

A Brief History of the GMPs for Pharmaceuticals

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A glance back at the achievements and the tragedies of the pharmaceutical industry reveals the importance of continuing compliance with current good manufacturing practices (GMPs).

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To obtain and maintain GMP compliance, every manager and supervisor should provide frequent, meaningful GMP reminders, train and develop all employees, and fully participate in formal, ongoing training programs. Senior management must state publicly and make it clear through their actions that following GMPs is the only way their company does business.

If you want people to move toward regularly following GMPs, they have to know why: why the regulations came about and what's in it for all of us as consumers to see them followed. Most requirements were put in place as responses to tragic circumstances and to prevent future tragedies. This article is not an all-inclusive history but a representative one.

The 1900s

Early in this country's history, traveling medicine shows sold bottles of ointment or "miracle elixir" from the backs of wagons. Such medication was said to be good for aches and pains; for catarrh, rheumatism, and gout; of course it completely cured cancer — and it worked on horses too. Luckily, those days are long gone.

In 1905, a book called *The Jungle* helped catalyze public opinion for change. The book was written by Upton Sinclair, a "muck-raker" journalist and social reformer. He wrote about the Chicago meat packing industry: about the unsanitary conditions in which animals were slaughtered and processed and the practice of selling rotten or diseased meat to the public. He also reported that ground meat sometimes contained remains of poisoned rats and even unfortunate workers who fell into the machinery. Sinclair's main interest was in bringing attention to the miserable working conditions and the plight of the impoverished factory workers, many of whom were immigrants (1).

The Jungle had a major impact on the American public. Congress passed the Pure Food and Drug Act in 1906, and for the first time it became illegal to sell contaminated (adulterated) food or meat. Also for the first time, labeling had to be truthful (no one could "promise the moon and the stars" on a label anymore).

In the old days, syrup to calm "colicky" babies and "tonics" for adults often contained alcohol, opium, or morphine, which addicted many people who used them. So the 1906 Act also required selected dangerous ingredients to be labeled on all drugs. Inaccurate or false labeling was called misbranding, and that became illegal. Misbranded applies to statements, designs, or pictures in labeling that are false or misleading as well as to the

Definition

The following definition is abstracted from the *Requirements of Laws and Regulations Enforced by the U.S. Food and Drug Administration* (2).

Drugs: The Food, Drug & Cosmetic (FD&C) Act defines drugs as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” It is the intended use that determines whether something is a drug. Thus, foods and cosmetics may be subject to the drug requirements of the law if therapeutic claims are made for them. The FD&C Act prohibits adulteration or misbranding of any drug and requires that “new drugs” be reviewed and approved by FDA before they go to market. Drug applications typically fall into three categories: a new drug application, a new animal drug application, or an abbreviated new drug application for generic products.

failure to provide required information in labeling (2). Over the years, the word *adulterated* has been expanded to include products manufactured without following GMPs.

The real reason the 1906 Act was passed is that Harvey Wiley and others had been pressing for such a law for 25 years. The act created one of the first government regulatory agencies, now known as FDA, and it also allowed for the seizure of illegal foods and drugs (3). Wiley later became chief chemist of the bureau given authority to enforce that act (the Bureau of Chemistry, U.S. Department of Agriculture), a forerunner of FDA (4).

Biologic products were first regulated a few years before *The Jungle*, when at least 12 children died from a diphtheria antitoxin that was contaminated with live tetanus bacilli (3). Congress responded to that tragedy by passing the Biologics Control Act of 1902, which required inspections of manufacturers and sellers of biological products and testing of such products for purity and strength (5).

The 1930s

A 1933 FDA exhibit of dangerous food, medicines, medical devices, and cosmetics illustrated the shortcomings of the 1906 law. Called “America’s Chamber of Horrors,” the famous exhibit included a womb supporter (also used as a contraceptive) that could puncture the uterus if inserted incorrectly; a weight-loss drug that caused death; a hair remover that caused baldness, even if not used on the head; lotions and creams that could cause mercury poisoning; hair dyes that could cause lead poisoning; and an eyelash dye that blinded women (3). Eleanor Roosevelt took that exhibit to the White House, asking Americans to campaign for stronger consumer protections. A tragedy was waiting around the corner that would make her case for her.

The wrong raw material and an elixir of sulfanilamide. Sulfa drugs were introduced in 1935. Many manufacturers began making the new anti-infectives. One company used diethylene glycol, a poisonous solvent and chemical analog of antifreeze, in an oral “elixir of sulfanilamide.” Before the problem was discovered, 107 people died, many of them children (3).

In response, Congress passed the Federal Food, Drug and Cosmetic (FD&C) Act of 1938. For the first time, companies were required to prove that their products were safe before marketing them (3). Still the major act covering our subject matter on the books, it extended FDA oversight to cosmetics and therapeutic devices, explicitly authorized factory inspections, required standards for foods, and added injunctions to previous penalties of seizures and criminal prosecutions (6).

The 1940s and 1950s

One tragedy in 1941 was not related to World War II. Nearly 300 people were killed or injured by one company’s sulfathiazole tablets, a sulfa drug tainted with the sedative, phenobarbital. That incident caused FDA to revise manufacturing and quality control requirements drastically, leading to what would later be called GMPs (6). The Public Health Services Act, passed in 1944, covered a broad spectrum

of concerns, including regulation of biological products and control of communicable diseases (7).

Also during the WWII era, batch certification by FDA became a requirement for certain drugs. It required companies to submit samples from each lot to FDA for testing, and the agency would give permission for their release. That practice, begun in 1941 for insulin and 1945 for penicillin, was later expanded to include all antibiotics. By 1983, the requirement for batch certification of drugs was dropped (7).

In 1955, Jonas Salk discovered a way to vaccinate against polio (8). Many manufacturers began making his polio vaccine. One company failed to inactivate the virus completely in a single lot. About 60 individuals inoculated developed polio, and another 89 of their family members contracted polio from them (9). We vaccinate our children to prevent them from getting a disease and also as a public health measure to protect society from the spread of disease.

The 1960s

Thalidomide was marketed in Europe as a sleeping pill and to treat morning sickness. When regulatory agencies gave permission to sell the drug for that indication, they had no knowledge of its serious side effects. It turned out to be teratogenic: It caused serious deformities in developing fetuses. Children whose mothers took thalidomide in the first trimester were born with severely deformed arms and legs. An estimated 10,000 cases of infant deformities in Europe were linked to thalidomide use (3).

The product was not allowed on the market in the United States. The drug reviewer responsible for the thalidomide application in the United States was a woman scientist, Frances Kelsey. In 1962 President Kennedy awarded her the President’s Distinguished Federal Civilian Service Award, the highest honor a government employee may earn as a civilian (3).

Thalidomide galvanized public opinion. Two legislators, Kefauver and Harris, pushed more-stringent legislation through Congress that required companies to test not only to ensure that products were safe, but that they were efficacious for their intended uses. Regulating clinical trials, the amendments required drugs to be tested in animals before people. They made investigators responsible for supervising drugs under study. Manufacturers were expected to inform participants if a drug was being used for investigational purposes and to obtain their consent before testing it on them. Drugs had to be shown to work before going on the market. Manufacturers were required to report unexpected harm (adverse events). And FDA was given authority to regulate advertising of prescription drugs (3).

The 1970s

The 1970s were a watershed for product regulation. GMPs for drugs (21 *CFR* Parts 210 and 211) and medical devices (21 *CFR* 820) were made final in 1978. They were intended to help ensure the safety and efficacy of all products:

The regulations ... contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. (10)

GMP requirements for devices were intended “to govern the methods used in and the facilities and controls used for the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished medical devices intended for human use,” as described in the most recent revision (11).

Good Laboratory Practices (GLPs) were made final in 1979. They are defined as follows:

... good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed. (12)

A few years earlier, the Medical Device Amendments (signed as law in 1976) strengthened FDA's authority to oversee medical devices. The law was precipitated by incidents involving a contraceptive intrauterine device that about two million women were using. Many users were seriously injured (3). The product was taken off the market in 1975 because it was associated with a high incidence of pelvic infections, infertility, and some deaths (13).

The Medical Device Amendments required manufacturers of most medical devices (particularly moderate- or high-risk devices) to provide FDA with safety and effectiveness data before marketing them. Furthermore, the law provided for a system of pre- and postmarket 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. Those provisions are things we take for granted today (14).

The 1980s and 1990s

Poisoned acetaminophen capsules. In 1982, 12-year-old Mary Kellerman told her parents that she felt like she had a cold. They gave her an extra-strength Tylenol acetaminophen capsule, and within a few hours she died. Six other people died in this tragic incident, including three members from one family (two brothers and one of their wives) and a woman who had just given birth to her fourth child (15).

Johnson & Johnson announced a nationwide recall of 31 million bottles of Tylenol. Their investigation revealed that a crimi-

nal tamperer (who has never been found or prosecuted) had opened up and laced some capsules with cyanide. The company destroyed all 31 million bottles of the largest-selling over-the-counter (OTC) medicine in the country.

FDA issued tamper-resistant packaging regulations for all OTC human drug products and incorporated them into the GMPs. Congress passed the Federal Anti-Tampering Act in 1983, making it a crime to tamper with packaged consumer products (7). The acetaminophen tragedy had a major impact on the industry. Not only do we need to provide ongoing GMP training to all of our employees, making sure they are adequately and thoroughly trained and supervised, but now we worry about how murderers could use our products to harm the public.

Guidance documents. In the 1980s, FDA began publishing a series of guidance documents that have had a major effect on our interpretation of current GMPs. One such document was the *Guide to Inspection of Computerized Systems in Drug Processing* published in 1983, which gave early expectations for the functioning of computer systems and perhaps signaled the beginning of computer validation (16). Of course, the very famous *Guideline on General Principles of Process Validation* in 1987 outlined current thinking or expectations of process validation for drugs and devices (17). Such documents, including the *Points to Consider*, provide guidance only on principles and practices that are not legal requirements. However, typically they reflect current agency thinking and expectations.

L-tryptophan. Active pharmaceutical ingredients (APIs) used to be called bulk pharmaceutical chemicals. The terminology recently changed to reflect the fact that some active ingredients are made using biological rather than chemical processes. The term *new chemical entity* also is now often referred to as *new molecular entity* for the same reason.

L-tryptophan and 5HTP, naturally occurring amino acids, used to be widely promoted as dietary supplements and were used as aids for insomnia, depression, obesity, and for children with attention deficit disorder. In 1989, an epidemic of eosinophilia-myalgia syndrome (EMS) was linked to dietary supplements containing L-tryptophan. The Centers for Disease Control identified more than 1500 cases of EMS, including at least 38 deaths, that were associated with L-tryptophan. In tests run by both FDA and the Mayo Clinic, impurities were confirmed in some L-tryptophan products on the market. One impurity was called Peak X. Although its significance remains unknown, Peak X was found in one case of EMS associated with L-tryptophan in 1991. Unfortunately, the exact cause of the 1989 epidemic and of the EMS associated with 5HTP continues to be unclear, in part because 5HTP is synthesized from L-tryptophan in the body. Research has not yet conclusively resolved whether EMS was caused by L-tryptophan, by 5HTP, by one or more impurities, or by some other factors (18).

Interestingly enough, some 70–80% or more of the APIs used to manufacture products for the United States come from sources outside the country, where manufacturing standards may not be as stringent. For this reason, both the European Union and the United States recently published draft guidance documents for the manufacture of APIs. The draft US document “Guidance for Industry: Manufacturing, Processing, or

A GMP timeline

1906 Pure Food and Drug Act

Creates one of the first government regulatory agencies (now known as FDA); the culmination of 25 years of lobbying, this act makes it illegal to sell "adulterated" or "misbranded" food or drugs.

1938 Federal Food, Drug and Cosmetic (FD&C) Act

Tragedy: Sulfanilamide made with poisonous solvent causes 107 deaths. Result: Requires manufacturers to prove the safety of products before marketing.

1941 Two unrelated events

Insulin Amendment requires FDA to test and certify purity and potency of insulin. Tragedy: nearly 300 deaths and injuries from distribution of sulfathiazole tablets tainted with phenobarbital. Result: FDA revises manufacturing and quality controls drastically, the beginning of what will later be called GMPs.

1962 Kefauver-Harris Drug Amendments

Tragedy: Thalidomide causes birth defects in thousands of European babies. Result: Manufacturers must prove efficacy of products before marketing them and ensure stricter control over drug testing.

1978 CGMPs Final rules for drugs and devices (21 CFR 210–211 and 820)

Establishes minimum current good manufacturing practices for manufacturing, processing, packing, or holding drug products and medical devices.

1979 GLPs Final Rule (21 CFR 58)

Establishes good laboratory practices for conducting nonclinical laboratory studies that support applications for research or marketing permits for human and animal drugs, medical devices for human use, and biological products.

1982 Tamper-resistant packaging regulations issued for OTC products

Tragedy: Acetaminophen-capsule poisoning by cyanide causes seven deaths. Result: revision of GMPs to require tamper-resistant packaging.

1983 Two unrelated regulatory events

The *Guide to the Inspection of Computerized Systems in Drug Processing* initiates tighter controls on computers and computer validation. Federal Anti-Tampering Act makes it a federal crime to tamper with packaged consumer products.

1987 Guideline on General Principles of Process Validation

Agency expectations regarding the need for process validation are outlined.

1992 Generic Drug Enforcement Act

Precipitated by illegal acts involving abbreviated new drug applications. Result: Creates debarment penalty.

1996 Proposed Revision to US CGMPs for Drugs and Biologics (21 CFR 21–211)

Adds detail for validation, blend uniformity, prevention of cross-contamination, and handling out-of-specification results.

1997 Electronic Records Final Rule (21 CFR 11)

Requires controls that ensure security and integrity of all electronic data.

1998 Draft guidances

Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients and Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production.

Holding of Active Pharmaceutical Ingredients" was released in 1998 (19). Drug GMPs (21 CFR 210–211) are also considered to apply to the manufacture of APIs.

Also in the 1990s, proposed revisions to the GMPs for drugs and biologics were issued. Although those revisions were not yet final when this article went to press, they do represent FDA's current thinking. The Electronic Records Final Rule (21 CFR Part 11), requires controls that ensure the security and accuracy of all data and computer systems used. It will have sweeping ramifications on the industry for years to come.

International harmony. The International Conference on Har-

monization (ICH) is a consortium of individuals from Europe, North America, and Japan working on a number of quality, safety, and effectiveness documents. As those documents are adopted or made final by ICH, they become "industry practice" in all participating countries. The 1996 ICH E6 guidance on good clinical practices has become the de facto standard on performing human clinical trials (20). A number of other guidance documents, including a draft guidance on handling out-of-specification results, recently became available (21). Even though guidelines and draft guidances are not legally binding, they represent current thinking on their subject matter and tend to be adopted rapidly and/or viewed as "current industry practice."

Generic drug scandal. Congress passed the Generic Drug Enforcement Act of 1992 to impose debarment and other penalties for illegal acts involving abbreviated drug applications (22). The 1992 Act resulted from a bribery and fraud case in which executives of one or more generic companies bribed FDA reviewers. Rather than testing its own generic version of a drug, the company committed fraud by testing the brand name version instead and sending those results with a generics application. Apparently one bribe accepted was for two \$500 gift certificates (23). Can you imagine risking your career or livelihood (much less potential lives) and going to prison for that? Although typically executives are indicted in fraud or other cases, the lowest-ranking employees successfully prosecuted in the generics companies falsified certificates of analysis, destroyed samples, directed others to change manufacturing procedures, and falsified records to hide or conceal manufacturing changes (22,23). Individuals found guilty in the generic drug scandal were

"debarred" from working in the industry.

Looking to the future

The Scale-Up and Postapproval Change documents presented on the FDA Web site provide guidance on what is needed before changes to approved drug applications can be made. The documents itemize the types of information or studies required based upon the magnitude or risk of proposed changes. For biological products, companies are now preparing "comparability protocols" to address proposed changes.

As we enter the twenty-first century, let's remember that we

are all responsible. We will see things in our day-to-day work that others will not, or we may reach a conclusion faster than someone else. In all the classes I teach, I always ask people to speak up — and continue to do so until important issues are addressed. Otherwise patients, companies, or employees may suffer.

Two characteristics define our industry: It exists to improve the quality of patients' lives, to relieve suffering or pain, and to find cures for diseases. It also is highly regulated. In an ideal world, we might not need to be regulated, but we do not live in an ideal world. Because of the tragedies that have occurred, most people see the regulations and world regulatory agencies as checks and balances on industry, believing as I do that we all have a similar goal in common: to bring innovative, safe, and effective products to market.

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References

1. S. Ward, "Summary of *The Jungle* by Upton Sinclair," *SparkNotes Online Study Guide* (TheSpark.com Inc., Cambridge, MA, 1999), www.sparknotes.com/guides/jungle.
2. *Requirements of Laws and Regulations Enforced by the U.S. Food and Drug Administration* (FDA, Rockville, MD, revised 1997), www.fda.gov/opacom/morechoices/smallbusiness/blubook.htm.
3. Office of Women's Health, *FDA Milestones in Women's Health: Looking Back as We Move into the New Millennium* (FDA, Rockville, MD, 2000), www.fda.gov/womens/milesbro.html.
4. *FDA History: FDA Commissioners and Their Predecessors* (FDA, Rockville, MD, rev. 6 April 2000), www.fda.gov/opacom/morechoices/comm1.html.
5. R. Roberts, *Safety Assessment in Pediatrics* (Center for Drug Evaluation and Research, FDA, 8 July 1999), www.fda.gov/cder/present/dia-699/sa-dia99/index.htm.
6. Center for Drug Evaluation and Research, *Time Line: Chronology of Drug Regulation in the United States* (FDA, Rockville, MD), www.fda.gov/cder/about/history/time1.htm.
7. "Milestones in US Food and Drug Law History," in *FDA Backgrounder: Current and Useful Information from the Food and Drug Administration* (FDA, Rockville, MD, August 1995), www.fda.gov/opacom/backgrounders/miles.html.
8. "Jonas Salk, MD — Biography" (American Academy of Achievement, 2000), www.achievement.org/autodoc/halls/sci and *Webster's New Collegiate Dictionary* (G&C Merriam Company, Springfield, MA, 1975).
9. I.B. Stehlin, "Assessing Risks with Polio Vaccines," *FDA Consumer* **29** (10) (December 1995), www.fda.gov/fdac/features/095_vacc.html.
10. *Code of Federal Regulations, Title 21, Food and Drugs*, "Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs," Part 210–211 (US Printing Office, Washington, DC, revised April 2000).
11. *Code of Federal Regulations, Title 21, Food and Drugs*, "Medical Devices: Current Good Manufacturing Practices (CGMP) Final Rule," Part 820 (US Printing Office, Washington, DC, revised April 1999).
12. *Code of Federal Regulations, Title 21, Food and Drugs*, "General: Good Laboratory Practice for Nonclinical Laboratory Studies," Part 58 (US Printing Office, Washington, DC, revised April 2000).
13. T. Nordenberg, "Protecting Against Unwanted Pregnancy: A Guide to Contraceptive Choices," *FDA Consumer* **31** (3) (April 1997), www.fda.gov/fdac/features/1997/397_baby.html.
14. T. Nordenberg, "FDA and Medical Devices: After 20 Years, a Look Back, a Look Ahead," *FDA Consumer* **30** (10) (December 1996), www.fda.gov/fdac/features/096_mdev.html.
15. T. Kaplan, "The Tylenol Crisis: How Effective Public Relations Saved Johnson & Johnson" (Penn State University Personal Web Pages, PA, 1998), www.personal.psu.edu/users/w/x/wxk116/tylenol/crisis.html.
16. National Center for Drugs and Biologics, *Guide to Inspection of Computerized Systems in Drug Processing* (FDA, Rockville, MD, February 1983), www.fda.gov/ora/inspect_ref/igs/csd.html.
17. Center for Drug Evaluation and Research, *Guideline on General Principles of Process Validation* (FDA, Rockville, MD, May 1987), www.fda.gov/cder/guidance/pv.htm.
18. Center for Food Safety and Applied Nutrition, *FDA Talk Paper: Impurities Confirmed in Dietary Supplement 5-Hydroxy-L-Tryptophan* (FDA, Washington, DC, 31 August 1998).
19. Center for Biologics Evaluation and Research, *Draft Guidance for Industry: Manufacturing, Processing, or Holding of Active Pharmaceutical Ingredients* (FDA, Rockville, MD, March 1998), www.fda.gov/cber/gdlns/active.pdf.
20. International Conference on Harmonisation, "Guide for Industry: E6, Good Clinical Practice — Consolidated Guidance," *Federal Register*, **62** (90), 25691–25709 (9 May 1997), www.fda.gov/cder/guidance/959fnl.pdf.
21. Draft Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, (FDA, Rockville, MD), September 1998, www.fda.gov/cder/guidance/1212dft.pdf.
22. T. Nordenberg, "Inside FDA: Barring People from the Drug Industry," *FDA Consumer* **31** (2), www.fda.gov/ora/compliance_ref/default.htm.
23. *Office of Regulatory Affairs Compliance Reference: Debarment List* (FDA, Rockville, MD), www.fda.gov/ora/compliance_ref/debar/default.htm.

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