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# FDA Regulatory Cultures and How They Originated

This article is first in a series focusing on FDA product regulation, especially biotechnology-derived drug and biological products. In order to have a frame of reference for this article on the FDA regulatory cultures, it is useful to establish a paradigm. The paradigm presented below depicts a product or concept evolution starting with Discovery, evolving through Development and implementation through Control.

| **Discovery** | | **Development** | | **Control** | | |
|---|---|---|---|---|---|---|
| 1 | → | 3 | → | 5 | → | 7 → 10 |

For example, remarkable breakthroughs such as Einstein's miraculous year in 1905 are a "1" in Discovery, and a very well-run McDonald's restaurant or excellent hotel are "in control" at a 10. Organizations that operate at a "10" are very predictable, e.g., the ordering of bath accessories at a fine hotel chain anywhere in the world.

To view this paradigm in light of the FDA cultures, we must go back to 1902, with the Biologics Control Act (*Table 1*). At that time, the St. Louis, MO Health Department prepared some diphtheria antitoxin that was contaminated with tetanus. As a result, 12 children died of lockjaw and 10 others became ill but recovered. The public was incensed that these children were killed or injured by a material that had been prepared and administered by a public agency to protect their health. Of course, the fact that children had been killed or injured gave added noteworthiness to the event. Enforcement of this 1902 legislation was placed under the predecessor to the Bureau of Biologics in the Public Health Service (PHS); the PHS dates its history back to 1798. Over time, it has evolved to include "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of diseases or injuries of man." Many of these products are complex mixtures of compounds that are very difficult to analyze to ensure consistent product quality and thereby help ensure safety. Processes that are not robust tend to stay near level 7 in the paradigm (e.g., they continue to have a strong development component). The regulation of the production of these complex materials was based on the licensing of manufacturers and the control through rigid standardization of their processes. This approach not only helped to reduce the clandestine production of inferior products, but also helped to ensure lot-to-lot consistency in the manufacturing process. Product safety is a development-type activity, perhaps in this instance at a 6, defining the critical control points and then bringing everything into tight control so that consistent safe materials can be produced. This starting culture has evolved into the Center for Biologics Evaluation and Research (CBER). Many of the CBER-regulated products continue to be poorly defined chemical entities, and the processes involved in their production are frequently not robust, e.g., small changes in the process may bring about significant changes in the product. These regulatory activities were transferred in 1974 to the FDA and this cultural impact will be addressed later.

A second FDA culture came into being because of concerns over adulterated and misbranded products. This concern had intensified through the 19th century, and was noted in an 1887 issue of *JAMA:* "A recent issue of the New York World contained a list of adulterants found in articles of food and drink . . . . On reading the list one is amazed at the ingenuity and dishonesty of civilized, Christian man."[1] The growing concern with these issues along with the publication of Upton Sinclair's book, *The Jungle*, sufficiently aroused the public and legislators to enact the 1906 Pure Food and Drug Act. This act is an

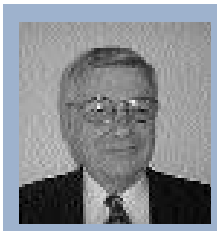

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Table 1

**FDA legislative and cultural highlights**

| Year | Event |
|---|---|
| 1902 | The Biologics Control Act is passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans. |
| 1906 | The original Food and Drugs Act is passed by Congress on June 30 and is signed by President Theodore Roosevelt. It prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs. |
| 1937 | Elixir Sulfanilamide, containing the poisonous solvent diethylene glycol, kills 107 persons, many of whom are children, underlining the need to establish drug safety before marketing and to enact the pending food and drug law. |
| 1938 | The Federal Food, Drug, and Cosmetic (FDC) Act of 1938 is passed by Congress, containing new provisions: requiring new drugs to be shown safe before marketing, starting a new system of drug regulation, and authorizing factory inspections. |
| 1941 | The Insulin Amendment requires the FDA to test and certify purity and potency of this life-saving drug for diabetes. |
| 1962 | The Kefauver-Harris Drug Amendments were passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers are required to prove to FDA the effectiveness of their products before marketing them. |
| 1976 | Tom joins FDA. |

adulteration and misbranding of truth in commerce law; this law enforcement act places the then USDA Bureau of Chemistry into operations at a 10. (It is interesting to note that about a century later, a company distributed millions of bottles labeled "baby juice," which contained only colored, sweetened water.) This legislation, which, along with the 1938 factory inspection authority, initiated an FDA control culture that has become embodied in the FDA Field Organization or Office of Regulatory Affairs (ORA). The investigator staff members of the Field at the entry level must have at a minimum an undergraduate degree in science and, after hiring, they receive extensive training in Control assessments, documenting what they do and doing what they document, to ensure a consistent product—a clear "10" in the paradigm. These Control elements have become formalized over time into the FDA's current Good Manufacturing Practices (cGMP) and Good Laboratory Practices (GLP) culture.

Another major FDA culture started in 1937 with the Elixir Sulfanilamide incident in which over 100 people died from drinking a solution of a sulfa drug in antifreeze. This disaster resulted in legislation requiring safety testing of drugs; along with the legislation came a new bureaucracy looking closely at the safety of products. Safety evaluation is a development concept that rates a 6 on the scale. It is instructive to note that prior to 1937, the first 30 years or so of the FDA, drug safety was not a part of the regulatory concept; enforcement was primarily a commerce issue.

The next FDA defining moment came after the thalidomide disaster. Although thalidomide posed a safety issue, the aftermath of the disaster was new legislation requiring efficacy. Dr. Frances Kelsey, the review chemist for this drug, held up the approval of thalidomide on the basis of inadequate data and her concern about the neuropathy associated with use of the product. While being held for that additional data, thalidomide, which had been approved for use in Europe, was indicated as a teratogen that caused terrible deformation in children. Because of this work, Dr. Kelsey became one of FDA's few heroines. She received an award from President Kennedy, and a school in her hometown was named after her. The thalidomide incident provided, in addition to the efficacy legislation, a great vindication and reinforcement to the FDA's safety culture. The reviewers in this culture tend to look toward absolute safety; no one wants to be known as the one who approved thalidomide and caused birth defects or deaths in the United States.

These transitions lead to the CBER safety evaluation culture at a 6, a similar CDER safety–efficacy culture also at a 6–7, and an ORA adulteration and misbranding control culture in the 8–10 range. The latter culture is generally associated with field investigators who historically have a track record of uncovering fraud and adulteration in the marketplace.

It is interesting to note that with the advancement of analytical technologies and computer data systems there is some convergence of the cultures. Through greater emphasis on process validation in cGMP inspections, the overall FDA culture is moving toward the biologics culture model, which focuses on control of manufacturing processes. While products become better defined analytically, biological products regulation is shifting more toward the commodity perspective. This is especially noteworthy with the scientific characterization of biotechnological products, where they are being regarded more as chemicals manufactured by a different technique. The Team Biologics approach for biotechnology product inspections reflects this evolution to improve the linkage between the cGMP Control culture of the field and the Development culture of the CBER.

Of course, it is easier to change facts than perceptions, and the FDA cultures have grown from perceptions. Max Planck once noted that "a new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it . . . ."[2] So it will be with the regulatory cultures. There will be only lukewarm support from the current regulators/regulatees culture to build this new biotechnology product-driven change.

"That mummification persisted well into the Roman era is just one example of how Egyptian culture, though varying in its details over time, remained in its broad outlines almost unimaginably consistent for more than 30 centuries."[3] The FDA cultures have a long way to go, but not all that far.

## References


1. JAMA 1887; 8:684–5 as quoted in JAMA1987; 257:3062.
2. Planck M. In: Gaynor F, translator. Scientific autobiography and other papers. New York, NY: Philosophical Library, 1949:33–4.
3. Stewart D. Eternal Egypt. Smithsonian magazine Jun 2001:76.


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