

A Brief History of the GMPs

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Friedrich Nietzsche once said, “If you know the *why* for living, you can endure any *how*.” Everyone in our industry should know the story of how the good manufacturing practices (GMPs) have come to be. Most requirements were put in place as responses to tragic circumstances and to prevent future tragedies.

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.

The 1900s

Early in the history of the United States, traveling medicine shows sold “miracle elixirs” from the backs of wagons. Such medication was said to be good for aches and pains, catarrh, rheumatism, and gout. 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. “Muckraker” and social reformer Upton Sinclair wrote about the Chicago meat packing industry—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 Pure Food and Drug Act.

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 longer could anyone promise on a label “the moon and the stars.”

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

Even before publication of *The Jungle*, Harvey Wiley and others had been pressing for a law such as the Pure Food and Drug Act for 25 years before its passage. The Act created one of the first government regulatory agencies, now known as the Food and Drug Administration, and 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 the Food and Drug Administration (FDA) (4).

Biologic products were first regulated a few years before *The Jungle*, when at least 12 children died from a diphtheria antitoxin 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. “America’s Chamber of Horrors” 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.

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

In 1941, 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 drastically revise manufacturing and quality control requirements, leading to what would later be called GMPs (6). The Public Health Services (PHS) 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; the agency would then 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 inoculated individuals developed polio, and another 89 of their family members (mothers, fathers, brothers, sisters, and grandparents) contracted polio from them (9). Today 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 sick-

Message from GMP Labeling

We hope this newsletter includes information that you can use. Our goal is to periodically publish articles, written by quality professionals, that are timely and informative to the companies in our marketplace. Of course, along the way, we also hope to reinforce our image as a valuable resource to our customers.

Businesses regulated by the FDA and/or are ISO 9000 registered will find GMP Labeling products helpful in maintaining compliance. More than 5000 facilities in the U.S., Canada and Europe use GMP Labeling products on a daily basis.

ness. When regulatory agencies gave permission to sell the drug for those indications, they knew nothing 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 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. Good manufacturing practices for drugs (21 CFR Parts 210 and 211) and medical devices (21 CFR Part 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 finalized in 1979. They define:

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 (IUD) 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 (14).

The 1980s and 1990s

In 1980, Congress passed the Infant Formula Act giving FDA authority to create and enforce standards and specify nutritional requirements for commercial infant formulas. That followed 1979 reports that more than 100 infants were made seriously

ill by a lack of chlorides in two soy-based formulas (15). Manufacturers are now required to analyze each batch of formula for nutrient levels and make safety checks, conduct stability tests, code each container with a lot number, keep detailed records of production and analysis, and so on (16). The food GMPs (21 CFR Part 110), which include special provisions for infant formulas, were finalized in the 1980s.

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 was dead. 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 (17).

Johnson & Johnson announced a nation-wide recall of 31 million bottles of Tylenol. Their investigation revealed that a criminal tamperer (who has never been found or prosecuted) had opened and laced some capsules with cyanide. The company destroyed all 31 million bottles of the largest selling over-the-counter medicine in the country.

FDA issued tamper-resistant packaging regulations for all over-the-counter 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).

Guidance documents. In the 1980s, FDA began publishing a series of guidance documents that have had a major effect on our interpretation of current good manufacturing practices. One such document was the 1983 "Guide to Inspection of Computerized Systems in Drug Processing," which gave early expectations for the functioning of computer systems and perhaps signaled the beginning of computer validation (8). Of course, the very famous "Guideline on General Principles of Process Validation" in 1987 outlined current thinking and expectations of process validation for drugs and devices (19). 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.

A GMP Timeline

1902 Biologics Control Act

Tragedy: At least 12 children die of tetanus contracted from contaminated diphtheria vaccine. Result: Requires inspections and testing of biologics manufacturers' facilities and products.

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.

1944 Public Health Services Act

Regulates biological products and control of communicable diseases.

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.

1975 CGMPs for Blood and Blood Components Final Rule

Establishes minimum current good manufacturing practices for blood establishments in the collecting, processing, compatibility testing, storing, and distributing of blood and blood components.

1976 Medical Device Amendments

Tragedy: the Dalkon Shield IUD seriously injures many patients. Response: New law strengthens FDA authority to oversee medical devices.

1978 CGMPs Final Rules for Drugs (21 CFR Parts 210-211) and Devices (21 CFR Part 820)

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

1979 GLPs (21 CFR Part 58) Final Rule

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.

1980 Infant Formula Act

Tragedy: 100 children reported seriously ill linked to lack of chloride in soy-based formulas. Result: Congress gives FDA authority to set and enforce nutritional and quality control standards.

1982 Tamper-Resistant Packaging Regulations Issued for OTC Products

Tragedy: Acetaminophen-capsule poisoning by cyanide causes 7 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 outlines expectations regarding the need for process validation.

1990 Safe Medical Devices Act

Tragedy: Shiley heart valves and other incidents. Result: FDA given authority to add preproduction design controls and tracking of critical or implantable devices to CGMPs; requires notification of serious device problems by user facilities to FDA. The agency gains ability to order device recalls.

1992 Generic Drug Enforcement Act

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

1996 Two Unrelated Events

Proposed revision to U.S. CGMPs for Drugs and Biologics (21 CFR 210-211) adds detail for validation, blend uniformity, prevention of cross-contamination, and handling out-of-specification results.

"ICH Guidance for Industry; E6, Good Clinical Practice, Consolidated Guidance from ICH" becomes the de facto standard for conducting human clinical trials.

1997 CGMPs for Medical Devices (Quality System Regulation) Final Rule

Major revision to current good manufacturing practices for medical devices becomes effective, with design controls in R&D the major change (design controls effective June 1998; rest of rule June 1997).

1997 Electronic Records Final Rule (21 CFR Part 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."

1999 QSIT Inspection Handbook

New FDA technique for inspecting device companies focuses on four major subsystems: management controls, design controls, production and process controls, and corrective and preventive action.

2001 ICH Q7A API Guidance

ICH's "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (APIs)" is adopted by the United States, Europe, and Japan, and becomes the de facto manufacturing standard for APIs.

2002 Drug Manufacturing Inspections Compliance Manual

New FDA technique for routine drug manufacturing inspections focuses on two or more systems, with mandatory coverage of the quality system. Other systems are: facilities and equipment, materials, production, packaging and labeling, and laboratory controls.

L-tryptophan. Active pharmaceutical ingredients (APIs) used to be called bulk pharmaceutical chemicals (BPCs). 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" (NCE) is also now often referred to as a "new molecular entity" (NME) for the same reason.

Naturally occurring amino acids L-tryptophan and 5HTP used to be widely promoted as dietary supplements and were used as aids for insomnia, depression, obesity, and 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 (CDC) identified more than 1,500 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. The significance of one impurity, called Peak X, remains unknown. It 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 continue 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 (20).

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 published draft guidance documents for the manufacture of APIs. Recently, the International Conference on Harmonization (ICH), a consortium of individuals from Europe, North America, and Japan, published "ICH Q7A on Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients." (21) This document has

been published and accepted in Europe, Japan, and the United States, and it is considered the de facto standard for manufacturing active pharmaceutical ingredients.

Illegal catheters. Most of the cases in this representative history were mistakes and/or mysteries; the individuals or companies involved had no intention or desire of harming anyone. The acetaminophen poisoning case was clearly criminal. Let's look at a different kind of criminal case.

In 1996, three former executives of a company that made balloon heart catheters in the United States each were sentenced to 18 months in prison followed by two years of supervised release for conspiring to defraud FDA by selling illegal heart catheters. The company itself pled guilty to similar charges in 1993 and agreed to pay \$61 million for health fraud. (The U.S. government estimated that total sales of illegal catheters had amounted to \$77 million.) It had been the first company to obtain approval to market a balloon angioplasty catheter in this country, and from 1980 to 1985 it was the only distributor of heart catheters in the United States.

Heart catheters are used in angioplasty to clear clogged arteries. In 1987, the company began to redesign those already approved by FDA and sold the new version without obtaining approval. The redesigned catheters often malfunctioned, but the company failed to report those problems to FDA. The company learned during illegal human clinical trials that the catheter tips broke off in the arteries of two percent of patients, but it kept that information from FDA. The agency approved the redesigned device in January 1989, unaware of the tip breakage problem. Within three months, the company received 33 reports of tip breakage. It redesigned the catheter again, again without informing FDA, and in March began distributing the redesigned catheters.

Upon learning of the malfunctions, FDA informed the company that its catheters were illegal and subject to seizure. In June 1989, it recalled previous versions or models. When FDA told the company that its latest model violated the law as well, the company recalled that model, modified it, renamed it, and continued to distribute it.

When FDA told the company it needed a premarket approval application for the model on the market, the company discontinued selling it and reintroduced the original model, which had major problems that had necessitated the redesign in the first place. Finally, FDA seized all the catheters and witnessed their destruction (22).

Those heart catheters were associated with at least one death and with emergency

heart surgery for at least 20 patients (23). A grand jury handed down a 393-count indictment against the three former executives and others in 1995. In sentencing those former executives, the judge emphasized that "corporate entities do not commit crimes; people do," and that "executives running other companies who might engage in such conduct should bear in mind the prison terms imposed in this case" (22).

Defective heart valves. The Bjork-Shiley Convexo-Concave mechanical heart valve was manufactured and sold between 1979 and 1986. About 86,000 of those valves are believed to have been implanted in patients worldwide, including 30,000 in the United States. In a small number of cases, the valves experience a "strut fracture" failure that necessitates immediate cardiac surgery.

As of November 1998, about 620 fractures had been reported to Shiley worldwide. In roughly two-thirds of those cases, a patient died following the fracture. The company, which no longer makes heart valves, has entered into a settlement agreement with the government to pay for the costs of valve strut failures and replacement surgeries, including hospital care, medical supplies, and the usual fees of physicians, surgeons, and other health care professionals. Furthermore, Shiley and its parent company will pay the costs incurred by each patient from admission through discharge, including emergency services. They will also pay for any complications directly resulting from the treatment over a reasonable period thereafter (24).

Medical device safety. In response to the Shiley heart valve and other cases, Congress passed the Safe Medical Devices Act of 1990, for the first time giving FDA authority to go into R&D regularly. The act authorized addition of preproduction design controls to the CGMP regulations; when FDA analyzed device recalls over a six-year period, it found that about 44% of quality problems leading to recalls were attributed to errors or deficiencies designed into those devices. When the agency analyzed software-related recalls, it found that over 90% of all software-related device failures were design related, particularly the failure to validate software before routine production (11).

In the 1990 Act, Congress authorized FDA to make its medical device regulations more thorough and consistent with other world standards, such as ISO 9000. The act required nursing homes, hospitals, and other facilities using medical devices to report to FDA all incidents in which a medical device probably caused or contributed to a death or serious injury. Manufacturers are required to conduct postmarket

surveillance on permanently implanted devices whose failure might cause serious harm or death and to establish methods for tracing and locating patients having those devices. The act also authorized FDA to order device product recalls (7). During the 1990s, the medical device regulations went through a major revision, with one major change being in design control, or the need to formally review and document product design at predetermined stages. The final rule became effective in June 1997; the design control portion of the regulations became effective a year later in June 1998.

In the late 1990s, FDA turned to a more directed inspectional approach to medical devices called the Quality System Inspection Technique (QSIT). That approach calls for focusing on several key systems, including management controls, design controls, production and process controls, and corrective and preventive actions (25).

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. Part 11 will have sweeping ramifications on the industry for years to come, and is perhaps the biggest change in our industry since CGMPs were first published.

International harmony. Besides producing the API guide, ICH has been working on a number of other quality, safety, and effectiveness documents. As these 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 (26). A number of other FDA guidance documents, including a draft guidance on handling out-of-specification results, recently became available (27). 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 (26). The 1992 Act resulted from a bribery and fraud case in which executives of one or more generic companies bribed FDA reviewers (one for as little as \$1,000 in gift certificates). Rather than testing its own generic version of a drug, the company tested the brand name version

and sent those results with a generic application.

Although typically executives (presidents, vice presidents, chairpersons, and so on) 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 (28, 29). Be sure to train all employees in your company to record data thoroughly and accurately. Teach them that making a false entry, falsifying dates or backdating, signing for someone else, making up data, and signing for something they did not do is fraud, and the consequences can be severe.

Individuals found guilty in the generic drug scandal were “debarred” from working in the industry. The names of all such individuals can be found along with many of their stories on the FDA website. Check that potential job candidates are not on that list before you make a job offer. When you submit any marketing application to FDA (whether an NDA, ANDA, BLA, 510(K), or PMA) you must certify in writing that no one who has been debarred worked on the product.

Similarly, before hiring any clinical trial investigators, check their backgrounds to ensure that they are not “disqualified.” Disqualification can occur if an investigator repeatedly or deliberately fails to comply with regulatory requirements, or if he or she has submitted false information to a study sponsor. Studies from individuals who become disqualified will be under great scrutiny and may be disallowed (30). With the recent death of a young man participating in a gene therapy trial, clinical trials undoubtedly will be under increased scrutiny (31).

Making better changes. The Scale-Up and Post-Approval Change (SUPAC) documents presented on the FDA website 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.

Abbreviated, routine drug inspections. In 2002, FDA went to a new, abbreviated inspection technique, focusing on two or more systems, including mandatory coverage of the quality system, in routine drug manufacturing inspections. The other systems? Facilities and equipment, materials, production, packaging and labeling, and laboratory controls. FDA has said publicly that they consider a company to be

Important Definitions: Drugs, Biologics, and Devices

The following definitions describing the major differences between drugs, biologics, and devices, are 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 (NDA), a New Animal Drug Application (NADA), or an Abbreviated New Drug Application (ANDA) for generic products.

Biologics

The Public Health Services Act defines a biological product as “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 ...”

Biologics include such vitally important products as polio and measles vaccines, diphtheria and tetanus toxoids, and skin test substances as well as whole blood and blood components for transfusions. Biological products are subject to all the adulteration, misbranding, and registration provisions of the FD&C Act. Because most biological products are derived from living organisms, they are by their nature

potentially dangerous if improperly prepared or tested. Under the PHS Act, manufacturers wishing to ship biological products in interstate commerce or for import or export must obtain the appropriate U.S. license(s). Previous licensing requirements called for both an Establishment and a Product License Application (ELA and PLA) to be filed. That has recently been streamlined into the single Biologics Licensing Application (BLA).

Devices

Medical devices include several thousand health products, from simple items such as thermometers, tongue depressors, and heating pads to IUDs, heart pacemakers, and kidney dialysis machines.

Under the FD&C Act, a device is defined as “any health-care product that does not achieve its principal intended purposes by chemical action in or on the body or by being metabolized.” Products that work by chemical or metabolic action are regulated as drugs. The term “devices” also includes components, parts, or accessories of medical devices, diagnostic aids such as reagents, antibiotic sensitivity disks, and test kits for in vitro (outside the body) diagnosis of diseases and other conditions. Three classes of medical device exist:

- Class I, General Controls (registration of manufacturers, recordkeeping and labeling requirements, compliance with GMPs)
- Class II, Special Controls including performance standards, postmarket surveillance, and patient registries)
- Class III, Premarket Approval (Implanted and life-supporting or life-sustaining devices).

Devices “substantially equivalent” to others may be filed using a 510(K) application; all others, and all Class III devices, require filing a premarket approval application (PMA).

“out of control if any system is out of control.” (32)

Brave New World? A Period of Enforcement

In a recent consent decree, one of the world’s largest diagnostics companies agreed to stop manufacturing and distributing many of its in vitro diagnostic tests until it corrects manufacturing problems. The company immediately paid a \$100 million civil money penalty and agreed to pay the U.S. Treasury 16% of the gross sales of all medically necessary devices (the company’s entire profit portion) until confirming that those products are produced by GMPs. In addition, it agreed to pay \$15,000 per day per process on medically necessary products until each process is validated and \$15,000 per day of operation until it is GMP compliant. (33)

In the most expensive consent decree to date, a major pharmaceutical and over-the-counter (OTC) company agreed to pay a record \$500 million dollars to the U.S.

Treasury, to disgorge profits made by the company on drug products produced over the past three years that were made in violation of CGMPs. The company also agreed to future monetary payments of up to \$175 million dollars and to disgorge additional profits should it fail to meet the timelines of the decree. The action follows 13 inspections at four East Coast and Puerto Rico plants since 1998 in which FDA found significant violations of CGMP regulations. The decree affects 125 different prescription and OTC drugs produced at those facilities. As part of the consent decree, the company has agreed to suspend manufacturing of 73 other products. (34)

Looking to the Future

As we enter the 21st 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.

Our industry exists to relieve suffering or pain and to find cures for diseases. It also is highly regulated. 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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"I never think of the future – it comes soon enough." — Albert Einstein.

The 21st century is here. Technology is advancing at a rapid pace and product complexity is increasing. Globalization and international trade are the way of the world. Old ways of doing things are falling by the wayside as we use existing and new technology in new ways. We are all changing the way we do business and so is the FDA. Although the GMPs have not changed significantly in recent years, FDA is reevaluating its interpretation and approach to the regulations. We, as employees, managers and decision makers, need to understand some of the key trends in the last few years in order to continue to bring safe and effective products to market.

Combination Products*

Technology, complexity and advances in innovation have unique challenges in a regulated industry. In April 2003, the FDA approved the first drug-eluting stent for use in angioplasty procedures, a unique combination of a drug and medical device (1). The drug coated stent, a catheter with an antimicrobial coating, an orthopedic implant impregnated with growth factors, and an iontophoretic drug patch with an electronic controller are just some examples of the collaboration of technology and innovation. These products, known as combination products (2), have been a 21st century adventure for manufacturers and regulators, requiring changes in the way we do business.

On October 26, 2002, the Medical Device User Fee and Modernization Act (MDUFMA) was signed into law as an amendment to the FD&C Act (3). MDUFMA created the Office of Combination Products (OCP) to serve as a focal point for combination product issues. If you go to the OCP website you will see lots of activity, e.g., new guidance documents, new terminology like "primary mode of action" (PMOA), and examples of recently approved combination products, reflecting the buzz in this business sector (4).

MDUFMA also created user fees for premarket reviews, allowed for establishment inspections by 3rd parties and created new regulatory requirements for reprocessed single-use devices, i.e., surgical tools such as forceps, catheters and saw blades (5). MDUFMA implemented performance goals for FDA and contained references to electronic labeling and filing

reflecting the growing focus on electronic technology.

Electronic Technology & Software

We face challenges adapting to the larger role of software in our business processes and our products. In March 1997, the FDA issued 21 CFR Part 11 which dealt with the use of electronic records and signatures (6). Several draft guidance documents were published and industry went through a transition as we attempted to comply with the regulation and the agency's published interpretations of the rule. In February 2003, the FDA withdrew four of the draft guidance documents in response to increasing concerns that implementation was significantly increasing the cost of compliance while stifling innovation without a significant public health benefit (7). In August 2003, the FDA published a new Part 11 guidance document to clarify how companies should interpret and comply with Part 11 requirements and how FDA would enforce the rule (8).

In an attempt to address the complexities of software, the agency has published guidance documents in recent years on the use of off-the-shelf software in medical devices (9), general principles of software validation (10) and the content of premarket submissions for software contained in medical devices (11). As software gets more complex, so do our businesses and products. These new complexities necessitate risk management techniques.

Risk Management

Although not new, the term "risk management" has permeated our environment. Maybe it's because one-third of medical device incident reports involve a use error (12). Maybe it's because, as complexity escalates, risk management helps us to identify the opportunities or problems that have the biggest impact. Or maybe it's because we can apply risk management approaches and tools to everything from reducing use errors, designing better manufacturing processes, or even FDA oversight of inspectional obligations. Here are just a few risk management sightings in the last few years.

In 2000, FDA introduced a guidance document on the incorporation of risk management into device development (13). In August 2002, the FDA announced a new initiative, Pharmaceutical cGMPs for the 21st Century—A Risk Based Approach. The September 2004 final report summa-

rized the significant changes in the development and implementation of a new operational framework based on quality system and risk management approaches (14). Also in September 2004, the publication of the Process Analytical Technology (PAT) Initiative guidance document supported innovation and efficiency in pharmaceutical manufacturing with a risk management foundation (15). The ISO Standard on risk management, ISO 14971:2000 (16), was mentioned as a critical element in the medical device review process (17) and has recently been translated into a Global Harmonization Task Force (GHTF) guidance document for medical device manufacturers (18).

Globalization

As the world shrinks and trade expands, managing global regulatory demands has become more challenging. The GHTF, a group of representatives from the European Union, USA, Japan, Canada and Australia, encourages convergence of regulatory practices on a global basis for medical devices. The International Conference on Harmonization (ICH), born in 1990, continues to harmonize regulatory requirements affecting pharmaceutical products. With the introduction of the process based quality standards, ISO 9001:2000 (19) and ISO 13485:2003 (20), and the adoption of ISO 13485 by Health Canada, we have a clear global foundation for standardization. Although a challenge to implement, our shifting focus on quality as a process should help continue to bring safe and effective products to market.

Enforcement

FDA continues to hold us accountable. Just look at some of 2003 enforcement statistics—7,813 FDA 483s, 545 warning letters, 4,627 recalls, 22 injunctions and over \$800 billion in fines and restitution (21). This should remind us all that this is a serious business with serious consequences. In our fast paced, high tech, global marketplace, the demands on us are high, as are the expectations from consumers and regulators. We can face our future by knowing our past.

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*21 CFR § 3.2(e) defines a combination product as:

- A product comprised of two or more regulated components that are physically, chemically or otherwise combined and produced as a single entity (e.g., drug-eluting stent.)

- Two or more separate products packaged together or as a unit comprised of a drug/device, device/biologic or biologic/drug (e.g., surgical instruments packaged with lidocaine swabs.)

- A drug, device or biologic packaged separately but according to its labeling intended for use with an approved, specific drug, device or biologic where both must be used together to achieve the intended action (e.g., iontophoretic drug patch and a separate electronic controller.)

Recent GMP Events

2000 ISO 9001:2000 & ISO 14971

The new international process based quality management and risk management standards are introduced affecting companies with ISO registration.

2000 Guidance on Incorporating Human Factors into Risk Management

FDA publishes new guidance aimed at reducing use-related hazards and errors through the incorporation of human factors engineering in the design and risk management processes for medical devices.

2002 Guidance on General Principles of Software Validation

The agency outlines expectations regarding the need for software validation.

2002 Pharmaceuticals for the 21st Century—A Risk Based Approach

The FDA announces a significant initiative to modernize the pharmaceutical cGMPs, bringing a fresh focus and approach to an industry whose regulations have not been significantly revised in 25 years.

2002 MDUFMA

With this law, the FDA introduces user fees for premarket reviews, authorizes 3rd parties to perform establishment inspections, regulates reprocessed single use devices, creates the Office of Combination Products, and begins to address electronic labeling and filing.

2003 Withdrawal & Introduction of Part 11 Guidance

In response to industry concerns, FDA withdraws several guidance documents related to electronic records and signa-

tures. A new guidance document is published clarifying the scope of the rule and enforcement.

2003 ISO 13485:2003

The ISO 9001:2000 standard is translated into an international standard specifically for medical devices affecting companies with ISO registration or who sell product in Canada.

2004 PAT—Final Guidance Document

The PAT Initiative recognizes the new tools and modern techniques available to improve pharmaceutical development, manufacture, and quality assurance.

2005 Guidance Software Contained in Medical Devices

In an attempt to keep pace with advances in technology, FDA supersedes prior guidance for software contained in medical devices by issuing new guidance.

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