

REGULATORY FOCUS

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Nothing Can Be Done Perfectly—We Learn Through Our Errors

The FDA culture-defining moment I want to present in this paper will be a bit lengthy because I feel that it must be considered in context. The time was right after World War II, the apex of the industrial revolution. It was the time of the “we” generation, where great sacrifices had been requested and granted. During the war, virtually every able-bodied man between the ages of 17 and 35 was in uniform and was prepared to make the ultimate sacrifice to save our society and culture. During that time, the entire scientific enterprise was dominated by military needs and development, and its hard-driving programs had been successful. Also at that apex came a great faith in technology that included a sense that anything could be accomplished with resources and will.

It was an interesting time because the wartime U.S. President, Franklin D. Roosevelt, was a polio victim.¹ In the 1920s, his quest to obtain a cure for his handicap led him to invest a large portion of his wealth in the Warm Springs, GA, resort. Roosevelt, then Secretary of the Navy, was convalescing from his illness when the enterprising promoter, Basil O’Con-

nor, approached him. O’Connor had offered Roosevelt a steady income in exchange for the simple privilege of putting his name on the letterhead of O’Connor’s Wall Street law firm. In 1928, when Roosevelt was elected Governor of New York, he told O’Connor that if he took over Warm Springs, it would be a good service for Roosevelt. In 1926, O’Connor had turned the resort into a nonprofit foundation, which allowed money to be raised from wealthy patients, their families, and friends, thereby helping Roosevelt avoid financial ruin in this venture. However, this effort did not generate sufficient funding to sustain the foundation. Upon Roosevelt’s election to the presidency, O’Connor used the prestige of the office to serve the cause. The National Foundation for Infantile Paralysis (NFIP)¹ was established, and a series of annual balls linked to Roosevelt’s birthday were held to raise additional funds. In 1935, there were 6000 President’s Birthday Balls, which amassed almost \$800,000. These balls began to lose momentum, and the NFIP, which had pledged to support the needs of polio patients, had to find new sources of revenue.

In 1938, entertainer Eddie Cantor coined the term “The March of Dimes” (MoD) to generate a new revenue stream for the Foundation. Because Roosevelt had many supporters in Hollywood, the Foundation was able to enlist the support of publicists and actors to promote the MoD. These resources were used by O’Connor to continue to fulfill his dream to eradicate polio in his lifetime. Persistent promotion through posters, leaflets, radio spots, and movie shorts kept the disease in constant focus. The downside of this attention was the looming dark and ominous fear that seized society. Polio continued its ravage of rich and poor alike, and summers brought virtual hysteria.² The now well-funded NFIP poured resources into research and treatment and society continued to support it heavily.

The break came with a Nobel Prize-winning discovery (scale 2) on how to culture the polio virus. Prof. John Enders and post-graduate students Thomas Weller and Frederick Robbins (Boston Children’s Hospital, Boston, MA) presented the discovery. Dr. Enders, Tom Weller, and I had discussed doing the development work



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for the vaccine. Tom and I were interested, "but Enders, in his thoughtful way, felt it was not the kind of work for which our laboratory was best suited. He considered the work to be rather routine and better suited to a commercial establishment."³ The ability to culture the virus opened the door to a vaccine, which could free society from this scourge.

With this breakthrough, the NFIP-MoD moved resources with a military model for the "war to develop the vaccine." Almost everything associated with the NFIP-MoD was astounding. Dr. Jonas Salk of the University of Pittsburgh Medical School (Pittsburgh, PA) developed a viable Inactivated Poliovirus Vaccine (IPV), and Dr. Thomas Francis, Jr., University of Michigan Director of the Poliomyelitis Vaccine Evaluation Center (Ann Arbor, MI), was responsible for conducting the 1954 field studies of the vaccine. "The Francis report was the culmination of a year-long field trial of the Jonas Salk vaccine, unprecedented in its scope and magnitude. Using a double-blind method of statistical analysis, where neither patient nor administering physician knew if the inoculation was the vaccine or a placebo, 440,000 children were given the vaccine and 210,000 the control substance. In addition, Francis agreed to a controlled observation trial involving more than 1 million children, participating either as knowing recipients of the Salk vaccine or as noninoculated children placed under observation for comparison. All told, approximately 1,830,000 children in 217 areas of the United States, Canada, and Finland were involved in the field trial."⁴ On April 12, 1955, Dr. Francis announced that the vaccine field trial results showed that the IPV was "safe, effective, and potent." "That same day six manufacturers were licensed to produce the vaccine. During the first two weeks after licensure, more than 10 million doses of IPV were released and approximately 4 million doses were actually administered The first cases of paralysis among Cutter vaccines were reported on April 25 and 26. Within 48 hours, a recall of Cutter vaccine had been initiated."⁵ In 1963, Nathanson and Langmuir published a very thorough and classic study of this incident.⁶

Table 1

Comparison of 20th century annual morbidity and current morbidity, vaccine-preventable diseases ⁷

| | 20th century annual morbidity | 1999 | Percent decrease |
|---|-------------------------------|------|------------------|
| Diphtheria | 175,885 | 1 | 100 |
| Measles | 503,282 | 100 | 100 |
| Mumps | 152,209 | 391 | 99.7 |
| Pertussis | 147,271 | 7298 | 95.0 |
| Polio (paralytic) | 16,316 | 0 | 100 |
| Rubella | 47,745 | 267 | 99.4 |
| Congenital Rubella Syndrome | 823 | 6 | 99.3 |
| Tetanus | 1314 | 42 | 96.8 |
| <i>H. influenzae</i> , type b and unknown | 20,000 | 254 | 98.7 |

The Cutter Incident brought process validation, scale-up verification, and hazard analysis-critical control point (HACCP) concepts very much to the regulatory fore. The astounding scale of the efficacy study, the ramp-up into production, and the epidemiology programs that had been established were heavily driven by the NFIP-MoD promotions that focused society on this disease and the war to end it. Basil O'Connor's years at the helm of the NFIP-MoD were probably a major factor in gaining societal support for this war-like approach to ending the disease.

That there were some casualties in the almost hysterical drive to get the children vaccinated against polio is not surprising when one considers the scope of the effort. Ten million doses were released in the first two weeks after licensure, and 20-20 hindsight shows the implementation could have been done better. However, all human enterprise has risk and we should keep the Cutter Incident, which had direct and indirect casualties of 260 polio cases, in perspective with other more recent tragedies. For example on July 17, 1981, two skywalks fell at the Kansas City Hyatt Regency killing 114 people and injuring more than 200 others—the deadliest structural failure in the nation's history.* The bottom line on the polio enterprise and

the NFIP-MoD was that it was an astounding success conducted by astounding people in an astounding time in our history.⁸ The results of that great enterprise are shown in *Table 1*.

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*Poor communication, pressure to finish on time, and a fatal design change all led to the collapse, according to Jack Gillum, the engineer of record for the hotel project. "This is a tragedy I think about 365 days a year. I think about it anytime I walk into a public building," Gillum says (*St. Louis Post Dispatch*, 7/17/01:1).