CHAPTER 1

UNDERSTANDING THE REGULATIONS

INTRODUCTION

Therapeutic products in development or in the marketplace require extensive and complete documentation. The position of the regulators in the United States and abroad is this: "If you didn't write it down, it didn't happen." What this caveat means is that companies must produce documentation through every phase of product development, manufacture, and distribution. But producing the documents is hardly enough if a company cannot lay its hands on the documents it needs when it needs them. Good documentation thus requires good controls. The way a company determines what controls it must put in place is first by understanding what documents it must have as proof of sound testing and control of its products to demonstrate that they are both safe and effective. Government agencies dictate what companies must do. Companies, in turn, institute good practices that show adherence to the agency requirements. This chapter addresses the regulatory environment and answers the following questions:

1. What agency in the United States oversees therapeutic products, and what authority does it have?
2. What do I need to know about the regulations?
3. How do regulations come to be?
4. What is the history of the regulations for therapeutic products in the United States?
5. Where can I find the actual regulations?
6. What is the purpose of the regulations, and must companies comply with all of them?
7. How can we know which regulations apply to us and what documentation we need?
8. Are clinical trials always in three phases?
9. Doesn't adherence to the regulations slow companies down?
10. Do the regulations tell you how to achieve compliance?

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11. What is the FDA position on regulations and guidances that are not US-based?
12. What is Sarbanes–Oxley, and does it require document controls?
13. What is Part 11, and how does it drive industry practices?
14. Does industry have a say in what goes into a law?
15. How does the FDA keep laws current?
16. What is an electronic record?
17. What is the purpose of 21 CFR Part 11?
18. Does 21 CFR Part 11 apply only to those systems that employ electronic signatures?
19. What is an electronic signature?
20. Is an electronic signature binding the way a handwritten signature is?
21. Which FDA programs does 21 CFR Part 11 apply to?
22. What is a predicate rule?
23. Is my consultant correct in saying that only files generated in a software program and signed electronically are Part 11 files?
24. Are all Word files subject to Part 11?
25. Do small companies also have to comply with 21 CFR Part 11?
26. Are there any other regulations that drive electronic record keeping besides Part 11?
27. Why should companies impacted by 21 CFR Part 11 look at HIPAA regulations?
28. Are there any other regulations that will affect patient records?
29. Why is Part 11 necessary, since the preexisting regulations call for record controls?
30. Does Part 11 override the other regulations for records management?
31. What's the difference between a final rule and a guidance document?
32. Does industry have to comply with guidance documents?
33. What are "best practices" and "industry standards"?
34. How do industry standards develop?
35. What is the scope of industry standards?
36. Are the HIPAA regulations predicate rules for medical records maintained electronically according to 45 CFR Part 164?
37. Does 21 CFR Part 11 apply only to electronic records that are inspected by the FDA?
38. Should an international company have worldwide procedures in place that address 21 CFR Part 11?
39. Why is the FDA revising Part 11?
40. What exactly does "risk" mean?
41. How will companies know which systems pose risk?

42. What will the changes to Part 11 entail?
43. When the FDA withdrew guidance documents in August of 2003, how did that affect Part 11?
44. When will the FDA require electronic submissions?
45. Do other countries accept validation standards based on US regulations?
46. Are the US industry standards for computerized systems comparable to industry standards elsewhere?
47. Is the scope of 820 larger than devices?
48. The regulators are good at telling industry what to do, but do they follow their own dictates?
49. How do companies comply individually?
50. If the regulations call for certain compliance practices, does that mean all companies pretty much do the same thing?
51. How does the FDA issue new regulations?
52. How can companies keep abreast of changes in the regulations and their interpretation?
53. What are warning letters, and how do companies get them?
54. What does it mean to redact sensitive information in warning letters?
55. What happens if a company doesn't fix its problems?
56. What is a consent decree?
57. What is an injunction?
58. What are common citations for companies?
59. What is the direction the industry is taking?
60. Are there plans to harmonize electronic records and signature requirements between the US and the European Union regulatory agencies?
61. Besides submissions and the documentation investigators request during inspections, what other types of documentation do regulators look at?

1. What Agency in the United States Oversees Therapeutic Products, and What Authority Does It Have?

The FDA is an agency within the United States Department of Health and Human Services. It consists of a variety of offices or centers, and the rules can vary from center to center, so companies need to understand which arm of the FDA governs their activities. Here are some of the centers and offices:

- Office of the Commissioner (OC) (1)
- Center for Biologics Evaluation and Research (CBER) (2)
- Center for Devices and Radiological Health (CDRH) (3)
- Center for Drug Evaluation and Research (CDER) (4)
- Center for Food Safety and Applied Nutrition (CFSAN) (5)
- Center for Veterinary Medicine (CVM) (6)

- National Center for Toxicological Research (NCTR) (7)
- Office of Regulatory Affairs (ORA) (8)

The agency has the authority to issue and enforce laws that affect therapeutic products that cross state lines (interstate commerce).

2. What Do I Need to Know About the Regulations?

Therapeutic product development, manufacturing, and distribution to the marketplace are highly regulated. Title 21 of The Code of Federal Regulations (CFR) addresses the requirements for therapeutic products from discovery through life in the marketplace. Parts within Title 21 address specific requirements for various product types. For instance, Parts 210 and 211 address solid dose pharmaceuticals, Part 820 addresses devices, and Part 606 addresses biologics. All the regulations require controlled documentation. In developing and making therapeutic products, other regulations come into play. If a company has a work environment that could potentially be injurious to its employees, it must adhere to the appropriate parts of Title 29 of the CRF, the Occupation, Safety and Health Administration (OSHA) requirements for worker safety (9). Similarly, if a clinical trial site that maintains patient records keeps them electronically, it must be in accordance with parts of Title 45 of the CRF that address Health Insurance and Portability.

3. How Do Regulations Come to Be?

The FDA proposes a final rule (law), usually as the result of industry discussion or agency observations. The proposed rule is published in the *Federal Register* (*FR*) (10) and industry responds with dialogue about the proposed rule. When there is resolution about a proposed rule, the FDA publishes the final rule and gives a date when the final rule will be effective. This allows industry time to implement and modify activities as necessary to comply.

4. What Is the History of the Regulations for Therapeutic Products in the United States?

In the early history of the United States, drugs could be bought and sold like any other commodity. Once problems with drugs surfaced, the government began to legislate therapeutic product development and marketing. Specific laws marking milestones over a period of 100-plus years have brought us to the regulated world of pharmaceuticals, devices, biologics, and biotechnology we know today. (See Box 1.1.)

5. Where Can I Find the Actual Regulations?

The FDA website (www.fda.gov) is a good place. You can search and bookmark the entire Code of Federal Regulations using a standard web browser. Regulatory agencies for other countries also have websites.

BOX 1.1

REGULATORY EVOLUTION IN THE UNITED STATES

The first US federal regulation dates back to 1848 when American soldiers in Mexico died after ingesting adulterated quinine to treat malaria. As a result of these deaths, the government passed the **Drug Importation Act**, which required customs inspections on drugs coming from overseas. In 1862, President Abraham Lincoln appointed a chemist to serve in the new Department of Agriculture. This was the start of the Bureau of Chemistry, the precursor to the Food and Drug Administration (FDA).

In 1902, **The Biologic Control Act** became law after 13 children died from a contaminated antitoxin for diphtheria. This act gave the government regulatory power over antitoxin and vaccine development. Shortly after, in 1906, the government passed the **Food and Drugs Act** to authorize the government to monitor food purity and safety of medicines.

In 1911, the **Sherley Amendment** was enacted. This amendment prohibited false and fraudulent label claims of therapeutic effectiveness. This law was unsatisfactory, however, since a promoter had to be proven to be deliberately fraudulent. In addition, the law covered labeling, but not advertising.

The control of narcotics under the Food and Drugs Act was also unsatisfactory, since it required manufacturers to state only the quantity of any alcohol, opium, morphine, or cannabis in the product. After babies died or suffered addiction from teething remedies containing opium, the government passed the **Harrison Narcotic Act** in 1914. This law required physicians and pharmacists to record the dispensing of narcotics.

In 1927, the government formed the **Food, Drug, and Insecticide Administration.** This agency was reorganized in 1930 as the **Food and Drug Administration**.

Several other events were significant in developing binding regulations designed to protect humans and animals. The 1932, Tuskegee Study of Untreated Syphilis in the Negro Male, conducted under the auspices of the US Public Health Service, deprived infected men of effective treatment so as not to interrupt the project.

Then in 1937, 107 people died after taking "elixir of sulfanilamide," which turned out to be an antifreeze solution. The FDA removed the product from the market, not because it caused fatalities but because it was mislabeled. In 1938, the government passed the **Food, Drug, and Cosmetics Act.** This Act expanded the role of the FDA to control of cosmetics and devices. It also mandated that safe tolerances be established for unavoidable poisonous substances such as pesticides; authorized standards of identify, quality, and fill of containers for foods; authorized factory inspections; added the injunctions as an act of the FDA in addition to penalties of seizure and prosecution; required drugs intended for humans to bear labels warning against habit forming; and defined drug, device, cosmetic, label, and labeling terminology that still applies today. Shortly after, in 1941, the government added the **Insulin Amendment** to the Food Drug and Cosmetic Act. This amendment added standards to ensure purity, quality, strength, and identify of insulin-containing products for diabetes treatment, and it required batch certification. The **Public Health Service Act** of 1944 further tightened controls by calling for regulation of biological products and control of communicable diseases. And then in 1945, the **Penicillin Amendment** was added; this amendment required FDA testing and certification of the safety and efficacy of all penicillin products since production technologies were uncertain. This legislation led to subsequent amendments in 1963 to cover any other antibiotics or derivatives.

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It was after World War II, however, that testing in humans received acute focus. During the war, experiments were done in large scale on unconsenting humans. The Nuremberg War Crime Trials brought these atrocities to light, and the result was the **Nuremberg Code**, which cited 10 standards for ethical human research, not just in the United States.

In 1952, the FDA added the **Durham–Humphrey Amendment** to the Code of Federal Regulations. This amendment clarified the obligations of pharmacists in dispensing drugs by defining the types of drugs that cannot be used safely without medical supervision. It restructured the sale of such drugs to prescription by a licensed physician, and it defined which drugs required prescription drug label and which could be over-the-counter (OTC). The label "Caution: Federal Law Prohibits Dispensing Without a Prescription" was required on all prescription drugs. The law also prohibited unauthorized refills.

The FDA began to pay closer attention to drug manufacturing activities. In 1953, FDA passed the **Factory Inspection Amendment**, which updated and clarified the FDA's authority to inspect. This amendment established the 483 form, which is issued at the close of inspections. It also removed the requirement for FDA to announce inspections. Then in 1958, the FDA added the **Food Additives Amendment**, which required makers of new food additives to establish safety standards before exposure to the public. The Delany Proviso prohibits approval of food additives shown to induce cancer in humans or animals. The law authorized the FDA to evaluate the safety of all new ingredients, including those in dietary supplements. The FDA then published a list entitled "Substances Generally Recognized as Safe"(GRAS) in the *Federal Register.* This was followed by the **Color Additive Amendments** of 1960, which authorized the FDA to establish the conditions of use for color additives in foods, drugs, and cosmetics and required manufacturers to test products for safety.

A wake-up call for better monitoring of development activities in the clinic came in 1962, when thousands of babies were born with defects, the result of their mothers taking thalidomide while pregnant. The drug had never been approved for marketing in the United States, but was undergoing research in American women. Of these women, nine gave birth to defective infants. This event induced the FDA to require notification of investigational use of drugs, which up until this time had not been required. The result was the **Kefauver–Harris Amendment to the Food, Drug, and Cosmetic Act.** This act also required manufacturers to institute Good Manufacturing Practices (GMPs); made FDA approval of the NDA a prerequisite for marketing; placed prescription drug advertising under the FDA's supervision, while allowing the FTC to continue supervision of OTC advertising; required registration and periodic inspections (at least once every two years) of manufacturing facilities; required manufacturers and distributors of new drugs to submit adverse event reports; required assurance of informed consent of research subjects; made qualification of drug investigations subject to review; and required manufacturers to include full information on adverse events and contraindications to provide a balanced picture for health-care professional. The last requirement led to the creation of package inserts.

At about the same time, President John F. Kennedy announced the **Consumer Bill of Rights** in a message to Congress. This Bill of Rights said that the people have the right to safety, the right to be informed, the right to choose, and the right to be heard. In the same period, in 1964, the World Medical Association issued the **Declaration of Helsinki,** and physicians were tasked with embracing this statement: "The health of my patients will be my first consideration." The declaration has been amended four times, and the CFR has incorporated the basic elements.

In 1966, the **DESI Review and Fair Packaging and Labeling Act** called for evaluating the effectiveness of 4000 drugs approved on the basis of safety alone between 1938 and 1962. This Act became known as the Drug Efficacy Study Implementation (DESI) Review. Also in 1966, the **Fair Packaging and Labeling Act** was passed; this act required consumer products in interstate commerce to have honest and informative labeling.

In 1970 the **Poison Prevention Packaging Act** was passed. This legislation required special packaging of controlled substances and prescription drugs for enhanced safety, especially for children. Certain products for children required "child-resistant packaging." The Consumer Product Safety Commission assumed responsibility for enforcing this statute. Also in 1970, the Environmental Protection Agency was established and assumed control of pesticide tolerances.

The **Drug List Act** of 1972 provided the FDA with a current inventory of all marketed drugs, and it required manufacturers to submit a semi-annual list of all drugs introduced or discontinued since the last submission. Four years later the requirement to list new medical devices was added. Also in 1972, the government passed the requirement for **Over-the-Counter Drug Review.** Formal OTC drug reviews were required to ensure safety, effectiveness, and correct labeling of drugs sold without prescription.

In 1972, the National Institutes of Health transferred the regulation of biologics to the FDA. This was followed by the **National Research Act,** which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Additional legislation has continued to promote ethical treatment of health-care recipients.

In 1974, the **National Research Act** was signed into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This committee had the purpose of identifying the basic ethical principles on which clinical research should be founded.

In 1976, landmark legislation was passed to ensure the safety and effectiveness of medical devices. The **Medical Device Amendments** established a risk-based classification system for devices: class I, II, or III, with class I being the least risky and class III having the most risk. Pre-amendment devices were grandfathered. New devices had to show substantial equivalence to a pre-amendment device to establish class I or II status. Class III devices would require a Pre-Market Approval (PMA) from this point on.

The **Vitamins and Mineral Amendments** of 1976 thwarted FDA efforts to establish standards for limiting the potency of vitamins and minerals in food supplements or regarding them as drugs. These amendments were precursors to legislation 18 years later that permitted the unrestricted use of dietary supplements.

In 1978, the FDA published the current Good Manufacturing Practices, 21 CFR Parts 210 and 211.

In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the **Belmont Report**. This report set forth basic ethical principles and guidelines for the protection of human research subjects: respect for persons; beneficence (an obligation to do no harm); and justice (fair and equal distribution of clinical research burdens and benefits). The FDA and the Department of Health and Human Services (HHS) subsequently incorporated the principles in the Belmont Report into laws regarding clinical research. These laws relate to the protection of human subjects, the responsibilities of Institutional Review Boards (IRBs), requirements for an NDA, responsibilities of investigators, control of drugs, record keeping, and record retention.

In the next years, these were passed into law: **The Tamper-Resistant Packaging Act** (1982), a result of cyanide-laced Tylenol reaching the market; and the **Orphan Drug Act** (1983), which provided incentives for drug makers to develop drugs for rare diseases or

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conditions. The **Drug Price Competition and Patent Term Restoration Act** (1984), which is also known as the Hatch Waxman Act, permitted the FDA to approve generic versions of brand drugs without repeating the extensive research. This act established the Abbreviated New Drug Application (ANDA). It also permitted brand drug makers to apply for up to five years of additional patent protection.

In 1988, the FDA became an agency of the Department of Health and Human Services. Since that time, the International Conference on Harmonisation (ICH) has been formed. A significant ICH goal is to maintain safeguards on quality, safety, efficacy, and regulatory obligation for the protection of the public. The **Clinical Laboratories Improvement Amendments** (CLIA) of 1988 established standards to improve the quality of clinical laboratory testing in US laboratories that conduct testing in humans for health assessment for the diagnosis, prevention, or treatment of disease. Then in 1990, representatives from Europe, Japan, and the United States met at the International Conference on Hamonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The objective was to effect better use of human, animal, and material resources, to eliminate duplication of testing, and to remove delays in development.

The **Safe Medical Devices Act** (SMDA) of 1990 expanded and strengthened some provisions of the 1976 Medical Device Amendments. This act codified the 510(k) process and refined the definition of "substantial equivalence"; required user facilities to report injuries; required post-marketing surveillance on implants; established procedures for tracking; and authorized the FDA to order recalls and impose fines. Also in 1990, the **Nutrition and Labeling Education Act** (NLEA) became law. This act required consistent nutritional labeling.

The **Generic Drug Enforcement Act** of 1992 was the result of the generic drug scandal, when generic manufacturers were caught bribing personnel at the FDA and falsifying data. Offenders were subject to drug approval denial for 18 months, suspension of drug distribution, civil penalties, and debarment.

The **Prescription Drug User Fee Act** (PDUFA) was passed in 1992 to accelerate FDA review of applications. Drug and biologics manufacturers would henceforth pay fees for review; these fees would support the hiring of more reviewers at the agency.

In 1992, the **Medical Device Amendments** clarified four provisions of the medical device regulation: tracking; postmarket surveillance, medical device reporting; and the repair, replacement, or refund stipulation.

Shortly after, in 1994, the **Dietary Supplement Health and Education Act** (DSHEA) became law. Under this legislation, dietary supplements were no longer subject to premarket safety evaluations. However, it authorized the FDA to promulgate GMPs and outlined permissible usage claims and nutritional support statements.

In 1996, medical devices became subject to the Quality System Regulation (QSR). In 1996, as well, The Department of Health and Human Services enacted the **Health Insurance Portability and Accountability Act** (HIPAA) into law. The next year, the **Food and Drug Administration Modernization Act** reauthorized the Prescription Drug User Fee Act of 1992 for five more years and instituted reforms in agency practices. These actions provided the forward momentum for broad changes in the health-care industry, but the specifics of the regulation were still being written. Shortly thereafter, also in 1997, **Electronic Records; Electronic Signatures** was enacted.

In 2000, the FDA and the National Institutes of Health (NIH), in response to the death of an 18-year-old receiving gene therapy, renamed and transferred the Office for Human Research protections (OHRP) (formerly the Office for Protection from Research Risks [OPRR]) from the NIH to the Office of the Assistant Secretary of the Department of Health

and Human Services (HHS). This move placed more emphasis on the protection of human subjects.

In 2002, the **Medical Device User Feed and Modernization Act** (MDUFMA) was enacted. This legislation parallels the PDUFA and applies to PreMarket Approvals (PMAs) and Biologic Licensing Agreements (BLAs), certain supplements, and 510 (k)s.

In September 2007, the president signed the **Food and Drug Administration Amendments Act** (FDAAA). This act became effective on March 25, 2008. The FDAAA is the most comprehensive revision to the FD&CA, particularly in pharmacovigilance. This act requires a risk evaluation and mitigation strategy (REMS) to ensure that the benefits of a medicine outweigh its risks, adjustments to safety labeling, postmarketing studies, and the payment of monetary penalties for violations of REMS.

The Government does not issue laws without forethought. The Office of the Federal Register issues the *Federal Register* (*FR*), a weekly disclosure publication that informs citizens of their rights and obligations by providing access to the official text of approved regulations and descriptions of federal organizations, programs, and activities. It also publishes texts of proposed regulations and changes to existing regulations. This gives industry the opportunity to react and share dialogue with the government agency that has ownership of the proposal. Reviewers can comment on content and wording, the date the regulation goes into effect, and the penalties for noncompliance. Comments are reviewed in a government forum, and the final regulation becomes the "final rule."

Once enacted, laws are published in the Code of Federal Regulations, issued annually on April 1. Laws are enforceable by the respective divisions within the Department of Health and Human Services. It's important to note, however, that once a final rule appears in the *FR*, companies are responsible for instituting compliance. Thus, keeping abreast of the regulations requires constant vigilance.

The *CFR* contains regulations of specific government departments and agencies. The *CFR* has 50 "Titles," each assigned to a different unit of government. Title 21, Food and Drugs, contains regulations mandated by the FDA. Title 45, Public Welfare, falls under the auspices of the National Institutes of Health (NIH). Each title of the *CFR* is then divided into chapters, and each chapter is divided into parts and subparts.

Remember, too, that as new regulations are enacted, they do not supersede existing regulations unless the government has rescinded them. New regulations in essence become adjuncts to the ones already in place. Companies must adhere to predicate rules and remain vigilant about industry best practices for compliance.

6. What Is the Purpose of the Regulations, and Must Companies Comply with All of Them?

The regulations are in place to ensure that therapeutic products are both safe and effective for their intended use. Companies must adhere to those regulations that apply to their products and business model.

7. How Can We Know which Regulations Apply to Us and What Documentation We Need?

Each company must fully understand its business model. The regulations that drive laboratory activities are different from those that govern manufacturing and

distribution. It's really a matter of understanding where the company is on the continuum of product development, manufacturing, and distribution. Research (concept development) is not covered by regulations, but once a company moves into development, following the regulations is mandatory. To bring a product to market requires extensive nonclinical testing and confirmation of safety, followed by testing in humans, typically in three trial phases. Companies need to document all their product-related activities as they apply to the business model wherever they are on the continuum. See Figure 1.1.

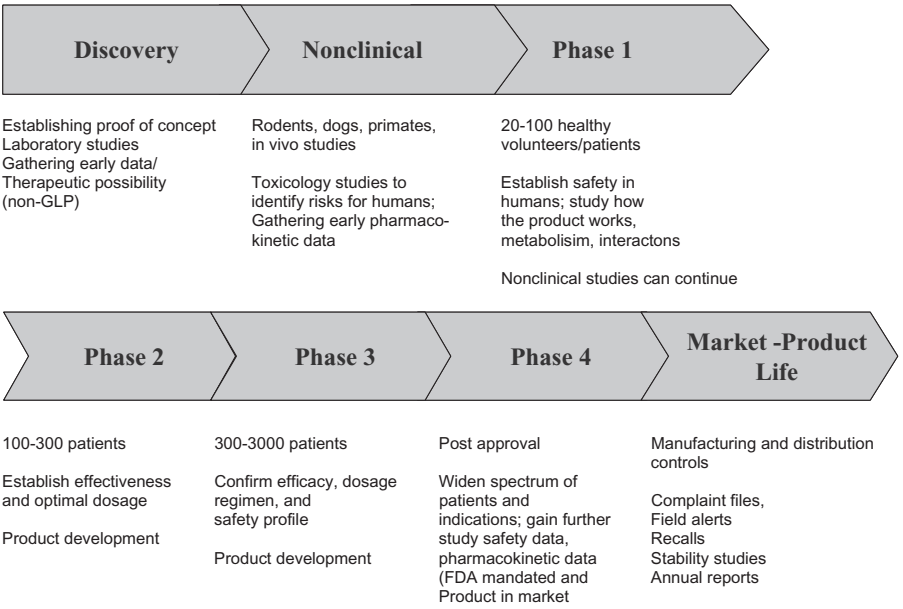

Figure 1.1. Therapeutic product life cycle.

8. Are Clinical Trials Always in Three Phases?

That has been the traditional model. But companies are now designing adaptive trials that are more efficient. In addition, some companies conduct Phase 0 trials in a limited number of volunteers to gather preliminary data on pharmacokmetics and pharmacodynamics. And the regulators very often require that companies conduct Phase 4 studies that track product in the marketplace. Companies also use Phase 4 studies to address product comparisons for effectivity versus price.

9. Doesn't Adherence to the Regulations Slow Companies Down?

That is often the argument for not putting controls in place. Yet the sooner a company institutes controls and has proof of controls in its practices and docu-

mentation, the easier it is for the company to move forward. Good controls speak to more than the regulations. Good controls support good business practices. A lack of controls early on can make for time-consuming and costly corrections going forward.

10. Do the Regulations Tell You How to Achieve Compliance?

The regulations are prescriptive, not descriptive. That is, they tell you what you must do, but they don't tell you how to do it. Each company must figure out for itself "how it happens here."

11. What Is the FDA Position on Regulations and Guidances that Are Not US-Based?

The United States strongly recommends adherence to the International Conference on Harmonisation Guidelines (11). These guidelines endorse common standards for reporting on therapeutic products. The United States, the European Community, Japan, and Australia are countries that have embraced these standards. The advantage of adhering to ICH guidelines is that they satisfy the requirements for more than a single country, so reporting is uniform, and companies significantly reduce the need to prepare separate documentation for each regulator.

12. What Is Sarbanes–Oxley, and Does It Require Document Controls?

Sarbanes–Oxley is legislation passed in 2002 by the Securities and Exchange Commission (12). It requires disclosure of financial interests of executives of publicly held companies to prevent conflicts of interest. Many companies now manage legal records in their document management systems.

13. What Is Part 11, and How Does It Drive Industry Practices?

21 CFR Part 11 Electronic Records; Electronic Signatures is a final rule for electronic record keeping. It became effective in 1997. It is a vaguely worded law, currently undergoing revision. It addresses how to maintain electronic records and employ electronic signatures. See the Appendix, page 261, for the text of the law.

14. Does Industry Have a Say in What Goes into a Law?

Yes. Before a law becomes effective, the FDA proposes the law in the *Federal Register* (*FR*), which is published daily. Industry has an opportunity to respond, and the comments are subsequently published in the FR. The final law is usually the result of dialog between industry and the agency.

15. How Does the FDA Keep Laws Current?

The FDA can amend existing laws. In September of 2007, for instance, the President of the United States signed the Food and Drug Administration Amendments Act of 2007 (13). This law became effective on March 25, 2008. This act represents a comprehensive revision to the Federal Food, Drug, and Cosmetics Act. It focuses heavily on pharmacovigilence. With this act, the FDA has the authority to (a) require a risk evaluation and mitigation strategy (REMS) if it thinks it will help ensure that the benefits of a new medicine outweigh its risks, (b) order safety labeling adjustments, (c) require postmarketing studies, and (d) impose civil monetary penalties for violations of new REMS provisions, postmarketing study/clinical trial requirements, or labeling violations.

16. What Is an Electronic Record?

Electronic records cover a wide scope. The Federal Register, in the mid-1990s, defined an electronic record as "any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system." Basically, any electronic data in any medium is an electronic record. An electronic record is any type of data retained in any format on any nonvolatile medium (semipermanent, such as a hard drive or removable media). Today's modern technology allows for electronic records to be included in PCs, laptop computers, memory sticks, personal digital assistants, and a wide range of portable devices.

17. What Is the Purpose of 21 CFR Part 11?

21 CFR Part 11 allows electronic records to be used in place of or in addition to paper records. It also allows an electronic signature, which is most often a user name and password, to be used in place of a handwritten signature. An electronic signature may also be a biometric signature, such as a fingerprint scan. Computer systems that are used to manage electronic records must be validated regardless of whether approval is made by handwritten or electronic signatures.

18. Does 21 CFR Part 11 Apply Only to Those Systems that Employ Electronic Signatures?

The regulation applies to all systems that manage records electronically. Electronic signatures are optional, but most companies choose to use them because they allow for the replacement of paper records.

19. What Is an Electronic Signature?

It is an electronic equivalent of a handwritten signature, usually a combination of a user name and password, but it can also be a biometric marker. Electronic signature is often used generically to mean an electronic form of approval. This now includes digital signatures and certificates, handwriting capture instruments

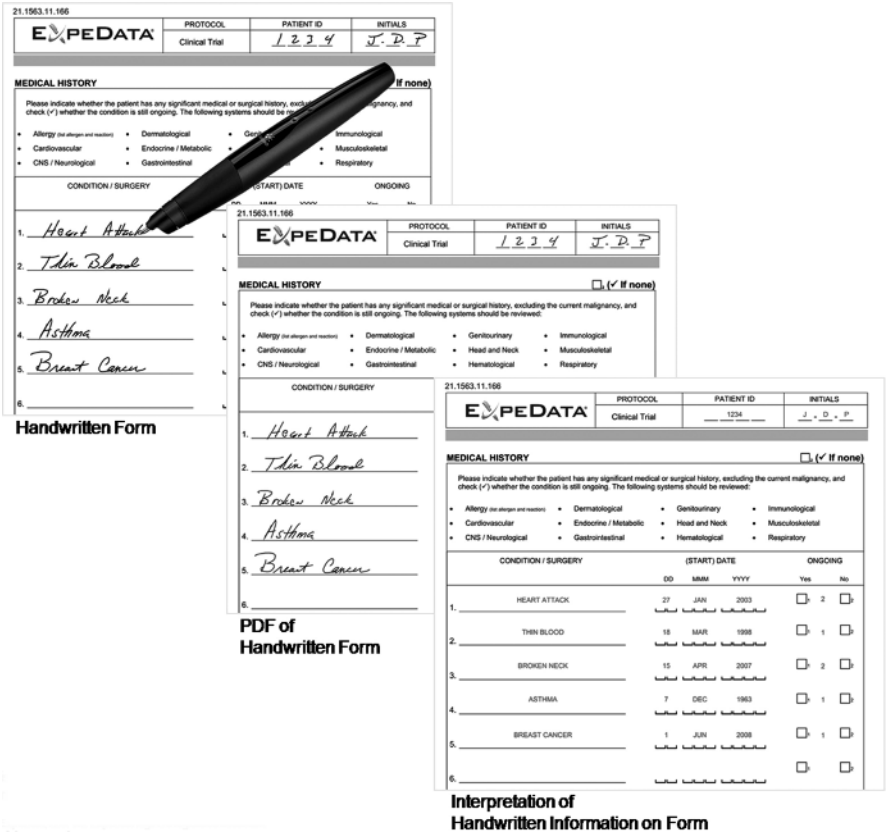

Figure 1.2. Expidata digital pen.

such as pens that remember what is written, or devices that capture handwriting. (See Figure 1.2.)

20. Is an Electronic Signature Binding the Way a Handwritten Signature Is?

Yes. Part 11 establishes an e-signature as the legally binding equivalent of a handwritten signature. Furthermore, in June of 2000, Congress passed the E-Sign Act which gave electronic signatures in other industries the same legal standing as pen and paper.

21. To Which FDA Programs Does 21 CFR Part 11 Apply?

It applies to all FDA programs, whether they address pharmaceutical, biologic, device, or combination products. Even if Part 11 applies, the applicable predicate rules do as well.

22. What Is a Predicate Rule?

A predicate rule is any Title 21 Code of Federal Regulation to which 21 CFR Part 11 applies. Predicate rules identify requirements for records and signatures. Since these predicate rules were written before computer systems were in widespread use, the predicate rules are generally thought to refer to paper records and handwritten signatures. Part 11 allows handwritten records and signatures to be replaced with electronic records and electronic signatures.

23. Is My Consultant Correct in Saying that Only Files Generated in a Software Program and Signed Electronically Are Part 11 Files?

Absolutely not. The regulation addresses minimum standards for electronic records and it applies to "records that are required to be maintained under predicate rules and that are maintained in electronic format in place of paper format" and to "records that are required to be maintained under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities" (14). That means your Word files are electronic records because you do not recreate an entire document every time you revise it; you use the electronic file. It also seems that many people think an electronic signature somehow makes an electronic record subject to Part 11 while a file used on a company's intranet is not subject to Part 11. Part 11 has no requirement for e-signatures, and it is actually optional in the regulation. Most electronic records subject to Part 11 never get an e-signature. The argument is totally misguided.

24. Are All Word Files Subject to Part 11?

Many, but not all, Word files are subject to Part 11. Part 11 applies to any documents that are required by any of the regulations. GXP is an abbreviation for all good practices for the industry, such as Good Manufacturing Practices (GMPs), Good Clinical Practices (GCPs), and Good Laboratory Practices (GLPs). Thus a Word file for a document such as an SOP is a GXP electronic record, and so are PDF files created from them. Electronic files need to be retained in a validated software Electronic Data Management System (EDMS) either purchased or built in house, or kept in a qualified network drive that has secure, limited access folders to ensure security of the files.

25. Do Small Companies Also Have to Comply with 21 CFR Part 11?

Yes. Here's what the FDA has said: "Because widespread use of electronic technology is relatively recent, the significance of official, legally binding electronic records may not be fully appreciated by everyone (15)." Part 11 has a positive impact on nearly all organizations subject to the rule, including small business. Right now, 93% of device firms are small businesses with less than 500 employees, and so are about 500 pharmaceutical companies.

26. Are There Any Other Regulations that Drive Electronic Record Keeping Besides Part 11?

21 CFR Part 11 Electronic Records; Electronic Signatures became law in 1997, and industry standards have evolved since then. In 2003, the Department of Public Welfare passed 45 CFR Parts 160, 162, and 164, as part of the Health Insurance, Portability, and Accountability Act (HIPAA) regulations, into law (16). The requirements of these regulations parallel those of 21 CFR Part 11. HIPAA requires the same types of electronic controls as Part 11, so the HIPAA-driven industry can use the already established standards developed by the Part 11-driven industry. In short, industry standards affect all electronic records regardless of industry. Since Part 11 and HIPAA are related for electronic records, industry standards in one will affect the other. (See Table 1.1.) See the Appendix, page 331, for the full text of the law.

27. Why Should Companies Impacted by 21 CFR Part 11 Look at HIPAA Regulations?

HIPAA will affect many of the Part 11-driven industries. Companies conducting clinical trials, for instance, need to adhere to the HIPAA regulations for electronic record keeping, since clinical trials rely on patient records.

28. Are There Any Other Regulations that Will Affect Patient Records?

Yes. The Department of Health and Human Services is facilitating the development of a nationwide "interoperable" (exchangeable) health data system that will allow sharing of patients' health information electronically (17). The expectation is that it will be law by 2014, so clearly we are moving toward electronic data overall.

29. Why Is Part 11 Necessary, Since the Preexisting Regulations Call for Record Controls?

An argument that industry does not require Part 11 is that the predicate rules call for management of documents, and it is implied that the same principles apply to electronic records as to paper records. However, with industry mandated to submit documentation to the FDA electronically, Part 11 provides a roadmap for achieving consistency within the industry. Also, since the predicate rules do not mention electronic records, Part 11 provides details related to electronic records that cannot be found elsewhere.

30. Does Part 11 Override the Other Regulations for Records Management?

No. All the regulations apply. The predicate rules, those in place outside Part 11, do not go away with Part 11. In fact, the argument that Part 11 is unnecessary stems from the realization that the preexisting laws already cover the requirement for documentation, whether it's paper or electronic.

TABLE 1.1. Comparison Matrix of Part 11 and the HIPAA Regulations

What Part 11 Says	What It Means	The HIPAA Parallel
Subpart A—General Provisions § 11.1 Scope. (a) The regulations in this part sets forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.	Before this regulation, paper records were the compliance focus. With Part 11, electronic records became equivalent to paper records. While paper records are inherently static, electronic records change to keep them current. Electronic records are thus the focus of compliance. By making electronic signatures equivalent to handwritten signatures, the FDA allows electronic signatures to replace handwritten signatures. Companies can retain paper systems, use hybrid paper and electronic systems, or use fully electronic systems.	**164.306 Security standards: General rules**
(b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.	The FDA sets the scope of electronic records to include all agency regulations. All previous and future regulations do not have to be rewritten to include a statement of acceptance for electronic records. This section specifically excludes facsimiles from the definition of an electronic record. Paper that is transmitted by fax remains a paper record, and the faxed copy is equivalent to a paper copy.	**160.103 Definitions for disclosure and electronic media and protected healthcare information**

TABLE 1.1 (*Continued*)

What Part 11 Says	What It Means	The HIPAA Parallel
§ 11.2 (e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.	Industry standards recognize a computer system to be hardware, operating system, software utilities, application software, user instructions, training materials, and validation documentation. The FDA is stating that it will inspect the computer system and the supporting procedural infrastructure related to it.	**164.304 Definitions (for computerized systems)**
Subpart B—Electronic Records § 11.10 Controls for closed systems. Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:	A procedural infrastructure is necessary: Facilities Security, Network Security, Computer System Back-up, Data Archiving, Computer System Maintenance Event Recording, Electronic Signatures. System-specific procedures are also required.	**164.306 Security standards: General rules** **164.308 Administrative safeguards** **164.310 Physical safeguards** **164.312 Technical safeguards** **164.314 Organizational requirements** **164.316 Policies and procedures and documentation requirements**
(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.	Computer System Validation and Computer System Change Control are applicable SOPs.	**164.310**
(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.	Data Archiving and Electronic Record Retention are applicable SOPs.	**164.316**

(*Continued*)

TABLE 1.1 (*Continued*)

What Part 11 Says	What It Means	The HIPAA Parallel
(d) Limiting system access to authorized individuals.	The procedure for granting system-specific access is similar to that included in a Network Security SOP. The procedure may employ handwritten signatures or electronic signatures to authorize issuance of security privileges that allow user access to a system. In some systems the request and issuance of user access is contained within the computer system itself.	**164.306** **164.308** **164.310** **164.312** **164.314** **164.316**
(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.	This requires an automated audit trail. Record changes must not obscure previously recorded information; previous data values must reside in the audit trail. The regulation does not define the audit trail as an electronic record but establishes a requirement to retain audit trail data for the same duration as the electronic records.	**164.312**
(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.	This expands the requirements of section (d) above. Controlled access rights to individual system functions must be granted to authorized users. This is often accomplished by creating roles that have predefined security access and then assigning the role to individual users.	**164.306** **164.308** **164.310** **164.312** **164.314** **164.316**

TABLE 1.1 (*Continued*)

What Part 11 Says	What It Means	The HIPAA Parallel
(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.	In the typical computer environment there are virtual connections between the input devices (client workstations) and the computer that retains the electronic record (server). Each time data transmits between the input device, such as a computer workstation, barcode reader, or instrument, the receiving software application must confirm that that it is appropriate for that device to be transmitting data at that time. Typically, this is done by capturing the network address of the input device at the time of log-on and then verifying that data received comes with the same network address. If a user logs on at one computer workstation and then starts transmitting data from another workstation, the receiving software application cannot confirm that the same person is responsible for the data and the data should be rejected.	**164.306** **164.308** **164.310** **164.312** **164.314** **164.316**
(i) Determination that persons who develop, maintain, or use electronic record/ electronic signature systems have the education, training, and experience to perform their assigned tasks.	This requirement restates the predicate rule for training. It specifically addresses the skill of the computer user to ensure that reliable electronic records are generated and maintained.	**164.308**
(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.	The Electronic Signature SOP is applicable. While FDA requires only one authorized notification of electronic signatures use, all users must understand and certify that their electronic signature is equivalent to their handwritten signature.	**164.308**

(*Continued*)

TABLE 1.1 (*Continued*)

What Part 11 Says	What It Means	The HIPAA Parallel
(k) Use of appropriate controls over systems documentation including: (1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.	Usually a master document delineates document control and distribution. Therefore, system-specific SOPs that describe the operation and maintenance of the system inherently have the appropriate controls.	**164.316**
(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.	A standard part of SOPs is the version change history. Use of existing, well-established SOP documentation practices ensures compliance with this regulation.	**164.316**
§ 11.30 Controls for open systems. Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in § 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.	So far the regulation has addressed closed systems. When users don't have direct control over the source of data, such as when the Internet is used, the FDA makes additional requirements. The objective is to make the open system as secure as a closed system. Industry standards employ end-to-end encryption in addition to all other security features. Digital signatures may provide a pathway for the next evolution of computer system security, but this technology is still immature.	**164.306** **164.308** **164.310** **164.312** **164.314** **164.316**

TABLE 1.1 (*Continued*)

What Part 11 Says	What It Means	The HIPAA Parallel
§ 11.300 Controls for identification codes/ passwords. Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to (a) ensure their security and integrity. Such controls shall include: (a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.	The electronic signature must be unique and assigned to only one user. The combination of the user name and password must be unique. There is no requirement to have passwords be unique.	**164.306 164.308 164.310 164.312 164.314 164.316**
(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).	Electronic signatures, like logon criteria, must be changed at regular intervals. Password aging is required for logon criteria and therefore meets the requirement for electronic signatures.	**164.306 164.308 164.310 164.312 164.314 164.316**
(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information and (b) issue temporary or permanent replacements using suitable, rigorous controls.	Regardless of the hardware and software components for making an electronic signature, procedures must be in place to issue and maintain them. For user name and password components, this doesn't have additional requirements.	**164.306 164.308 164.310 164.312 164.314 164.316**

(*Continued*)

TABLE 1.1 (*Continued*)

What Part 11 Says	What It Means	The HIPAA Parallel
(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.	The system must allow only authorized persons to use electronic signatures at the appropriate time and in association with objects within the scope of each user's allowed responsibilities. The system must detect any security breaches. In most systems, failure to provide a log-on password after a certain number of predefined tries causes a lockout. A system administrator must unlock the account.	**164.306** **164.308** **164.310** **164.312** **164.314** **164.316**
(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.	When devices are used as electronic signature components, procedures must account for all devices and ensure their proper operation on a continual basis.	**164.306** **164.308** **164.310** **164.312** **164.314** **164.316**

31. What's the Difference Between a Final Rule and a Guidance Document?

A final rule is a law; it is akin to a directorate in Europe. You must comply with the laws that apply to your operations. The FDA and other regulatory agencies often issue guidance documents to help industry comply; guidance documents are not legally binding, but they reflect the agency's current thinking on a subject.

32. Does Industry Have to Comply with Guidance Documents?

No. Guidance is simply advice. That said, most companies adhere to best practices, and these usually reflect the intent of the guidance documents. In the beginning of every guidance, there is a disclaimer that says the guidance is not binding.

33. What Are "Best Practices" and "Industry Standards"?

Best practices and industry standards are synonymous. These terms refer to how industry as a whole interprets and complies with the laws.

34. How Do Industry Standards Develop?

It takes about five years to establish industry standards after a rule becomes final. Dialogue between industry leaders and the regulators help shape standards; professional discourse among industry members provides a "give and take" and sharing of "tried and true" practices for industry to reach a modicum of standardization in accord with an applicable regulation.

35. What Is the Scope of Industry Standards?

Industry standards develop across all branches of the federal government and are primarily related to the FDA, the National Security Agency (NSA) (18), and the Health Insurance and Portability Act (HIPAA). Industry standards for record keeping evolve as computer hardware and software evolve in order to address exploited and anticipated vulnerabilities.

36. Are the HIPAA Regulations Predicate Rules for Medical Records Maintained Electronically According to 45 CFR Part 164?

The HIPAA regulations are predicate rules to Part 164, just as the FDA has predicate rules and 21 CFR Part 11.

37. Does 21 CFR Part 11 Apply Only to Electronic Records that Are Inspected by the FDA?

No. The regulation also applies to electronic records not submitted to the FDA that are relative to the company's design, development, manufacture, packaging, distribution, and tracking of its products.

38. Should an International Company Have Worldwide Procedures in Place that Address 21 CFR Part 11?

FDA doesn't expect a company to have a set of procedures that are applicable to every site the company may have. Each facility should have procedures specific to the operations that take place there. Bear in mind that, for FDA-regulated products marketed in the United States, the company must have SOPs that cover the predicate rules as well Part 11.

39. Why Is FDA Revising Part 11?

The current Part 11 does not call for grandfathering of systems in place prior to the issuance for this law. That means that companies have to validate any systems housing electronic records. Industry was slow to comply, since validation of working systems could be extremely costly. Revision of Part 11 will make it more understandable and efficient for companies to comply with the intent of the law. The revision to Part 11 will address risk.

40. What Exactly Does "Risk" Mean?

Risk means that the users of the software and their management understand what hazards can potentially occur, and what the potential effect could be.

41. How Will Companies Know Which Systems Pose Risk?

It is up to companies to determine which systems pose risk. For instance, software that reports on adverse events during a trial is high risk because it is directly related to safety. The methodology for identifying risk in systems is often called "Gap Analysis and Remediation Planning." A gap analysis compares the industry standards with the actual functionality of the system. While a general level of risk can be determined to prioritize computer systems, a detailed measure of risk is performed during the validation of the computer system when the Hazard Analysis document is created.

42. What Will the Changes to Part 11 Entail?

The current Part 11 law is vague and uses language that has changed since 1997. The rewrite for Part 11 will most likely update the language and make more clear how electronic records and predicate rules work together. The concepts of Part 11 will not change. Computer systems will need to be validated to ensure they are secure and are capable of maintaining data integrity.

43. When the FDA Withdrew Guidance Documents in August of 2003, How Did that Affect Part 11?

Much of industry took the withdrawal of guidance documents as an indicator that Part 11 was also going away. This was a misconception; the law remains in place.

44. When Will FDA Require Electronic Submissions?

The FDA established December 31, 2007 as the last day to file paper submissions. While the agency has waived requirements on a per-case basis since then, it has announced that after June 2009 it will no longer issue waivers.

45. Do Other Countries Accept Validation Standards Based on US Regulations?

Yes, the current industry standard for computer system validation employs the risk-based approach. This approach contains all of the essential documentation components required for process-level validation of software supplied by software vendors, which is also known as commercial or configurable off-the-shelf (COTS) validation.

46. Are the US Industry Standards for Computerized Systems Comparable to Industry Standards Elsewhere?

Yes, industry standards for computer systems are uniform throughout the world. Most computer systems are accessible via the Internet from almost anywhere, so standards must be kept uniform to ensure security and reliability.

47. Is the Scope of 820 Larger than Devices?

In the FDA Guidance Document Part 11 Electronic Records; Electronic Signatures part C, there is a reference to 21 CRF 820.70. The scope of 21 CRF 820 is devices and is the most recent of the GMP regulations. As such, it is the benchmark for the other regulations. The expectation is that 820 will be the standard for any revisions to the other GMP regulations.

48. The Regulators Are Good at Telling Industry What to Do, But Do They Follow Their Own Dictates?

Yes. The FDA validates agency systems that read and maintain regulatory submissions from industry.

49. How Do Companies Comply Individually?

Companies adhere to the regulations that apply to them, and they document what they do in procedural documents such as Standard Operating Procedures and Work Instructions. They train the workforce in those procedures, and they keep records of all activities as they occur. They maintain quality through self-audits, monitoring, and corrective action. Everything is documented, and documentation provides the proof of quality and compliance.

50. If the Regulations Call for Certain Compliance Practices, Does that Mean All Companies Pretty Much Do the Same Thing?

The concepts of what has to be done to be compliant are about the same from company to company, but the methods for implementation vary widely.

51. How Does the FDA Issue New Regulations?

The FDA publishes proposed rules in the *Federal Register*, a daily publication available online. Industry can then comment on the regulations. Generally, there is a common consensus, and then a proposed rule becomes final rule, or law. The FDA publishes rules that establish or modify the way it regulates drugs, biologics, radiation-emitting electronic products, and medical devices. “These rules are not created arbitrarily or in a vacuum. They are formed with the public’s health in mind,” according FDA’s own website (19).

52. How Can Companies Keep Abreast of Changes in the Regulations and Their Interpretation?

Changes in regulations are far less common than changes in industry standards, and the regulations are always available in the Code of Federal Regulations. However, the FDA rulings between an existing CFR and the next annual copy indicate how the FDA is interpreting industry practices. Companies must be vigilant in watching trends in regulations and interpretations. Good sources are newsletters, such as the Drug GMP Report and the Pink Sheet. The FDA website also publishes warning letters that can serve as a source for gauging the perspectives of the agency. Daily newsletters, available online, also provide information. And companies attend conferences and seminars to stay current. (See Chapter 13.)

53. What Are Warning Letters, and How Do Companies Get Them?

The agency inspects companies who are developing and manufacturing therapeutic products. They inspect not just the physical facility, but the records and information the organization must maintain. Drug and device manufacturers are inspected about every two years. Suppliers can expect inspections less frequently. If the investigators find noncompliance, they will issue a Form 483 that cites violations at the end of the inspection. If the citations are serious, the agency will send a warning letter to the company, and the company must respond with a plan for corrective action. The FDA posts warning letters on its website, and they become a matter of public record (19).

54. What Does It Mean to Redact Sensitive Information in Warning Letters?

Redaction is annotation to conceal certain parts of sensitive documents. In FDA-posted warning letters, redaction is simply a black strike through of information that may be proprietary to the company who has received the warning letter.

55. What Happens If a Company Doesn't Fix Its Problems?

If a company fails to fix its problems, it can expect another warning letter at the next inspection. Repeated failures to implement corrective action can lead to a consent decree, and beyond that they can lead to an injunction and even prosecution.

56. What Is a Consent Decree?

A consent decree means that the agency is looking over your shoulder very carefully and that it is often onsite to monitor how you fix things. A consent decree is usually very costly in terms of fines to the agency.

57. What Is an Injunction?

Injunction means the company can no longer conduct business. If violations are serious—such as for willfully fraudulent activities—there may also be legal action.

58. What Are Common Citations for Companies?

Companies are often cited for lack of adequate documentation and document controls. Statements such as "failure to adequately document …" or "failure to develop adequate written procedures …" appear in warning letters posted on the FDA website (19).

59. What Is the Direction the Industry Is Taking?

Globalization is definitely here. That means that US companies are now conducting clinical research outside the country. Many clinical trials are now in progress in Brazil, Russia, India, and China (BRIC). In the United States, the FDA has issued a Critical Path Initiative with the goal of modernizing the critical path of medical product development to move products through the development process and to patients more quickly. This initiative has six priorities: biomarker development; streamlining clinical trials; bioinformatics; efficiency in manufacturing; development of antibiotics and countermeasures to combat emerging infections and bioterrorism; and developing therapies for children and adolescents (20).

60. Are There Plans to Harmonize Electronic Records and Signature Requirements Between the US and the European Union Regulatory Agencies?

Available EU documents that delineate electronic record keeping embody the same principles and controls that 21 CFR Part 11 spells out. Annex 11 for Computerised Systems provides a Guide to Good Manufacturing Practice for Medicinal Products.

61. Besides Submissions and the Documentation Investigators Request During Inspections, What Other Types of Documentation Do Regulators Look At?

Regulators watch what industry is doing; they read press releases, web information, and publications; attend industry conferences to sit through presentations and view posters and exhibits; and monitor web blogs and peer communications forums.

REFERENCES

1. Office of the Commissioner (OC), www.fda.gov/oc/
2. Center for Biologics Evaluation and Research (CBER), www.fda.gov/Cber/
3. Center for Devices and Radiological Health (CDRH), www.fda.gov/cdrh/
4. Center for Drug Evaluation and Research (CDER), www.fda.gov/CDER/
5. Center for Food Safety and Applied Nutrition (CFSAN), www.cfsan.fda.gov/
6. Center for Veterinary Medicine (CVM), www.fda.gov/cvm
7. National Center for Toxicological Research (NCTR), www.fda.gov/NCTR/
8. Office of Regulatory Affairs (ORA), www.fda.gov/ORA/
9. Occupation, Safety and Health Administration (OSHA), www.OSHA.gov/
10. *Federal Register*, www.accessdata.fda.gov/scripts/oc/ohrms/index.cfm
11. International Conference on Harmonisation, www.ich.org/

12. Sarbanes–Oxley Act, www.sec.gov
13. Food and Drug Administration Amendments Act, 2007, www.fda.gov/regulatoryinformation/legislation
14. Guidance for Industry: Part 11, Electronic Records; Electronic Signatures, gov/cder
15. Supporting Statement for Electronic Records; Electronic Signatures 21 CRF Part 11, docket 05N-0045.
16. Health Insurance, Portability and Accountability Act, www.dhhs./gov/privacy/index.html, Department of Health and Human Services, www.ihe.net/Technical_Framework/upload/IHE-PHDSC_Public_Health_White_Paper_2008-07-29.pdf
17. National Security Agency (NSA), www.nsa.gov/
18. www.nsa.gov
19. www.fda.gov
20. Critical Path Initiative, www.fda.gov/oc/initiatives/criticalpath/initiative.html