"God, Motherhood and the Flag:"
Implementing the First Pharmaceutical Current Good Manufacturing Practices (CGMP's) Regulations

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> *"It takes a lot of hard work, but most things that are worthwhile do. I don't know; it's a difficult area, and it's not one that is going to be resolved by going back to the concept that God, motherhood, and the flag constitute GMP if you're going to really treat GMP's as how-to regulations."*
>
> *Al Barnard* [1]

Introduction

In announcing the agency's new Pharmaceutical cGMP initiative (Pharmaceutical cGMP's for the 21st Century: A Risk Based Approach) to agency employees last year, Deputy Commissioner Lester Crawford paid tribute to the historic origins of formal drug cGMP's in the 1962 Drug Amendments, as well as to the upcoming twenty fifth anniversary of the last major revisions to the drug cGMP regulations. The current initiative's ambitious goals include "integrating quality systems and risk management approaches into the existing programs to encourage industry to adopt modern and innovative manufacturing technology" as well as enhancing the agency's "consistent application of the new principles."[2] If the best predictor of future behavior is past behavior, much of the success of the new initiative will depend on how well both industry and the agency work together to anticipate the changing needs of both institutions in the twenty first century. FDA's oral histories provide some interesting and often contrasting perspectives on the early implementation of drug cGMP's, which may be of interest in the current revisionary climate.

Historically, in spite of the official sounding terminology eventually adopted (cGMP's), manufacturing regulations for foods and medical products have generally been adopted as a necessary evil, and always more of a negotiated process than a finished product. Companies with innovative products want to get to market quickly and maintain profitability, while regulators are charged with insuring that marketability is not achieved through shortcuts in research and production that could harm consumers or other producers through unfair competition. Whether referred to merely as "manufacturing controls," in a statute, or formally promulgated as "current good manufacturing practice" regulations, historical circumstances have always determined both the form and the substance, as well as the extent of the manufacturing controls under consideration. In 1902, Congress elected to have biological product manufacturing establishments licensed individually to protect the public from dangerously contaminated sera

and vaccines. In contrast, Harvey Wiley was unable to simply outlaw the use of sodium benzoate in foods early in the twentieth century, so he was left with only his not inconsiderable powers of persuasion to convince manufacturers to abandon their preserving chemicals. He did so by putting his chemists in their catsup plants to demonstrate that shelf stable catsup could be made using sanitary ingredients and sanitary methods alone.[3] In 1938, Congress mandated that new drugs be safe and that manufacturing methods, facilities, and controls be "adequate," in the wake of the Elixir Sulfanilamide crisis.[4] The first set of interpretive questions designed to guide manufacturers in determining the adequacy of their manufacturing controls did not become part of the NDA process, however, until after Winthrop Chemical Company produced sulfathiazole tablets contaminated with Phenobarbital in 1940, which killed or injured over 300 people nationwide.[5]

Obstacles of Voluntary Compliance

By the 1950s, assuring that drug manufacturers were actually using the adequate manufacturing controls they had specified in their approved NDA's fell to agency inspectors. In a 1997 oral history interview with Arthur Beebe, a respected Northeast Regional Food and Drug Director, who retired after forty years with the agency, Beebe described FDA's expectations of him as an inspector in the 1950s.

> If you wanted to get a new pen at that time--you know, things were very tight money wise; the agency was very frugal--you had to turn in your pen to get a new one. If you went on a two-week trip and you didn't come back with one or two seizures, you were looked at with a little suspicion about what you'd been doing.(p. 6). In the limited time I was in Boston, I developed three prosecution cases and collected a good number of samples that resulted in seizure of adulterated and misbranded products. Today there's not a district or even a region that has three prosecutions a year. It shows how the pendulum has changed over the years from the emphasis on regulatory action to voluntary correction and education. [In the 50s] If you weren't skilled enough to develop a case when violations were present, you didn't get ahead in the agency. Today it's not that there aren't violations, it's just that they are handled in a different manner. Firms are given an opportunity to correct before action is taken. They're given one bite of the apple, and too often in my opinion, two or three bites of the apple before regulatory action is taken. [6]

When asked whether he felt that this approach resulted in more or less compliance than in the past, Beebe sagely replied, "Well it may be cost effective, that's a difficult question to answer.

Let me just say I believe it's unfair to the majority of the industry that complies with the law that those who don't comply are able to have an unfair advantage before correction is made." [7]

According to Beebe, large pharmaceutical companies in those early years had occasional problems with labeling, sometimes with potency, cross contamination and sterility, but in his opinion, "the big drug problems came much later on after GMP's were promulgated."[8] Beebe himself helped develop the first case in which an injunction was granted by the courts solely on the basis of GMP violations. The company made over 160 drugs that could not be distributed again until the company could demonstrate they were being made in compliance with GMP's. [9].

Intensified Drug Inspection Program

And in fact, so many pharmaceutical companies had difficulty complying with the early drug cGMP's that FDA initiated what became known as the Intensified Drug Inspection Program (IDIP). According to Al Barnard, the genesis of the IDIP program came in an office conversation in which a colleague was arguing with him that "the only way to regulate the drug industry was through certification, and that we should move promptly to place all drugs, not just antibiotics, under the certification system." Barnard responded "in effect, that he was out of his mind, that the certification system didn't do any more to ensure perfection in the drug supply than any other system, and that what we really needed was some kind of an inspection system that stayed with an operation long enough to really learn how the operation was conducted, and what went on, and whether or not the process was one that could be consistently repeated. . . . It was out of that concept that the IDIP program was born." [10]

"Simply put," as one former official succinctly summarized it, "the stated mission of these inspections, some of which lasted nearly a year was "to stay there to inspect them into compliance or determine that they couldn't get in compliance and put them out of business." In fact, Gerald Vince, a former director of the Office of Regional Operations, recalls his own success in helping to develop, process, recommend and see to its conclusion, "with a lot of nervousness on the behalf of the Center for Drugs or whatever it was called at the time and our Office of General Counsel," he notes, "the first GMP seizure of a drug product under 501 A(2)(b) as adulterated by virtue of lack of compliance with GMP's. I believe the case was US v Quadrisect Tablets. [It] was a precedent case. It was appealed, obviously, and was upheld, and it's one of the cases that's cited by the agency in its pleadings when it comes to adulteration under 501A (2) (b) charges in the litigation process. [11]

According to former Associate Commissioner of Regulatory Affairs, Paul Hile, this program had wide ramifications.

> "I don't think we perceived it at the time, but in hindsight, perhaps it was a step toward the FDA assuming the responsibility for telling the industry exactly what it had to do to comply with the law. For a long time prior to that, our attitude, I believe, was, it was their responsibility to find out what the law required and to do what it did require. But with this kind of campaign of direct intervention, we were taking on a responsibility for telling them how to run their business." [12]

Interviewed in 1998, Gerald Vince, a drug inspector who became the coordinator of the IDIP, viewed the IDIP as worthwhile, but not without its imperfections.

> There were a number of what I would consider now, at least, marginal or sub-marginal in some cases drug firms who were in business at the time and simply didn't see the light or recognize the fact that the newly enacted GMP's for pharmaceutical production were real, and that they applied to everybody who was making human drugs and some veterinary drugs. These firms chose to disregard what at that time was some of the very basic, essential procedures and controls that are necessary. On the other hand, I also believe that perhaps the agency overreacted to that situation with the pharmaceutical industry and spent a little bit too much time and effort in the firms that were in fact acceptable at the time, just looking too intensely for problems or deviations or things that were not serious and were perhaps even in the process of being fixed or corrected, but management simply hadn't had time yet based upon the explosive technology and the application of the GMP's to that industry. . . . In retrospect, I believe it was probably the right thing to do, but I also believe that perhaps it was a bit overdone . . . it was a very intensive process, very expensive for the agency, because many of these firms were not in cities where there was a resident post, and it was an interesting and challenging time. But I believe, in many instances it was something that was the right thing to do by virtue of the very marginal operations and lack of voluntary effort by some of the firms who chose to continue doing business as they had for the twenty years prior to that. . . ." [13]

Setting Industry Standards

An alternative perspective on the early drug cGMP's comes from Richard E. Williams, an FDA inspector hired in 1939, a month after passage of the 1938 Act, who studied food and drug law with William Goodrich and Vincent Kleinfeld at New York University, but who left his position as a district director in 1962 to join Richardson-Merrell following the company's Mer-29 and thalidomide debacles. GMP regulations, therefore, had just become part of food and drug parlance at the time he joined the company and he helped implement cGMP's for his company worldwide in the next decades. Williams opined that cGMP's

> “are a very, very reasonable body of regulations. They make sense. Now, of course, I may be thinking that they make sense because all the good companies were able to adapt to them. Maybe it's just because I'm so well acquainted with them that I think they are good. I think they have done a lot to improve the reliability of the drug. No question in my mind but they do contribute to assurance of safety of the drug. So I'm all for them. As you may know, I became more and more active later in my career with the company in the GMP area than any others because it was a very burning subject with the industry generally and with the FDA for many years. . . As an industry person, I was always very much in favor of strict enforcement by the FDA. It was good for my company to have the law strictly enforced because we were trying to strictly comply. So we hoped that our competitors would strictly comply."[14]

Williams' firm was not one of the firms under the IDIP program, so perhaps not unexpectedly, his complaints about implementation of drug cGMP's centered around FDA's implementation of the requirements.

> "I was quite unhappy with the quality of the work of many Food and Drug inspectors in many, many instances. I felt that they were not adequately trained in what the law requires, particularly in the GMP field. They couldn't answer some of my questions about GMP regulations, which I thought they should know by heart and be able to apply in a common sense way."[15]

Some FDA field officials even agreed. In 1997, Arthur Beebe lamented that FDA had "too many drug inspectors who think they're God, and they interpret the GMP's, and "you either do it the way I interpret it or else. Everything's either black or white. . . they don't use any judgment."[16] Gerald Vince recalled some problems stemming from inexperience with the early cGMP and especially GLP inspections, but counters that this stimulated some of the earliest "team inspections."

> "By the mid-sixties, the late sixties, the automated analyses, the gas chromatographs, etc. were coming on. I knew diddle-squat about the proper way to evaluate and assess the system suitability of an instrument like that, etc. We did, it was a first at that point, take some of our laboratory folks along with us on inspections primarily related to the labs. This was a practice that for some reason was sort of overlooked or disregarded for the next twenty years. It wasn't until again perhaps in the early 90's that management in ORA was reawakened and said, "Gee, we have a tremendous resource in our laboratories, primarily the drug analyst and in those cases of a sterile operation, a microbiologist. So let's get our act together and make up a team and go out and really do this thing thoroughly and completely and adequately." [17]

Conclusion

The last major revisions to the pharmaceutical cGMP's were initiated in an environment characterized by major scientific advances, tremendous industry growth, and changes in the organization and orientation of FDA itself, both symbolized and characterized by the appointment of FDA's first Commissioner from outside the agency, Dr. James Goddard. Under his leadership, the agency had begun to move away from its traditional focus on individual legal actions, became more public health oriented, and more interested in educating industry on what it needed to do to comply with the law. This initiative will be led by Dr. Mark McClellan, the agency's first commissioner with a formal economics background, in an atmosphere also

characterized by major scientific advances, but also marked by international concerns about terrorism and its potential health effects, concerns about the impact of pharmaceutical regulation in the context of an aging population and ever-rising health care costs, and in an economy that has been less than robust in the past few years. The cGMP changes being discussed and proposed will undoubtedly reflect some of these new realities.

Endnotes

[1] FDA Oral History Interview, May 14, June 4, 1987 and March 2, 1989, p. 45.

[2] Memo to FDA Employees from Deputy Commissioner, re: Pharmaceutical cGMPs Initiative, August 21, 2002

[3] Andrew F. Smith, Pure Ketchup: A History of America's National Condiment (University of South Carolina, 1996), p. 80-83.

[4] Dale E. Cooper, Adequate Controls for New Drugs: Good Manufacturing Practice and the 1938 Federal Food, Drug, and Cosmetic Act, Pharmacy in History, vol. 44, no. 1 (2002), pp. 12-23.

[5] John P. Swann, The 1941 Sulfathiazole Disaster and the Birth of Good Manufacturing Practices, PDA Journal of Pharmaceutical Science and Technology, vol. 53, no. 3, May-June, 1999, pp. 148-153.

[6] FDA Oral History Interview with Arthur James Beebe, Jr. and Robert A. Tucker, August 6, 1997, p. 4.

[7] Ibid., p. 5.

[8] Ibid., p. 15.

[9] Ibid., p. 18.

[10] FDA Oral History Interview with Al Barnard and Ronald Ottes, May 14, June 4, 1987; March 2, 1989), p. 45.

[11] FDA Oral History Interview with Gerald E. Vince and Ronald Ottes and Robert Tucker, December 2, 1998, p. 17

[12] FDA Oral History Interview with Joseph Paul Hile and Fred L. Lofsvold, Ronald T. Ottes, and Robert G. Porter, October 22, 1986, p. 114.

[13] Vince Oral History, p. 14.

[14] FDA Oral History Interview with Richard E. Williams and Ronald T. Ottes, March 20, 1989, p. p. 37

[15] Ibid., p. 43.

[16] Arthur Beebe Interview, p 47." Beebe continued: But the trauma! The FDA people don't realize how much trauma they can cause. You know, "Let's send him a citation." But you're sitting out there behind a desk and you get a letter from the Federal Government that says, "You've got to come in and tell us real quick why you shouldn't be prosecuted in the federal courts," it has a hell of a lot more impact than the guy that wrote it thinks it does. He ought to get a letter from IRS saying, "We want you to come in immediately to tell us why we shouldn't throw you in the penitentiary." It would give him a feel for how it is when the shoe's on the other foot.

[17] Vince, p. 16