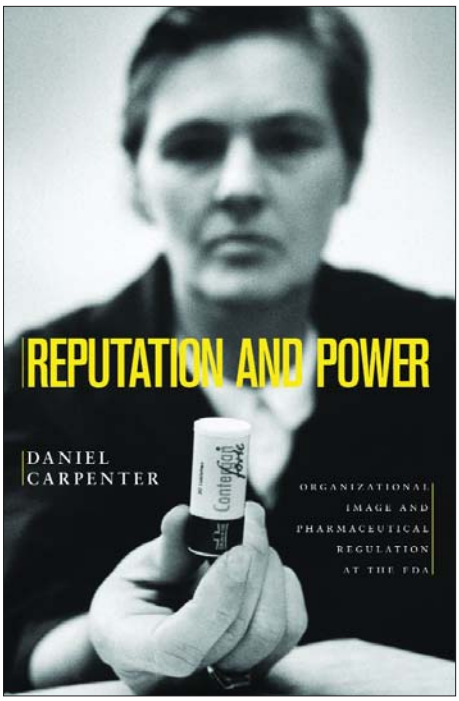
From the Sidelines to the Center

How the FDA Emerged as One the World's Most Powerful Regulators

By Bob Yeoman



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"Reputation and Power" by Daniel Carpenter (Princeton University Press: $29.95) chronicles the morphing of the Food and Drug Administration (FDA) from a watchdog organization operating predominantly on the sidelines of the US pharmaceutical regulatory arena 75 years ago, into arguably the single most powerful and far reaching regulatory body the world has ever known. In the book, Carpenter examines how FDA cultivated their reputation as highly formidable guardians of the US drug supply, and used that reputation to enhance and expand the scope and reach of their authority over time to all corners of the globe. This article will recount some of the key turning points in FDA's reputation and power, and how the lessons in this book can be applied to the gas industry's dealings with the agency today.

Few if any people reading this article can remember a time when FDA was not both the gatekeeper controlling which drugs enter the US market, and the toughest cop on the beat enforcing our nation's pharmaceutical regulations. However, prior to the late 1930s, the FDA was essentially a toothless tiger holding very limited authority. The American Medical Association (AMA) held the bulk of the prestige and authority over drug approval at the time. As the country began to crawl out of the Great Depression there was debate in the US over changing existing laws governing pharmaceuticals. People inside FDA sought to use this debate to increase the agency's role in regulating drugs. President Roosevelt's administration was focused on jumpstarting the economy and showed little interest in this issue, so Congress was the epicenter of the discussions. Then, as now, the pharmaceutical industry's lobby was out in force and it seemed that an industry-compatible version of the proposed regulations would pass. And it is likely that FDA would have lost power, instead of gaining it, had the original version of the bill passed. However, the landscape changed quickly and dramatically in 1937 when a series of deaths, all linked to a new drug on the market containing Sulfanilamide and produced by a manufacturer in Tennessee, were reported. The FDA seized this as an opportunity to showcase the agency to Congress and the public in a highly visible role as a protector of the US drug supply by championing the recall and removal of the drug from stores. The FDA went as far as sending agents to scour all of the country's pharmacies, and made sure members of Congress and the public were fully informed of these actions. The agency very effectively aligned itself with public interest lobbies to campaign for stronger drug laws, and for FDA's primacy in policing them. Groups like the Women's Temperance Movement, a highly vocal public/consumer lobby at the time, took up FDA's cause. Politics being what they are, once this issue evolved from a discussion inside the halls of Congress into a public debate, with significant media exposure, the Roosevelt administration went from disinterested to becoming a staunch supporter of the more conservative regulatory approach.

This culminated in the 1938 passage of the Federal Food, Drug, and Cosmetic Act (FD&C). Congress passed what was considered the most conservative version of the law, taking out only one major provision — price controls on drug companies (shades of 2010). The new law included provisions for pre-market approval of drugs, and established FDA as the gate keeper on all new drug approvals. The US was the first nation in the world to pass legislation requiring pre-market drug approvals, and by being first, essentially established the blueprint that the rest of the world would follow. This newly conferred authority transformed the FDA. By the end of the Second World War they had put themselves in a position to begin exerting ever more control over pharmaceutical firms. Power and prestige was on the rise within the FDA.

The next expansion of FDA's power came without any expansion of FDA's regulatory authority. The agency began recruiting the best and brightest authorities on every aspect of medicine and science that touched on the drug review and approval process. This group began designing and implementing a flood of new policies and procedures for the drug application and approval process. This influx of talented individuals totally transformed the technical and scientific capabilities of the agency, and pharmaceutical firms were forced to staff up to stay abreast of FDA's increasingly scientific and complex drug approval process. The drug approval process was quickly becoming much more sophisticated, and the FDA used this control to further expand its powers.

The FDA leveraged its new technical capability to gain more authority by withholding approval from companies who either failed to provide, or resisted FDA's requests for, additional new data and scientific studies. The FDA now had the power to virtually control a drug company's new product pipeline, and therefore a company's future revenue streams. The new drug application process of the late 1940s and early 1950s also provided FDA with the power to significantly influence a wide range of activities inside pharmaceutical manufacturing companies, such as methods of research, what drugs could be submitted for consideration, the design of clinical studies, and even who was qualified to conduct these clinical studies. These powers were not defined in the 1938 FD&C Act. Firms that didn't want to cooperate or challenged FDA's new requirements in court suddenly found their drug applications

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languishing in an administrative no-man's land. Industry believed FDA was exceeding their regulatory authority, and the subsequent battles over FDA's power and reputation laid the foundation for what was to come next.

The third major evolution in the image and shape of FDA authority came in the early 1960s and involved the drug Thalidomide. Based on what many believed to be FDA's unmandated post-war expansion of power, Congress was again debating significant changes to US drug laws by the late 50s. The chief proponent of change at the time was Senator Estes Kefauver. His push in Congress was to basically codify the expansions of authority the FDA had already implemented, but Senator Kefauver's bill was largely bottled up in Committee by its opponents. Simultaneously, Merrell Pharmaceuticals was seeking US approval for the drug Thalidomide. One of FDA's new star recruits, Dr. Frances Kelsey, was assigned to review Merrell's application, and immediately began identifying issues with the new drug's application. Merrell fought hard to get their drug approved but Dr. Kelsey held fast, and Thalidomide never received US clearance. By the fall of 1960, physician reports began to surface in Europe indicating there was a problem with the drug. Over the next year the tragic effects of the drug became widely reported, but FDA's role in protecting the US drug supply was not well known until July 15, 1962 when the Washington Post published an article proclaiming Dr. Kelsey as the Heroine of FDA. The Post's report gave readers a detailed recounting of Kelsey's actions to keep what she correctly believed to be an unsafe drug off the market.

Politics and politicians generally being the same in 1962 as they are today, Senator Kefauver immediately called upon President Kennedy, who had shown scant interest in the drug law change debate up to this point, to recognize Dr. Kelsey's actions. In a highly publicized White House ceremony on August 7, 1962 President Kennedy presented Dr. Kelsey with the Distinguished Federal Civilian Service Medal, the first such distinction to be awarded to a federal civilian employee since 1955 when President Eisenhower presented the same medal to Dr. Jonas Salk for his discovery of the Polio vaccine.

This event was a huge boost to Dr. Kelsey's personal prestige and to power inside and outside of the FDA. The media heralded her as a model of FDA ethics, and she was named in 1962 as one of the 10 most admired women in the world. She ultimately became head of FDA's Bureau of Medicine, and supervised all drug approval activities at FDA. What's more, this event provided a windfall boost to FDA's prestige both inside the US government and around the world.

It also had an important affect on FDA's power base. President Kennedy directed his staff to send a letter to Congress citing seven amendments that he required be attached to the Kefauver amendments to the FD&C Act to garner his approval of the bill. President Kennedy's intervention broke the Congressional log jam, and once again, in late 1962, FDA saw Congress pass a piece of legislation containing virtually all of the key provisions they had been seeking, and ushering in a new and significant expansion of their power and reputation.

Carpenter's book makes the point that the mid-to-late 1960s was the zenith of the FDA's reputation and power, and that power has been eroding ever since. While for many that may sound hard to believe, consider FDA's involvement in the so-called War on Cancer. In the early 1970s, the FDA became embroiled in a battle with the National Cancer Institute (NCI) for approval authority over new cancer drugs entering the market. NCI became frustrated with the FDA and publicly sought to circumvent FDA authority, going so far as to lobby for full authority over both cancer drug research and new cancer drug approvals. FDA viewed the loss of any of their authority over cancer drug approvals as a potential major blow to their prestige and power, and the two groups waged war for nearly a decade. Ultimately the two organizations settled their differences and issued a joint memo of understanding in 1979, just ahead of Congress stepping in to settle the fight. This episode ultimately did damage the FDA's reputation and the NCI successfully assumed a portion of some of FDA's power. FDA's prestige was further eroded in the late 70s over the debate surrounding the cancer drug Laetrile. The agency believed the drug to be without merit and would not authorize human trials. However, the drug had a large and vocal group of supporters, including numerous celebrities of the day, most notably Steve McQueen. While the agency eventually did permit trials, and those trials ultimately found the drug without merit, the damage had been done. The FDA had been portrayed as a road block to approving new, potentially lifesaving drugs, rather than a gatekeeper preventing the introduction of dangerous or meritless drugs.

As people tried desperately to find a cure and stop the spread of AIDS/HIV in the 80s, the same issues arose. Gay activism had become organized in the 60s, and its members were generally articulate as well as skilled at utilizing available media sources to get their message out. When the AIDS crisis emerged, this group utilized its existing organizational structure to begin lobbying for faster approval of new AIDS related drugs. The FDA bureaucracy at the time was not particularly oriented towards quick approvals of new drugs. After all, Dr. Kelsey had become the stuff of legend and gained significant power and prestige by holding fast and demanding more information. But the AIDS activists were quickly becoming desperate, and this set the two groups on a collision course. Many readers will remember AIDS groups picketing FDA headquarters in the 80s, and the media coverage portraying FDA as insensitive. It is not my intent to judge whether this portrait of FDA at the time was true or not, but these public demonstrations further eroded public and Congressional confidence in FDA.

Changing Protocols for Drugs

In the late 60s and early 70s, other unforeseen events challenged the FDA's power base. When the 1962 Kefauver amendments were added to the FD&C Act, the predominant type of drug manufactured was a compound designed to cure a condition. Most drugs were meant for a patient to take only until cured. So the FDA's regulatory model was primarily focused on that business model for drug approvals and compliance inspections of manufacturers. Once a new drug was through the gate and approved, the FDA was considered out of the loop. At this time, the whole concept of preventative drug therapy for chronic conditions, like high cholesterol or high blood pressure, was in its infancy and the agency's regulatory model was not set up to focus on potential consequences of taking a drug for decades. As we all know, this changed.

In the mid 60s, the concern over the potential for dislodged blood clots to cause fatal strokes in women taking oral contraceptives opened a new chapter in FDA history. Unlike previous incidents, this issue did not come to a quick head, and festered for decades. This was due in large part to FDA not having the ability to require drug companies to conduct additional trials of an already approved drug. There were also other practical limitations on FDA's power at this point. Millions of women were using this contraceptive, and to simply withdraw it would be difficult since there was insufficient hard evidence at the time on which to base a withdrawal. The FDA had no authority or mechanism in place to require the collection and reporting of post-market drug problems in the mid-60s. It took nearly a decade for sufficient data to surface which confirmed the link between contraceptives and strokes and to draw conclusions.

Oral contraceptives were not the only drug to display problems long after they had been approved for use. Many readers will remember the more recent sudden withdrawal of the very popular anti-arthritis drug Vioxx by Merck. That drug was withdrawn due to concerns over increased incidents of heart attacks by users. Ultimately, the 2007 revision to the FD&C Act implemented new requirements for adverse event reporting, and post-approval monitoring and reporting of approved drugs. While the revisions expanded the FDA's power and authority by adding requirements to conduct Phase 4 post-market studies and instituted a new adverse event reporting system, many view 2007 as a rather late date for the FDA to finally arrive at this point. Other nations had recognized and acted on the need for post-market analysis of drug safety well before this time.

Lessons

There are lessons that can be drawn from this analysis of FDA's history that can be applied to medical gases, whose current FDA status is "marketed un-approved drugs." Unlike virtually every drug sold in a pharmacy today, medical gases have never passed through the proverbial FDA approval gate, and are relegated to a form of quasi-accepted/tolerated status. FDA is currently moving to have all US drugs either go through the approval process or be withdrawn from the market. Since it would be neigh impossible to remove medical gases from the market, ultimately, medical gases will have to apply for and receive official approved drug status. Due to the unique properties and business model of medical gases the process whereby that will happen has not yet been established. When that approval process is established and it becomes time for medical gases to navigate it, we need to bear in mind that FDA views the drug approval process as their main opportunity to ensure a drug's safety, as well as their primary regulatory function.

Over the last 70 years the agency has built up science-based, highly bureaucratic, drug approval processes and requirements. These include specific agency viewpoints on the type and format of information and data FDA expects will be produced to verify a drug's safety. While FDA generally acknowledges the gases industry has a relatively good product safety record, the safety of medical gas products has never been formally documented in a scientific study. The whole concept of reviewing study data to determine safety is at the core of FDA's drug approval process, and I do not believe gases' un-documented track record of safety, in and of itself, will be a sufficiently compelling basis for FDA to approve them. I expect FDA to request scientifically produced and prepared data generally consistent with how other drugs are approved, that will provide the basis and justification for the agency approving medial gases. These requests will likely be relatively non-negotiable.

Our industry also needs to recognize that attempting to pressure FDA directly or through Congress, to circumvent some or all of their approval process, is subject to backfiring. The agency successfully resisted such attempts during the Thalidomide approval process 50 years ago and gained significant power and prestige as a result. FDA has not forgotten that lesson, and in fact, still teaches it to new recruits.

In seeking approved drug status for medical gases our industry must recognize that FDA's willingness to expedite the medical gas approval process, along with their readiness to accommodate our specific issues and business model, ultimately ends up being balanced against their ever-present need to preserve their own reputation and power. Understanding FDA motivation and balance is the key to successfully transitioning medical gases to an approved drug status.

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