FOOD AND DRUG LAW AND REGULATION

THIRD EDITION

EDITED BY
DAVID G. ADAMS,
RICHARD M. COOPER,
MARTIN J. HAHN
and
JONATHAN S. KAHAN

Published by the Food and Drug Law Institute
FDLI

FOOD AND DRUG LAW AND REGULATION

THIRD EDITION

Edited by

David G. Adams
Partner, Venable LLP
Adjunct Professor, George Washington University Law School

Richard M. Cooper
Partner, Williams & Connolly LLP

Martin J. Hahn
Partner, Hogan Lovells LLP

Jonathan S. Kahan
Partner, Hogan Lovells LLP
Adjunct Professor, George Washington University Law School

 ISBN 978-1-935065-73-9

To order additional copies of this publication, please visit our website at www.fdli.org.

1155 15th St. NW, Suite 910, Washington, DC 20005
Tel: (202) 371-1420 Fax: (202) 371-0649
email: comments@fdli.org
website: www.fdli.org

CHAPTER 10

DRUGS: INDS AND FULL NDAS

JAMES N. CZABAN AND GEOFFREY M. LEVITT*

Introduction

Genomic research by a pharmaceutical company identifies a targeted genetic mutation leading to the development of a powerful new cancer drug.[1] High-throughput molecular screening at an academic research institution identifies a promising treatment for multiple sclerosis.[2] An ancient local custom of rubbing a white flower on the forehead leads to a new therapy for Alzheimer's disease.[3] What do these diverse discoveries have in common? Before American patients could benefit from the resulting treatments, a sponsor must have successfully navigated the gauntlet of the Food and Drug Administration's (FDA) new drug development and application process.

Indeed, from the moment a new drug compound enters preclinical testing, it is comprehensively regulated by FDA at every step of the way. The agency not only decides when and whether the drug has met the substantive standards required for marketing approval but also establishes and enforces the rules governing virtually every aspect of the drug's life cycle, including testing, manufacturing, labeling, marketing, and safety monitoring.

---

* The authors gratefully acknowledge the contributions of Claire Frezza, J.D., Pharm.D. in updating and expanding this chapter.

1 *See* Leslie A. Pray, *Gleevec: the Breakthrough in Cancer Treatment*, 1 Nature Education 37 (2008), *available at* http://www.nature.com/scitable/topicpage/gleevec-the-breakthrough-in-cancer-treatment-565.

2 *See* Joanne Kotz, *Small (Molecule) Thinking in Academia*, SciBX 4(22); doi:10.1038/scibx.2011.617 (June 2, 2011), *available at* http://www.nature.com/scibx/journal/v4/n22/full/scibx.2011.617.html.

3 *See Chemistry in its element: compounds*, Royal Society of Chemistry (2014), *available at* http://www.rsc.org/chemistryworld/podcast/CIIEcompounds/transcripts/galantamine.asp; M. J. Balunas & A.D. Kinghorn, *Drug Discovery From Medicinal Plants*, 78 Life Sciences 431-441 (2005), *available at* http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=2&cad=rja&uact=8&ved=0CCsQFjAB&url=http%3A%2F%2Fwww.snupharm.ac.kr%2Fshsung%2Ferp%2Ferpmenus%2Flesson_pds%2FupLoadFiles%2Fdrugdiscoveryfromplant2005.pdf&ei=d6sYVLXJN5ORyATTuoKwBg&usg=AFQjCNGrSxNwjrXtbZ3d1g8ZADsZapMdsw&bvm=bv.75097201,d.aWw.

In short, FDA holds literally life-and-death power over a new drug. And that power is exercised in an arena populated by influential players with vital interests at stake—drug companies, patient groups, doctors, pharmacists, managed care organizations, healthcare payors, and others. It is no wonder that FDA's regulation of human drugs is a perennial target of criticism and proposals for reform.

For many years—from the 1980s into the early 2000s—the debate focused on the issue of speeding up the drug review process. The result was a series of regulatory and legislative initiatives aimed at making drugs available to patients sooner, ranging from user fees to accelerated approval.

The picture changed dramatically in the mid-2000s with the withdrawal of several prominent drugs from the market for safety reasons. Almost overnight it seemed that criticism of FDA's failure to review new drugs fast enough gave way to concerns that the agency was moving too fast to allow new drugs onto the market before their safety risks were adequately understood. These concerns—fueled by allegations that drug sponsors had not always been fully forthcoming in their handling of safety data—triggered intense congressional interest in legislative reform, aimed in large part at bolstering FDA's drug safety oversight powers. The result was the Food and Drug Administration Amendments Act of 2007 (FDAAA),[4] which notwithstanding its prosaic name was widely viewed as the most significant piece of food and drug legislation in many years. While the FDAAA covered a great deal of ground, for purposes of this chapter its most important contributions are in the areas of safety evaluation in the drug review process and management of postmarketing safety issues.

In 2012, Congress expanded on the FDAAA by passing the Food and Drug Administration Safety and Innovation Act (FDASIA).[5] In addition to re-authorizing and amending several provisions of the FDAAA that were scheduled to sunset, FDASIA aimed to expedite the development and review of innovative medicines.

It is safe to say that both the FDAAA and FDASIA have had a major impact on new drug review and oversight in the United States. But the FDAAA and FDASIA will not be the last word in the debate, as drug review user fees must be legislatively re-authorized every five years. Ongoing congressional scrutiny of FDA's oversight of new drugs is inevitable.

This chapter should therefore be viewed as a snapshot of a regulatory system in a state of continuing evolution. At each phase the discussion will address both the fundamental constants of the FDA regulatory process and the more important and enduring of the recent changes to that process. The chapter tracks the key regulatory phases through which the typical new drug must pass, from preclinical testing to clinical investigation to new drug application review to postmarketing oversight.

---

4 Pub. L. No. 110-85, 121 Stat. 823 (2007). The FDAAA was enacted in the course of the legislative re-authorization of prescription drug user fees, which occurs on a five-year cycle that began with the enactment of the Prescription Drug User Fee Act in 1992. See *infra* for a discussion of the user fee authority.

5 Pub. L. No. 112-144, 126 Stat. 993 (2012).

The New Drug Approval Requirement

The Federal Food, Drug, and Cosmetic Act (FDCA) requires that all "new drugs" be approved before marketing.[6] As described more fully in Chapter 9 *supra*, the act defines the term "drug" broadly[7] and differentiates between prescription and over-the-counter (OTC) drugs. Today, virtually all prescription drugs, and some OTC drugs, are deemed by FDA to be "new drugs" within the meaning of the act.[8]

The two exceptions to the "new drug" category are drugs that are "generally recognized as safe and effective" (a category whose main practical importance is in the context of OTC drugs, discussed in Chapter 13), and "grandfathered" drugs, a historically anomalous category that FDA has essentially interpreted out of the statute.

The "generally recognized as safe/effective" (GRAS/E) standard is in practical terms almost impossible for a company to establish for a prescription drug outside the context of full clinical studies, in part because FDA and the courts have essentially incorporated the new drug approval requirement—that the safety and effectiveness be shown by "substantial evidence" from adequate and well-controlled clinical trials[9]—into the "new drug" definition itself.[10] Moreover, the courts have agreed with FDA that the clinical trials must be published in the scientific literature to support a GRAS/E determination.[11]

Both the 1938 and 1962 acts included grandfather clauses that would exempt pre-existing drugs from the "new drug" classification of the 1938 act, and from the effectiveness requirement of the 1962 act, under limited circumstances. FDA, however, has taken the position that "there are very few drugs on the market that are actually entitled to grandfather status because the drugs currently on the market likely differ from the previous versions in some respect, such as formulation, dosage or strength, dosage form, route of administration,

---

6 FDCA §§ 301(d), 505 (a), 21 U.S.C. §§ 331(d), 355(a).

7 The definition includes 1) articles recognized in the U.S. Pharmacopeia, the U.S. Homeopathic Pharmacopeia or the National Formulary; 2) articles "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease"; 3) articles (other than food) "intended to affect the structure or any function of the body"; and (4) articles intended for use as a component of any of the above. FDCA § 201(g)(1), 21 U.S.C. § 321(g)(1). This definition explicitly excludes foods and dietary supplements for which certain kinds of health-related claims are made, FDCA § 201(g)(1)(D), 21 U.S.C. § 321(g)(1)(D).

8 This outcome is not readily apparent from the "new drug" definition, which refers to drugs that are "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ." FDCA § 201(p)(1), 21 U.S.C. § 321(p)(1). *See also*, FDA, Guidance for FDA Staff and Industry: Marketed Unapproved Drugs—Compliance Policy Guide, § 440.100 Marketed New Drugs Without Approved NDAs or ANDAs (revised, Sept. 2011) *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070290.pdf ("the Agency believes it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a *new drug*.").

9 *See* FDCA §§ 505(b)(1)(A), 505(d)(1), 505(e)(3), 21 U.S.C. §§ 355(b)(1)(A), 355(d)(1), 355(e)(3), and 21 C.F.R. § 314.126.

10 *See* Weinberger v. Hynson, Wescott & Dunning Inc., 412 U.S. 609, 632 (1973) ("a drug can be 'generally recognized' by experts as effective [and thus escape 'new drug' status] . . . only when that expert consensus is founded upon 'substantial evidence' as defined in § [355(d)]."

11 Weinberger v. Bentex Pharmaceutical, Inc., 412 U.S. 645, 652 (1973).

indications, or intended patient population. If a firm claims that its product is grandfathered, it is that firm's burden to prove that assertion."[12]

Thus "new drug" status is essentially just a legal "hook" that gives FDA its extensive regulatory oversight authority. The term has nothing to do with the novelty of the drug, nor the length of time it has been on the market. Drugs approved 50 years ago are still legally "new drugs," as are equivalent generic versions of previously approved drugs.[13]

The "Full NDA"

The statute requires that each new drug be the subject of an approved new drug application (NDA) or abbreviated new drug application (ANDA) prior to marketing. As described more fully below, an NDA must be approved based on, *inter alia*, clinical studies. In a traditional, or "full" NDA, the NDA applicant must have rights to the data in the studies. As described more fully in Chapter 11, NDA applicants can also rely on studies in the public domain and on NDAs submitted by others, by submitting applications known as 505(b)(2) NDAs.[14] Applicants seeking to market similar or identical "generic" versions of approved drugs based on bioequivalence to the approved drug can submit an ANDA, which will not involve submission or review of clinical safety and efficacy data.

This chapter addresses the "full NDA," including the clinical development process, standards and processes for approval, and postapproval requirements.

Preclinical and Clinical Testing

The process of bringing a new therapeutic compound onto the market through the submission of a "full NDA" generally follows a clinical development program involving preclinical investigations and human clinical trials.

Preclinical Investigation and Good Laboratory Practices

The first stage in a drug's regulatory life cycle is preclinical (nonhuman) investigation, which can include in vitro experiments and animal testing. The basic goals of preclinical investigation are 1) to identify reasons to believe that a compound may have beneficial effects in humans, through the use of both in vitro experimentation and animal testing, and 2) to gather sufficient data regarding the pharmacology and toxicology of the potential new drug to conclude that it is reasonably safe to begin preliminary testing in humans.[15]

FDA's regulatory interest in preclinical investigations arises largely after the fact. No FDA approval is required to commence a preclinical investigation, and unapproved drugs

12 FDA Compliance Policy Guide § 440.100, *supra* note 8.
13 *See* United States v. Generix Drug Corp., 460 U.S. 453 (1983).
14 *See* Chapter 11.
15 21 C.F.R. § 312.23(a)(8).

shipped interstate as part of such an investigation are exempted from the FDCA's general prohibition of such shipment, as long as the drugs are appropriately labeled and adequate records of shipment and receipt are maintained.[16] FDA, however, may terminate a preclinical investigator's ability to ship unapproved drugs if the agency determines that continuing the investigation is "unsafe or otherwise contrary to the public interest" or that the drugs are being used for purposes other than "bona fide scientific investigation."[17]

FDA involvement in preclinical investigations ordinarily comes only after the investigation is done, when the agency reviews the investigational new drug application (IND) that a drug sponsor must submit before beginning human clinical trials.[18] At that point, FDA evaluates the soundness and integrity of the relevant preclinical data and practices, as well as the investigational methodologies used. This evaluation focuses upon the preclinical pharmacological and toxicological data that the sponsor relied upon to reach the required conclusion that it was "reasonably safe to conduct the proposed clinical investigations."[19] The sponsor must also provide information on the identity and qualifications of the individuals who evaluated the preclinical studies and determined that clinical trials could reasonably commence.[20]

FDA has promulgated regulations on preclinical testing that are commonly referred to as the Good Laboratory Practices (GLP) regulations.[21] The GLP regulations govern the laboratory work and facilities associated with any preclinical study intended to support a marketing application for an FDA-regulated product, including all human and animal drugs, medical devices and biologics, as well as food and color additives, animal food additives, and FDA-regulated electronic products.[22] These regulations are intended to assure the quality and integrity of data to be submitted to FDA in support of marketing applications, and do so by establishing certain minimum requirements for different aspects of a testing laboratory's practices, subjecting the testing laboratory to FDA inspectional oversight and providing penalties for noncompliance.

In general, the GLP regulations operate by specifying minimum standards in such areas as personnel, facilities, equipment, and operations. As with the regulations pertaining to current Good Manufacturing Practices (cGMPs) (discussed elsewhere in this treatise), the GLP regulations typically set these standards through procedural and structural safeguards, rather than through specific substantive requirements.[23]

For example, in the area of personnel, the GLP regulations require that individuals involved in preclinical studies be sufficiently trained to conduct the study appropriately, but do not specify what such training must encompass.[24] The personnel controls also require

16 *Id.* §§ 312.160, 312.2(b)(3).
17 *Id.* § 312.160(b)(2).
18 FDA regulation of clinical trials is discussed in detail later in this chapter.
19 21 C.F.R § 312.23(a)(8).
20 *Id.*
21 21 C.F.R. pt. 58.
22 *Id.* § 58.1.
23 FDA's Good Laboratory Practices Guidance has remained in essentially unaltered form since 1981.
24 21 C.F.R. § 58.29.

the designation of a study director to oversee, monitor and certify the study,[25] and the establishment of a separate quality assurance unit charged with independently monitoring the progress and scientific soundness of any study being conducted.[26] This quality assurance unit must, among other tasks, maintain copies of study schedules and written protocols, conduct periodic inspections to ensure compliance with all regulations and specifications, submit regular status reports to the management of the testing facility, and prepare and sign a written statement outlining quality assurance efforts, to be included in the final study report.[27]

The GLP regulations also require facilities of suitable size and construction, the appropriate separation of various types of materials, and proper animal care facilities, as applicable.[28] Under the GLP regimen, any study to be submitted to FDA must proceed by way of a detailed protocol specifying the study's objectives and methodologies,[29] and all relevant records and data from the study must be retained for various specified periods.[30] In addition, FDA may inspect any GLP-covered facility to determine that facility's compliance with applicable standards.[31] The regulations give the FDA inspector authority to inspect the records and facilities of the laboratory itself, and to review the inspection procedures that the institution's quality assurance unit is required to maintain.[32]

A testing facility's failure to conform with applicable GLP requirements can result in its disqualification if the nonconformance "adversely affected the validity of the nonclinical laboratory studies" and "[o]ther lesser regulatory actions" are inadequate.[33] Any studies undertaken at a disqualified testing facility that are submitted in support of a subsequent FDA application may be excluded from consideration in the evaluation of that application.[34] Indeed, FDA may disregard a preclinical laboratory study from a nonconforming facility even if the facility's nonconformance with GLP regulations would not warrant a formal disqualification.[35] In addition, if studies performed at a particular facility were submitted as part of a marketing application, and that facility later becomes disqualified, the corresponding study data must be eliminated from consideration (unless the data are determined to be either not essential to the application or otherwise acceptable). This may lead to the termination or withdrawal of approval of the application in question.[36]

In sum, the direct burden of GLP compliance is on the testing facility itself.[37] Yet the GLP regulations create strong incentives for sponsors who plan to rely on preclinical studies for subsequent FDA applications to take an active role in ensuring their proper execution.

---

25 *Id.* § 58.33.
26 *Id.* § 58.35.
27 *Id.*
28 *Id.* §§ 58.41-51.
29 *Id.* §§ 58.120-130.
30 *Id.* §§ 58.185-195.
31 *Id.* § 58.15.
32 *Id.* § 58.35(d).
33 *Id.* § 58.202.
34 *Id.* § 58.200.
35 *Id.* § 58.215(b).
36 *Id.* § 58.210(a).
37 *Id.* § 58.219.

Clinical Investigation

As discussed above, a primary purpose of the preclinical investigation is to gather sufficient evidence about the proposed new drug to proceed to the next regulatory stage; i.e. clinical investigation. The primary goal of a clinical investigation, in turn, is to gather sufficient information about the safety and efficacy of the drug to support advancing to the next investigational or regulatory stage; i.e., to support the next phase of expanded human studies, and ultimately to support a new drug application. Clinical investigations may also be conducted to answer questions related to an approved application or to support claims in product promotion. In contrast to the preclinical stage, clinical trials involve significant contemporaneous FDA oversight, designed both to protect the health and safety of the human test subjects and to ensure the integrity and usefulness of the data derived therefrom.

The Investigational New Drug Application

Unlike the preclinical stage, commencement of clinical trials requires formal notification to FDA. At least 30 days before the drug's sponsor wishes to begin such trials, the sponsor must submit an IND to the agency.[38] Although FDA does not "approve" an IND, it can object to the IND and place the proposed studies on "clinical hold" until the problem is resolved to the agency's satisfaction.[39] While a clinical hold can occur at any time during an investigation, the critical juncture for applicants is the first 30 days after IND submission. If FDA does not object within those 30 days, the IND becomes "effective" and the proposed clinical trials may begin.[40]

The specific contents of an IND depend both upon the nature of the drug and the scope of the proposed trials. However, all INDs must include the following basic elements: 1) a detailed cover sheet; 2) a table of contents; 3) an introductory statement and general investigative plan; 4) an investigator's brochure (except in the case of sponsor-investigator INDs; i.e., where the individual investigator is also the sponsor); 5) a set of comprehensive investigative protocols; 6) information on the proposed drug's chemistry, manufacturing, and controls; 7) pharmacology and toxicology information from preclinical studies; 8) a summary of previous human experience with the drug; and 9) such additional information as FDA deems necessary.[41]

Thus, the IND covers two basic categories of information: information on the study drug itself, and information on the proposed clinical investigation. As to the drug itself, the sponsor must provide the pharmacological and toxicological data from preclinical studies upon which the sponsor concluded it was reasonably safe to propose clinical trials involving humans.[42] The IND must also include information describing the manufacturing and control

---

38 *Id.* § 312.40. In 2013, FDA released a guidance document to help clarify whether an IND is needed. *See* FDA, Guidance: Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND (Sept. 2013), *available at* http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf.

39 *Id.* § 312.42. Clinical holds are discussed in more detail later in this chapter.

40 *Id.* In practice, FDA often communicates informally with the sponsor to indicate that clinical trials may proceed.

41 21 C.F.R. § 312.23.

42 *Id.* § 312.23(a)(8).

of the study drug,[43] as well as comprehensive details on the drug's chemical composition, structural formula, proposed dosage form, and proposed route of administration. Information on any prior human experience with the drug is also required, including any relevant foreign experience,[44] as well as any prior history of the drug's being withdrawn from investigation or marketing.

As to the information on the proposed investigation, the IND must include proposed study protocols, with varying levels of detail depending upon the phase of the clinical trial concerned.[45] Generally, protocols must identify the objectives and purpose of the study, names and qualifications of investigators, patient selection criteria, study design and methodologies, and the study's measurement criteria, including clinical or laboratory monitoring.[46] The IND must also identify the person(s) with overall responsibility for monitoring the study, as well as any participating contract research organizations.[47]

In addition, the IND must include an "investigative plan" containing, among other things, a detailed plan for the drug's investigation, including the rationale behind the research, an outline of the proposed approach, the types of clinical trials to be conducted, an estimate as to the number of patients involved, and a discussion of any significant anticipated patient risks, based upon prior toxicological data.[48] Further, the IND must contain a commitment from the sponsor to conduct clinical trials under the supervision of an Institutional Review Board (IRB), and to follow all applicable rules and regulations, including those pertaining to informed consent.

Informed Consent and Institutional Review Boards

A fundamental goal of FDA regulations on informed consent[49] and IRBs[50] is to assure the protection of the rights and welfare of human subjects.[51] FDA investigators regularly check for compliance with these regulations, and an institution's or sponsor's noncompliance can result in the temporary suspension or formal termination of a clinical study, as well as other administrative sanctions or legal proceedings.

The thrust of the informed consent regulations is to ensure that the subjects' participation in clinical trials is voluntary and knowing. Potential participants must be adequately informed about risks, possible benefits, alternative courses of treatment, and other relevant information before making the decision to participate in the experimental research.[52] Such consent must

---

43 *Id.* § 312.23(a)(7).
44 *Id.* § 312.23(a)(9).
45 *Id.* § 312.23(a)(6). The phases of a clinical investigation are discussed later in this chapter.
46 21 C.F.R. § 312.23(a)(6)(iii).
47 *Id.* § 312.23(a)(1).
48 *Id.* § 312.23(a)(3).
49 *Id.* pt. 50.
50 *Id.* pt. 56.
51 *See id.* § 56.102(g).
52 *Id.* § 50.25. The informed consent regulations, however, provide a narrow exception to the informed consent requirement in cases where a subject is in a life-threatening situation for which available treatments are unproven or unsatisfactory, the subject cannot provide effective consent due to his or her medical condition, and treatment must be administered before consent from a legal representative is feasible. This exception is also subject to additional substantive requirements including that the use of the experimental drug holds

be documented,[53] and research subjects cannot be forced to waive any potential future claims for negligence against the study's investigator, sponsor or institution.[54] Moreover, the patient may withdraw his or her consent at any time for any reason without penalty or loss of benefit.[55] Furthermore, in the case of prisoners used as research subjects, additional restrictions and requirements exist to ensure truly voluntary participation in light of the inherently more coercive penal environment.[56]

The regulations pertaining to IRBs obligate the institution under whose auspices a clinical study is conducted to take a sufficiently active role in the conduct of that study to ensure that the rights of the human test subjects are adequately protected, while, at the same time, rigorous scientific and medical standards are maintained.[57] The IRB itself is essentially a committee designated by the respective institution to review biomedical research involving human subjects.[58] The responsible IRB must review and approve any proposed clinical study before the study commences, and must continue to monitor the research as it progresses.[59] An IRB may approve a proposed clinical study only after determining that certain conditions are met, including that the proposed research appropriately minimizes patient risks, and that such risks are reasonable in relation to anticipated benefits.[60]

The IRB regulations also set up relatively detailed requirements for an IRB's internal "housekeeping." Thus, the IRB must establish written procedures detailing, among other things, its review processes and criteria and its procedures designed to ensure the prompt reporting of changes in ongoing clinical research or in informed consent documents.[61] Moreover, the IRB members must come from sufficiently diverse disciplines to enable the board to review the study not only in terms of specific research issues but also in terms of the study's acceptability under existing community and legal standards, as well as professional conduct and practice norms.[62] The IRB must also keep detailed records of its activities, which are subject to FDA inspection.[63]

The Phases of a Clinical Investigation

Clinical investigations are typically divided into three pre-approval phases,[64] and possible postapproval "Phase 4" studies. Although these phases are analytically distinct, in practice they often overlap, with significant FDA involvement throughout.

Phase 1 studies involve the initial administration of the drug to a small number (typically 20 to 80) of healthy test subjects. Such studies are designed "to determine the metabolism and

the potential to benefit the patient, the investigation could not practicably be carried out without the waiver, and additional patient protections are provided. 21 C.F.R. § 50.24.

53 21 C.F.R. § 50.27.
54 *Id.* § 50.20.
55 *Id.* § 50.25(a)(8).
56 *Id.* pt. 50, subpt. C.
57 *Id.* pt. 56.
58 *Id.* § 56.102(g).
59 *Id.* pt. 56, subpt. C.
60 *Id.* § 56.111.
61 *Id.* pt. 56, subpt. C.
62 *Id.* § 56.107.
63 *Id.* § 56.115.
64 *Id.* § 312.21.

pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness."[65] The drug's sponsor must also derive sufficient pharmacokinetic and general pharmacological data from Phase 1 trials to devise appropriate Phase 2 studies.

Phase 2 investigations involve an expanded patient group (up to several hundred patients) afflicted with the disease or condition being studied. The thrust of Phase 2 trials is to obtain evidence of the drug's effectiveness against the targeted disease, to explore further risk and side effect issues, and to confirm preliminary data regarding optimal dosage ranges.[66]

Phase 3 clinical trials may commence, with FDA clearance, once the drug's sponsor has gathered "preliminary evidence suggesting effectiveness of the drug."[67] Such studies may involve up to several thousand patients.[68] They frequently take place at multiple locations and involve more clinical investigators than in earlier phases. The primary goal of a Phase 3 clinical trial is to collect the data necessary to meet the safety and efficacy standards required for FDA approval.

In many cases, a sponsor will also conduct Phase 4 studies after initial approval. As discussed *infra*, Phase 4 studies may be mandated under the accelerated approval provisions of 21 C.F.R. § 314 Subpart H; may be agreed to between FDA and the sponsor to further address safety issues or to comply with deferred pediatric study requirements; may be voluntarily conducted by the sponsor to expand the labeling for the drug; or may be required by FDA under the authority of the FDAAA.

Collaboration With FDA Regarding Clinical Investigations

The Food and Drug Administration Modernization Act of 1997[69] sought to formalize opportunities for sponsors of clinical trials to meet and seek agreement with relevant FDA review divisions on drug development approaches and the design, scope, and adequacy of proposed clinical trials.[70] The policy goal was to reduce the cost and time needed for drug development and approval by allowing sponsors to obtain binding FDA advice for designing and conducting clinical trials in support of product approval.[71] More recently, under FDASIA, FDA implemented "the Program," a new review model aimed at "promot[ing] greater transparency and improve[ing] communication between the FDA review team and the applicant."[72] The Program recommends that sponsors request pre-submission meetings, a mid-cycle communication, and a late-cycle meeting.[73] The three most common and

---

65 *Id.* § 312.21(a)(1).
66 *Id.* § 312.21(b).
67 *Id.* § 312.21(c).
68 *Id.*
69 Pub. L. No. 105-115, 111 Stat. 2296 (1997).
70 21 U.S.C. § 355(b)(5)(B).
71 *See* 21 C.F.R. § 312.47(b).
72 *See* PDUFA Performance Goals Fiscal Years 2013-2017, at 5, *available at* http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.
73 *Id.* at 6-8.

important types of FDA meetings are the Pre-IND meeting, the End-of-Phase 2 (EOP-2) meeting, and Special Protocol Assessment (SPA) meetings.[74]

Pre-IND meetings are typically available in connection with drugs for life-threatening or severely debilitating diseases. These meetings are designed primarily to discuss and reach agreement on the design of preclinical animal studies necessary to support initial human testing, and may also be used to address the scope and design of Phase 1 studies.[75] Under the Program, sponsors may additionally request a written response to its pre-IND questions.[76]

EOP-2 meetings are perhaps the most useful and important type of FDA meeting, as they are conducted with the purposes of "minimizing wasteful expenditures of time and money and thus in speeding the drug development and evaluation process." To achieve this goal sponsors are encouraged to request and conduct EOP-2 meetings "before major commitments of effort and resources to specific phase 3 tests are made."[77] While primarily intended for sponsors developing new molecular entities or major new uses of approved drugs, EOP-2 meetings are available to sponsors of any IND upon request.[78] Sponsors must submit a meeting package at least one month prior to the scheduled meeting date. Such meeting packages should include, among other things, summaries of Phase 1 and Phase 2 data, specific proposed protocols for Phase 3 studies or additional nonclinical studies and, if available, tentative proposed labeling for the drug.[79] The significance of a well-planned and well-conducted EOP-2 meeting is that agreements reached between FDA and the sponsor with respect to the overall Phase 3 plan and the design of particular studies will generally preclude FDA from later questioning the agreed design or demanding new or additional studies.[80]

SPA meetings are a more focused variation of an EOP-2 meeting, and are intended to reach specific agreements on detailed fully developed proposed protocols submitted by a sponsor for FDA review. Like EOP-2 meetings, SPA meetings can focus on Phase 3 pivotal safety and efficacy studies, but may also be used to seek agreement on protocols for carcinogenicity and stability protocols.[81] Because SPA meetings focus closely on specific protocol questions for a drug, prior agency understanding of the drug's overall development context is considered an essential prerequisite for an SPA meeting. Thus in most cases SPA meetings will follow and build upon, rather than substitute for, EOP-2 meetings.[82] Like agreements reached in EOP-2 meetings, SPA agreements are generally considered binding upon FDA and preclude

74 Other types of clinical-stage meetings include End-of-Phase 1 meetings (21 C.F.R. § 312.82(b)), "Pre-NDA" meetings (21 C.F.R. § 312.47(b)(2)), "Critical Path" meetings, and issue-specific meetings not encompassed by any of the enumerated meeting types.

75 21 C.F.R. § 312.82(a).

76 See PDUFA Performance Goals, *supra* note 72, at 17.

77 21 C.F.R. § 312.47(b), (b)(1)(iii).

78 *Id.* § 312.47(b)(1)(ii).

79 Additional background and procedural instructions for most FDA-sponsor meetings are provided in FDA, Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants (May 2009), *available at* http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf.

80 FDCA § 505(b)(5)(C)-(F), 21 U.S.C. § 355(b)(5)(C)-(F); 21 C.F.R. § 312.47(b)(1)(iv) ("Barring a significant scientific development that requires otherwise, studies conducted in accordance with the agreement shall be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug").

81 FDA, Guidance for Industry: Special Protocol Assessment (May 2002), *available at* http://www.fda.gov/downloads/Drugs/Guidances/ucm080571.pdf [hereinafter the SPA Guidance].

82 *Id.* at 5-7.

the agency from later altering its perspective on issues of design, execution, or analysis of the studies, absent compelling public health concerns.[83]

Obligations of Clinical Sponsors and Investigators

Throughout all phases of a clinical investigation, both the sponsor of the study and the individual investigators have responsibilities and duties designed to ensure patient safety as well as the integrity and soundness of the data derived from the investigation. Noncompliance with these requirements may provoke FDA regulatory actions including Warning Letters, exclusion of a disqualified individual investigator's study results, suspension of an IND or new drug approval predicated upon discredited study data or, in the case of serious violations, civil or criminal proceedings.

The study sponsor is responsible for ensuring patient safety and appropriate scientific conduct, and has the primary responsibility to keep FDA informed of the progress of the study and of any significant safety-related events.[84] The sponsor also has numerous specific obligations regarding such matters as selecting appropriate investigators, adherence to proper protocols and practices, recordkeeping, and shipping and handling of investigational product.[85] In addition, sponsors are responsible for compliance with applicable regulations on informed consent and IRBs.[86]

The sponsor also bears responsibility for reporting to FDA and to clinical investigators any adverse safety events that occur during clinical trials.[87] If the adverse event is serious and unexpected—e.g., it suggests a significant life-threatening hazard or side effect that is not sufficiently identified in the written investigative materials accompanying the study—the sponsor must make such a report within 15 calendar days of receiving the information.[88] Moreover, a sponsor "must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information."[89]

In September 2010, FDA issued a final rule and in December 2012, issued a final guidance document on safety reporting requirements for human drugs and biological products being investigated under an IND and for drugs that are the subjects of bioavailability and bioequivalence studies.[90] The 2010 rule requires, *inter alia*, that adverse events be reported in INDs in the aggregate rather than as individual cases in an effort to eliminate sponsor

---

83 *Id.* at 9.

84 21 C.F.R. §§ 312.32, 312.50-70. Under the regulations, a sponsor may have either an investigating or non-investigating role, in addition to its role of shouldering primary responsibility for and initiating the clinical investigation. *Id.* § 312.3(b).

85 21 C.F.R. § 312.50-70.

86 *Id.*

87 *Id.* § 312.32.

88 *Id.* § 312.32(a), (c)(i).

89 *Id.* § 312.32(c)(2).

90 *See* 75 Fed. Reg. 59,935 (Sept. 29, 2010), amending 21 C.F.R. pts. 312 and 320; FDA, Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (Dec. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf.

reporting of individual cases with serious adverse experiences that have little correlation to the drug itself.[91]

Increasingly, sponsors establish independent Data Safety Committees, also known as Data Safety Monitoring Boards (DSMBs), to review on a regular basis the data accumulating from clinical trials, and to advise the sponsor regarding the continuation or discontinuation of the trial based on subject safety and any changes to the scientific validity of the clinical trial in light of the developing data. Although sponsors are in all cases required to monitor the ongoing safety of their clinical trials,[92] formal establishment of DSMBs is not required except in emergency research where informed consent has been waived.[93] Nevertheless, the use of DSMBs has increased significantly in recent years, and FDA has issued guidance on the establishment and use of DSMBs.[94]

For their part, investigators are required, among other things, to obtain valid informed consent from any participating subjects,[95] to follow study protocols, to ensure that other study personnel follow the required protocols, and to report significant adverse events.[96] An investigator may be disqualified from participation in a study for repeated violations of the regulations or be subject to further administrative, civil, or criminal proceedings.[97] If an investigator disqualification occurs, the study's sponsor will be required to establish that the study's overall viability is not threatened by the investigator's misconduct.[98] Investigator misconduct may also result in an FDA determination that the IND can no longer remain in effect, or that a new drug approval predicated upon the data must be withdrawn.[99]

Public Disclosure Requirements for Clinical Trials

Under the FDAAA, the sponsor is required to post on a public registry certain summary information about any clinical trial for a serious or life-threatening disease, other than a Phase 1 investigation, that was underway as of December 26, 2007 (the effective date of the requirement), no later than that date.[100] For any such trial started after that date, the sponsor is required to post the summary information within 21 days after the first patient is enrolled in the trial. For clinical trials that are not for a serious or life-threatening disease and that were underway as of September 27, 2007 (the date of enactment of the FDAAA), the posting requirement went into effect on September 27, 2008. Sponsors are required to certify to FDA that they have complied with these requirements at the time they submit any "application"

91 *Id.* at 2-3. The guidance provides significant clarification in introducing new terms and definitions in an effort to harmonize safety reporting internationally. *Id.* at 3-7. The guidance also reminds sponsors to review safety information from a variety of sources during drug development and to notify FDA of any potentially serious risks from clinical trials, cognizant of the further requirement of reporting serious and unexpected suspected adverse reactions. *Id.* at 8-13. FDA also provides guidance on the format and time frame for reporting. *Id.* at 21-24.

92 21 C.F.R. § 312.50.

93 *Id.* § 50.24(a)(7)(iv).

94 FDA, Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (Mar. 2006).

95 21 C.F.R. § 312.60.

96 *Id.*

97 *Id.* § 312.70.

98 *Id.*

99 *Id.*

100 *See generally* 42 U.S.C. § 282(j) (added by FDAAA § 801(a)).

under section 505 of the FDCA (for drugs) or section 351 of the Public Health Service Act (for biologics). In 2009 FDA issued a guidance setting forth a broad interpretation of the statutory term "application" for purposes of requiring clinical trial registration.[101] Finally, the registry database was expanded to include certain basic information about clinical trial results for approved drugs and biologics; some, but far from all, clinical trial entries include results.

Expanded Access to Investigational Drugs

Notwithstanding the availability of accelerated approval processes (discussed below), drugs that show promise for serious diseases often are not available to patients until many years after the drug's potential benefit has been identified. This has long created patient-generated pressure on FDA and pharmaceutical companies to make promising experimental drugs available to patients other than those enrolled in clinical trials for the drug. This dynamic was dramatically portrayed in the 2013 Academy Award-nominated film, *Dallas Buyers Club*, which portrayed the struggles of acquired immune deficiency syndrome (AIDS) patients and FDA to quickly provide access to treatments for that then-emerging, and previously untreatable disease.

Since 1987 the "treatment IND" mechanism has been available to allow an investigational drug to be provided outside controlled clinical trials to treat patients with serious or immediately life-threatening diseases for which no comparable or satisfactory alternative therapy is available.[102] The treatment IND program, however, became widely viewed as inadequate and underutilized, with FDA itself noting that "the existing regulations did not adequately describe the full range of [expanded access] programs available,"[103] and raising the concern that "the lack of specific criteria and submission requirements results in disparate access to treatment use for different types of patients and diseases."[104]

In 2009 FDA revised its regulations to make it easier for patients with serious or life-threatening diseases to gain access to experimental drugs prior to approval.[105] The final rules created three categories of expanded access situations: 1) individual patients, including for emergency use (essentially the former categories known as "single patient INDs" or,

---

101 FDA, Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff – Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, added by Title VIII of The Food and Drug Administration Amendments Act of 2007 (Jan. 2009) *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm.

102 21 C.F.R. § 312.34.

103 FDA, Speeding Access to Important Therapeutic Agents, *available at* http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/default.htm.

104 71 Fed. Reg. 75,147, 75,149 (Dec. 14, 2006).

105 74 Fed. Reg. 40,872 (charging for drugs under INDs) and 40,900 (expanded access) (Aug. 13, 2009), amending 21 C.F.R. pts. 312 and 316. In 2013, FDA issued a draft guidance discussing the controversial issue of when it is appropriate to charge for the use of an investigational drug. *See* FDA, Draft Guidance: Charging for Investigational Drugs Under an IND — Qs & As (May 2013), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351264.pdf.

depending on the context, either "compassionate use" or "emergency use" INDs[106]); 2) intermediate-size patient populations;[107] and 3) Treatment INDs or Treatment Protocols.[108]

The baseline criteria for allowing expanded access to investigational drugs are 1) that the drug is intended to treat a "serious or immediately life-threatening disease or condition" for which there is "no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition"; 2) that the potential patient benefit outweighs the potential risks; and 3) that providing the drug for treatment uses will not interfere with the clinical investigations that could support marketing approval.[109] Under the 2009 rule, FDA evaluates the operative criteria on a sliding scale, which in some cases could provide access to drugs based on as little as early Phase 1 safety data.[110] The 2009 rule applies "not only to the use of investigational new drugs but also to approved drugs whose availability is limited because the drugs are subject to a risk evaluation and mitigation strategy (REMS)," and clarifies that eligible patients must have a serious disease or condition but do not need to be currently considered seriously ill with that disease or condition. In 2013, FDA issued a draft guidance to answer questions about its 2009 rule.[111]

In addition, under section 564 of the act, as amended by the Project BioShield Act of 2004,[112] FDA may authorize widespread use of an unapproved drug or other medical product "during a declared emergency involving a heightened risk of attack on the public or U.S. military forces, or a significant potential to affect national security."[113]

The issue of early access (or rather the relative lack thereof) also spawned constitutional litigation against FDA by the Abigail Alliance for Better Access to Developmental Drugs, a nonprofit advocacy group, which challenged FDA's refusal to allow general access to investigational drugs by dying patients. In 2006 the U.S. Court of Appeals for the D.C. Circuit issued a surprising 2-to-1 decision finding a constitutional right to access to unapproved investigational drugs. As the court stated, "where there are no alternative government-approved treatment options, a terminally ill, mentally competent adult patient's informed access to potentially life-saving investigational new drugs determined by the FDA after Phase I trials to be sufficiently safe for expanded human trials, warrants protection under the Due Process Clause."[114] FDA sought en banc reconsideration of this decision and on August 7, 2007, the full court rejected the panel's constitutional analysis and held that "there is no fundamental right . . . of access to experimental drugs for the terminally ill."[115] The Supreme Court declined to consider the case further.

---

106 *See* 21 C.F.R. § 312.310.

107 *See id.* § 312.315.

108 *See id.* § 312.320.

109 *See* 71 Fed. Reg. at 75,150-51.

110 *See id.* at 75,151.

111 *See* FDA, Draft Guidance: Expanded Access to Investigational Drugs for Treatment Use — Qs & As (May 2013), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf.

112 Pub. L. No. 108-276, 118 Stat. 835 (2004).

113 *See*, FDCA § 561, 21 U.S.C. § 360bbb; 21 C.F.R. § 312.36; and Guidance: Emergency Use Authorization of Medical Products (July 2007) *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm.

114 Abigail Alliance v. von Eschenbach, 445 F.3d 470, 486 (D.C. Cir. 2007).

115 *Id.* at 697 (D.C. Cir. 2007).

FDA Oversight: Clinical Holds

Through the imposition of a "clinical hold," FDA may delay a proposed clinical investigation or suspend an existing one.[116] A clinical hold can be imposed for a number of reasons, including an unreasonable and significant risk to patients, the use of improperly qualified investigators, a deficient or disregarded investigative protocol, or any other serious deficiency in the IND or a particular clinical trial.[117] FDA must communicate the imposition of a clinical hold by telephone or other form of rapid communication, and must provide the drug sponsor, within 30 days, with a written explanation of the basis for the clinical hold.[118] As a general rule, until the agency's consent to lift a clinical hold is obtained, any clinical trial or trials subject to the hold cannot commence or resume.[119]

Starting in the early 1990s, FDA undertook various initiatives to evaluate whether clinical holds traditionally had been imposed in a consistent and fair manner, ultimately concluding that the regulations had generally been followed.[120] A committee was also established within the Center for Drug Evaluation and Research (CDER) "to review selected clinical holds for scientific and procedural quality."[121] This committee meets semi-annually to review both randomly chosen clinical hold orders and those orders forwarded by drug sponsors who disagree with the agency's grounds for imposing the hold.[122] In 2008, CDER revised the *Manual of Policies and Procedures* (MAPP) for the Clinical Hold/Refuse to File Committee to, among other things, call for continued meetings of the committee and expand the scope of its inquiry to also specifically evaluate cases where a clinical hold was considered but not imposed.[123]

IND Termination and Suspension

As with the imposition of a clinical hold, FDA can halt further use or distribution of an investigational drug through termination or suspension of an IND.[124] Similar concerns, such as undue patient risk or serious deficiencies in the IND or the clinical protocol, trigger both types of agency action, with IND withdrawal obviously reserved for the more serious cases.

Where the continuation of a clinical study poses, in FDA's judgment, an immediate and substantial danger to human subjects, the agency may order immediate termination of an IND, subject to possible reinstatement.[125] Where no such immediate risk is present, however, if FDA proposes to withdraw an IND, the agency will notify the sponsor in writing and "invite correction or explanation within a period of 30 days."[126] The sponsor's failure

116 21 C.F.R. § 312.42.
117 *Id.*
118 *Id.* § 312.42(d).
119 *See generally*, FDA, Manual of Standard Operating Procedures and Policies, Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications, SOPP 8201 (1999).
120 *See* Investigational New Drugs; Procedure to Monitor Clinical Hold Process; Meeting of Review Committee and Request for Submissions, Notice, 60 Fed. Reg. 43,804 (1995).
121 *Id.* at 43,805.
122 Investigational Biological Product Trials; Procedure to Monitor Clinical Hold Process; Meeting of Review Committee and Request for Submissions, Notice, 61 Fed. Reg. 1032 (1996).
123 CDER MAPP 6010.7 (Jan. 2008).
124 21 C.F.R. § 312.44.
125 *Id.* § 312.44(d).
126 *Id.* § 312.44(c)(1).

to respond within the specified time frame results in the termination of the IND.[127] The sponsor may, however, request a formal hearing if FDA refuses to accept the submitted correction or explanation.[128]

The New Drug Application: Standards and Procedures

Once Phase 3 clinical trials are completed, with satisfactory results, the applicant prepares to submit its new drug application.[129] This preparation process ordinarily includes a pre-NDA meeting with appropriate FDA staff, with the goal of helping to ensure that the NDA will be submitted in the proper format and will contain all required data. After this consultation, the applicant formally submits its NDA.

Contents of the NDA

The regulatory requirements that govern the contents of an NDA are intended to give FDA sufficient information to meaningfully evaluate the drug for which the applicant seeks approval.[130] Although the specific data requirements are lengthy and detailed, there are seven broad categories into which the required data fall: 1) preclinical data, such as animal and in vitro studies, evaluating the drug's pharmacology and toxicology;[131] 2) human pharmacokinetic and bioavailability data;[132] 3) clinical data—i.e., data obtained from administering the drug to humans,[133] which must include "adequate tests" to demonstrate that the drug is safe for use under the proposed conditions of use,[134] as well as "substantial evidence" that the drug is effective under the proposed conditions;[135] 4) a description of proposed methods by which the drug will be manufactured, processed, and packed;[136] 5) a description of the drug product and drug substance;[137] 6) a list of each patent claiming the drug, drug product, or method of use, or a statement that there are no relevant patents making such claims;[138] and 7) the drug's proposed labeling.[139]

In addition to these requirements, the applicant also must provide a summary of the application "in enough detail that the reader may gain a good general understanding of the

127 *Id.* § 312.44(c)(2).
128 *Id.* § 312.44(c)(3).
129 In some cases, Phase 3 trials may continue after submission of the NDA (the so-called "Phase 3B" trial).
130 FDCA § 505(b), 21 U.S.C. § 355(b); 21 C.F.R. § 314.50.
131 FDCA § 505(b)(1)(A), 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. § 314.50(d)(2).
132 21 C.F.R. § 314.50(d)(3).
133 *Id.* § 314.50(d)(5).
134 FDCA § 505(d)(1), 21 U.S.C. § 355(d)(1).
135 FDCA § 505(d)(5), 21 U.S.C. § 355(d)(5); 21 C.F.R. § 314.50(d)(5)(iv).
136 FDCA § 505(b)(1)(D), 21 U.S.C. § 355(b)(1)(D); 21 C.F.R. § 314.50(d)(1)(i)-(d)(1)(ii).
137 FDCA § 505(b)(1)(B)-(b)(1)(C), 21 U.S.C. § 355(b)(1)(B)-(b)(1)(C); 21 C.F.R. § 314.50(d)(1)(i)-(d)(1)(ii).
138 21 C.F.R. § 314.50(h)-(i).
139 FDCA § 505(b)(1)(F), 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 314.50(e). NDA applications also must contain a certification that the applicant has not and will not use the services of any person who has been debarred by the Secretary of the Department of Health and Human Services (DHHS) due to a conviction for conduct related to drug approval, or for conspiring, aiding, or abetting with respect to such an offense. FDCA § 306(k), 21 U.S.C. § 335a(k).

data and information in the application, including an understanding of the quantitative aspects of the data."[140] The summary must conclude with a presentation of both the risks and benefits of the new drug.[141]

Unless an application is publicly disclosed or acknowledged by the sponsor, FDA may not disclose the contents of an application or even its existence until the agency sends an approval letter.[142] The FDAAA requires FDA to publish on its website the action package for approval of any biologics license application (BLA) or any NDA for a new chemical entity within 30 days of approval; for any other new drug or biologic, the action package must be published within 30 days of receipt of the third Freedom of Information Act request for the package.[143] FDA must also publish on its website within 48 hours of approval a summary review documenting conclusions about the drug from all reviewing disciplines and noting any critical issues or disagreements that arose during the review and how they were resolved.[144] The FDAAA further provides that the scientific review of an application "is considered the work of the reviewer and shall not be altered by management or the reviewer once final."[145]

Risk Evaluation and Mitigation Strategy

An additional element that may be required as part of an NDA is the risk evaluation and mitigation strategy (REMS), as provided under the FDAAA.[146] FDA may require a sponsor to include a REMS in its NDA when the agency deems it "necessary to ensure that the benefits of the drug outweigh the risks of the drug."[147]

A REMS must contain, at a minimum, a timetable for submission by the sponsor to FDA of assessments of the REMS 18 months, three years, and in the seventh year after approval, subject to possible variations in frequency within those time frames and to possible elimination of the assessment requirement altogether after the initial three-year period if FDA determines that the drug's serious risks have been adequately identified and are being adequately managed.[148] A sponsor may also submit an assessment of an existing REMS to FDA at any time, along with a proposed modification of the REMS.[149] A proposal to modify

140 21 C.F.R. § 314.50(c).

141 *Id.* § 314.50(c)(2)(ix).

142 *Id.* § 314.430(b), (d). If an application has been publicly acknowledged, however, FDA may, in its discretion, disclose a summary of selected portions of safety and efficacy data that are appropriate for public consideration. For instance, data to be considered at an open session of an advisory committee that is evaluating the drug could be released in summary form.

143 FDCA § 505(l)(2)(A), 21 U.S.C. § 355(l)(2)(A) (added by FDAAA § 916).

144 FDCA § 505(l)(2)(B), (C), 21 U.S.C. § 355(l)(2)(B), (C).

145 FDCA § 505(l)(2)(D), 21 U.S.C. § 355(l)(2)(D).

146 *See generally* FDCA § 505-1, 21 U.S.C. § 355-1 (added by Pub. L. No. 110-85, tit. IX).

147 FDCA § 505-1(a)(1), 21 U.S.C. § 355-1(a)(1). A REMS may also be required for an approved NDA at any time after approval if FDA becomes aware of new safety information and determines that a REMS is necessary to ensure that a drug's benefits outweigh its risks. FDCA § 505-1(a)(2), 21 U.S.C. § 355-1(a)(2).

148 FDCA § 505-1(d), 21 U.S.C. § 355-1(d).

149 In addition, a sponsor must submit a REMS assessment (which may include a proposal for modification of the strategy) when submitting a supplemental application for a new indication; if the agency determines that new safety or efficacy information indicates that any REMS element should be modified or added; or if the DHHS Secretary determines there may be cause to withdraw the drug's NDA under section 505(e) (21 U.S.C. § 355(e)) of the act. FDCA § 505-1(g), 21 U.S.C. § 355-1(g). For a discussion of NDA withdrawal *see infra*.

a REMS strategy is not, however, required to be included with an assessment and also can be submitted to FDA at any time.[150]

In addition to the required periodic assessments, a REMS may also be required to provide for the distribution of a Medication Guide[151] or a patient package insert to each patient when the drug is dispensed if FDA determines that such a requirement may help "mitigate a serious risk of the drug."[152] A communication plan aimed at healthcare professionals may also be required if FDA determines that such a plan may support implementation of an element of the REMS.[153]

A more stringent set of REMS elements may be required if FDA determines that it is necessary to "assure safe use of the drug, because of its inherent toxicity or potential harmfulness." These Elements to Assure Safe Use (ETASU) may require that healthcare professionals who prescribe or dispense the drug have particular training or experience or are specially certified; the drug be dispensed only in specified settings such as hospitals; or patient testing, monitoring, and/or enrollment in a registry be required in connection with dispensing the drug.[154]

Whenever a REMS assessment is submitted, FDA must initiate discussion with the sponsor within 60 days, except for assessments required because the Secretary of the Department of Health and Human Services (DHHS) has determined there may be cause to withdraw the NDA, in which case such discussions must begin within 30 days after submission.[155] For proposed REMS modifications submitted as part of an NDA or supplement, FDA must describe the final REMS or any modification to the REMS, as applicable, in the action letter on the application.[156] For proposed REMS modifications submitted as part of a REMS assessment, FDA must describe the final REMS, in most cases, within 90 days of the beginning of the required discussions with the sponsor.[157] Detailed dispute resolution processes apply if FDA and the sponsor disagree on a REMS or REMS modification.[158] Use of the REMS dispute resolution processes, however, "shall not be the sole source of delay of action on an NDA or supplement."[159] Existing REMS also apply to generic versions of the innovator drug, with special procedures and limitations.[160]

---

150 *See* FDCA § 505-1(g) (as amended by FDASIA § 1132(a)(4)). For information on how to propose a REMS modification, *see* FDA, Draft Guidance: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications (Sept. 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf.

151 *See* 21 C.F.R. pt. 208.

152 FDCA § 505-1(e)(2), 21 U.S.C. § 355-1(e)(2).

153 FDCA § 505-1(e)(3), 21 U.S.C. § 355-1(e)(3).

154 FDCA § 505-1(f), 21 U.S.C. § 355-1(f).

155 FDCA § 505-1(h)(2), 21 U.S.C. § 355-1(h)(2).

156 FDCA § 505-1(h)(3), 21 U.S.C. § 355-1(h)(3).

157 *Id.*

158 FDCA § 505-1(h)(4)-(5), 21 U.S.C. § 355-1(h)(4)-(5).

159 FDCA § 505-1(h)(9), 21 U.S.C. § 355-1(h)(9).

160 Drugs approved under ANDAs or 505(b)(2) NDAs that reference an approved drug with a REMS are subject to all elements of the REMS except the requirement to submit assessments and proposed modifications. For those REMS elements involving restrictions on distribution and use, the generic drug applicant and the reference drug applicant are to use a single, shared system, unless FDA determines that the burdens of such a system outweigh the benefits, or that any aspect of the REMS elements in question is patent-protected or

When the REMS authority was enacted as part of FDAAA there were concerns that FDA would overuse this new tool in ways that would overburden sponsors, delay approvals, and dilute the safety messages for drugs generally by overwarning doctors and patients with excessive, but marginally important, safety information. Once FDA created its REMS infrastructure there was indeed an increasing number of REMS required, including many REMS that went beyond just a medication guide by requiring ETASUs of various degrees of complexity. And, there were several examples of NDAs that were delayed beyond their PDUFA action dates due to unresolved REMS issues.

More recently, however, FDA has begun to realize that the burdens of REMS are greater than it imagined, and that they may not be commensurate with the potential safety improvements. Indeed, the agency has received strong criticism from unexpected quarters about the burden of REMS. For example, major health insurance plans and integrated wholesale pharmacy companies have been critical of the burdens some ETASUs, such as physician, patient, and pharmacist registration and recordkeeping requirements, place on their ability to serve their customers and patients. FDA for its part has responded to these concerns with public meetings, an apparent reduction in the percentage of REMS required, and a focus on establishing class-wide and standardized REMS where feasible.[161] Under its PDUFA V Commitment Letter, FDA further stated it "will continue to use user fees to enhance and modernize the current U.S. drug safety system."[162]

Filing of the NDA

When an NDA arrives at FDA, the agency considers it to be "received," not "filed." The application is considered "filed" when FDA formally accepts it for filing. FDA must determine whether or not to file an application within 60 days of its receipt.[163] If no grounds for refusing to file the application exist, FDA must file it; the filing date will be 60 days after the date of receipt.[164]

FDA will accept an application for filing only if the application is "sufficiently complete to permit a substantive review."[165] FDA has the authority to refuse to file an application on several grounds, such as 1) if the application is incomplete or in improper form or omits data

proprietary and the ANDA applicant is not able to obtain a license. In this connection, the law prohibits an NDA sponsor from using any REMS element to "block or delay" approval of an ANDA. FDCA § 505-1(i), 21 U.S.C. § 355-1(i).

161 The establishment of class-wide REMS has not, however, been any easier than the imposition of individual-product REMS. For example, FDA has struggled to establish a class-wide REMS for extended-release opioid products, starting with a notice in February 2009. After at least seven formal meetings with sponsors and interested parties, in April 2011 FDA finally issued a notice of the required REMS, but has given the industry working group (consisting of 21 different companies) an initial 120-day period to propose a system whereby all sponsors would collaborate in implementing a shared implementation system for the REMS. *See generally* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm for details on FDA's opioid REMS programs.

162 *See* PDUFA Performance Goals, *supra* note 72, at 25.

163 21 C.F.R. § 314.101(a)(1).

164 *Id.* § 314.101(a)(2). FDA uses confusingly different terminology for ANDAs, which are considered "submitted" upon physical delivery to FDA, and "received" after FDA has determined that the ANDA is sufficiently complete to permit a substantive review. See 21 C.F.R. § 314.101(b).

165 *Id.* § 314.101(a)(1).

critical to assessing safety, efficacy, or adequate directions for use;[166] 2) if the application fails to make required certifications regarding how the preclinical and clinical trials were conducted;[167] or 3) if the application covers a drug product that is already covered by another application.[168]

Although its refusal to file (RTF) authority sounds quite broad, FDA typically uses that authority only for obvious deficiencies in the application, not in cases that involve "matters of subtle judgment."[169] As the agency's 1993 RTF guideline states: "It is important . . . that [RTF] be reserved for applications . . . plainly inadequate, non-reviewable without major repair, or that make review unreasonably difficult."[170] Applications that contain deficiencies this severe will be subject to refusal, because FDA believes that accepting applications in need of extensive repair is unfair to new drug sponsors whose submissions were complete and properly formatted.[171]

There are three circumstances in particular where FDA is especially likely to use its RTF power: 1) omission of a required section of the NDA, or presentation of a section in so haphazard a manner as to render it incomplete on its face; 2) clear failure to include evidence of effectiveness that can meet the statutory and regulatory standards; and 3) omission of critical data, information, or analyses needed to evaluate safety and effectiveness, or to provide adequate directions for use.[172] Because the agency's RTF power is discretionary, however, FDA can choose not to use the RTF procedure for particularly critical drugs even if specific grounds for invoking it are present.[173] In practice, potential RTF issues are usually addressed and resolved before the NDA is submitted. The pre-NDA meeting often provides a forum for this process.

In 2013, FDA sought to clarify its RTF practice in a new *Manual of Policies and Procedures*.[174] Among other reasons, the MAPP specifies that FDA will RTF applications that are "[m]aterially incomplete or inadequately organized," or "contain inadequate information for one or more indications."[175] If FDA chooses to use its RTF authority, it will notify the applicant, which can then request an informal conference on the issue of whether its application should be filed.[176] After the conference, the applicant can request that FDA file the application, with or without amendments to correct the deficiencies. The agency will then file the application "over protest."[177] As a practical matter, however, an applicant has little or no incentive to ask

166 *Id.* § 314.101(d)(1)-(2).

167 *Id.* § 314.101(d)(6)-(7). For instance, an application that fails to state that preclinical studies were conducted in conformity with GLPs can be refused. Similarly, FDA may refuse to file an application that does not state that clinical studies were conducted in accordance with informed consent and IRB requirements.

168 *Id.* § 314.101(d)(8).

169 Center for Drug Evaluation and Research, Food and Drug Administration, New Drug Evaluation Guidance Document: Refusal to File (July 12, 1993), at 3.

170 *Id.*

171 *Id.* at 1.

172 *Id.* at 4-5.

173 *Id.* at 3.

174 *See* MAPP Good Review Practice: Refuse to File (Oct. 11, 2013), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM370948.pdf.

175 *Id.* at 5.

176 21 C.F.R. § 314.101(a)(3). Such a meeting must be requested within 30 days of FDA's notification.

177 *Id.*

the agency to do this. If FDA believes the application contains deficiencies egregious enough to warrant an RTF response, there is little chance of subsequent favorable FDA action on the application.[178] Therefore, requests to file an application "over protest" are a rarity.[179]

Substantive Standards for Review

FDA reviewers must find that an application meets several substantive requirements before the agency will approve the NDA. The most basic requirements are that the drug be "safe" and "effective." These words have specialized meanings in the new drug approval context.

The FDCA, as enacted in 1938, did not require a showing of efficacy as a condition for marketing a new drug—only proof of safety. The Drug Amendments of 1962[180] added the requirement that a new drug must be supported by "substantial evidence" that the drug will have the effect it purports to have under the indicated conditions of use.[181] "Substantial evidence" means evidence from adequate and well-controlled clinical studies.[182] Normally, FDA requires two independent studies to demonstrate efficacy.[183] In 1995, however, the agency issued a statement memorializing a practice it had begun to follow in recent years: namely, that if it is possible to replicate efficacy results within one large, well-designed, multicenter study and those study results are strong,[184] a single study may suffice for approval.[185] This policy clearly remains the exception rather than the rule, however. In addition to this policy, the Act was later amended by FDAMA to provide expressly that FDA may accept a single study as "substantial evidence" of efficacy "[i]f the [agency] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness."[186]

---

178 In one instance, after FDA determined that an application for the drug deprenyl was insufficiently complete for substantive review, the applicant requested that FDA file the application over protest. FDA reviewed the application as filed and then proposed to disapprove it because it had numerous problems and deficiencies. See Discovery Experimental and Development, Inc.; Deprenyl Gelatin Capsules and Liquid (Deprenyl Citrate); Proposal to Refuse to Approve a New Drug Application; Opportunity for a Hearing, Notice, 59 Fed. Reg. 26,239 (1994).

179 In the event that an application is filed over protest, the review clock (*see* discussion *infra)* will begin on the date the applicant requested the conference rather than on the day the application was received (New Drug and Antibiotic Regulations, Final Rule, 50 Fed. Reg. 7452, 7479 (1985)), and the filing clock will begin 60 days after the applicant's conference request (21 C.F.R. § 314.101(a)(3)). The triggering dates are moved back in this fashion because the hearing on whether the application should be filed consumes part of the review and filing periods. Review and filing clocks are discussed in more detail later in this chapter.

180 Pub. L. No. 87-781, 76 Stat. 780 (1962).

181 FDCA § 505(d), 21 U.S.C. § 355(d); 21 C.F.R. § 314.105(c).

182 FDCA § 505(d), 21 U.S.C. § 355(d).

183 Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices, Notice, 60 Fed. Reg. 39,180, 39,181 (1995).

184 "Strong" results are those that are not "statistically marginal." *Id.*

185 *Id.*

186 FDCA § 505(e), 21 U.S.C. § 355(e).

FDA has a special Combination Drug Policy[187] governing how an applicant must demonstrate effectiveness of a drug that contains more than one active ingredient.[188] Although this regulation on its face reads as a permissive policy, it was actually promulgated in order to require additional evidence of efficacy for many fixed combination drug products already on the market.[189] For an NDA for a combination drug containing two (or more) active ingredients, the combination policy means that evidence of safety and efficacy would be required not only for the drug as a whole, but also for each of the components. In other words, each component must be shown to contribute individually to the claimed overall effects of the product. This contribution, however, need not relate to efficacy—a component may also be added if it is shown to increase the safety of the other component or components. Of key importance under the combination drug policy is the principle that prior efficacy (or safety) results on individual active components cannot be extrapolated to a proposed combination drug—rather, that combination drug must undergo its own clinical investigations to demonstrate safety, efficacy and the contribution of the active components.[190] Like many such principles in the drug approval setting, however, this one is not necessarily absolute, and FDA may exhibit more (or less) flexibility in individual cases.

In addition to proof of effectiveness, a drug may not be approved unless there are "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof."[191] In applying this statutory standard, FDA recognizes that there is no such thing as an absolutely safe drug; in addition to the benefits it provides, every drug will present some risks. Therefore, FDA's assessment of safety necessarily contemplates consideration of efficacy. In the agency's words, "FDA weighs the product's demonstrated effectiveness against its risks to determine whether the benefits outweigh the risks."[192] This risk/benefit analysis takes account of information such as the seriousness of the disease, the presence and adequacy of existing remedies and adverse reaction and any other safety data.[193] FDASIA further requires FDA to implement a structured risk/benefit assessment framework that will facilitate the review of drug risk and benefit considerations. A draft five-year plan describing FDA's proposal to implement and develop such a framework was released in 2013.[194]

---

187 Combination *Drug* Products are not to be confused with "Combination Products" which, as discussed in Chapter 17 *infra*, involve a combination of two or more different types of products; e.g., drug/device, or biologic/device products.

188 The agency's regulations state that:

> (a) Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Special cases of this general rule are where a component is added:
>
> (1) To enhance the safety or effectiveness of the principal active component; and
>
> (2) To minimize the potential for abuse of the principal active component.

21 C.F.R. § 300.50.

189 *See* Combination Drugs for Human Use: Proposed Statement Amplifying Policy on Drugs in Fixed Combinations, 36 Fed. Reg. 3126 (1971).

190 *See, e.g.*, U.S. v. Articles of Drug…Promise Toothpaste, 826 F.2d 564 (7th Cir. 1987).

191 FDCA § 505(d)(1), 21 U.S.C. § 355(d)(1).

192 60 Fed. Reg. 39,180 (1995).

193 *Id.*

194 FDCA § 505(d), 21 U.S.C. § 355(d) (as amended by FDASIA § 905).

Under the Pediatric Research Equity Act (PREA)[195] (made permanent by FDASIA in 2012), an NDA or BLA must include assessments of the safety and efficacy of the product in all relevant pediatric subpopulations (as defined by FDA in consultation with the sponsor) as well as data to support dosing and administration for each pediatric subpopulation for which the product is safe and effective.[196] The applicant must first, however, submit an initial pediatric study plan prior to submission of the assessment.[197] Upon meeting with or receiving comments on the initial pediatric study plan from FDA, the applicant must document its agreement with the plan, which may be amended at any time.[198] FDA then must confirm its agreement with the plan and provide its recommendation in response to requests for deferral, partial waiver or waiver as described below.[199] The content of and process for submitting initial and amended pediatric study plans is described in a draft guidance released by FDA in July 2013.[200]

Assessment requirements may be deferred for various reasons, including an FDA finding that the product is ready for adult approval before pediatric studies are complete.[201] They may also be waived partially or entirely on a variety of grounds, including that 1) the necessary studies are impossible or highly impractical; 2) there is evidence strongly suggesting that the product would be ineffective or unsafe in children; 3) the product does not represent a meaningful benefit over existing therapies for children and is not likely to be used in a substantial number of children; or 4) (for a partial waiver applicable to a specific age group) reasonable efforts to produce a pediatric formulation necessary for that age group have failed.[202] FDA also has authority under PREA to require pediatric assessments for marketed products if the agency finds that 1) the product is used in a substantial number of children for the labeled indications and adequate pediatric labeling could confer a benefit on pediatric patients; 2) there is reason to believe the product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for one or more claimed indications; or 3) the absence of adequate pediatric labeling could pose a risk to pediatric patients.[203]

PREA was amended by FDASIA to permit the extension of deferrals by FDA on its own initiative or in response to an applicant's request for a new deadline.[204] The request for a new deadline must be submitted to FDA 90 days prior to the expiration of the existing deadline.[205] FDA is also required to issue noncompliance letters to any applicant that fails to submit or defer a required assessment, or if the applicant does not submit a request for approval of a pediatric formulation.[206]

---

195 Pub. L. No. 108-155, 177 Stat. 1936 (2003).
196 FDCA § 505B(a)(2), 21 U.S.C. § 355c(a)(2).
197 FDCA § 505B(e)(2)(B) (as amended by FDASIA § 506(a)).
198 FDCA § 505B(e)(3) (as amended by FDASIA§ 506(a)).
199 *Id*.
200 FDA, Draft Guidance, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (July 2013), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.
201 FDCA § 505B(a)(3)(A), 21 U.S.C. § 355c(a)(3)(A).
202 FDCA § 505B(a)(4), 21 U.S.C. § 355c(a)(4).
203 FDCA § 505B(b), 21 U.S.C. § 355c(b).
204 FDCA § 505B(e)(3)(B) (as amended by FDASIA § 505(a)).
205 *Id*.
206 FDCA § 505B(d) (as amended by FDASIA § 505(c)).

In addition to evidence of safety and effectiveness, there must also be adequate manufacturing controls in place before FDA will approve a drug.[207] In particular, the methods used in, and the controls and facilities used for, manufacturing, processing, packing, and holding the drug substance and finished product must comply with FDA's cGMPs, and must be adequate to maintain the drug's purity, quality, strength, identity, and bioavailability.[208] A pre-approval inspection of the applicant's facilities will typically be conducted to verify compliance with these requirements.[209]

An additional prerequisite to approval is that the drug's labeling meets applicable statutory and regulatory requirements. The labeling cannot be false or misleading in any particular,[210] and must comply with general requirements concerning both the content and form of the information that must accompany a drug, such as indications, clinical data, warnings, precautions, side effects, and dosage and administration information.[211]

Comparative Effectiveness Research

In 2009 Congress passed the American Recovery and Reinvestment Act (ARRA) in support of comparative effectiveness research (CER).[212] Congress appropriated $1.1 billion to the Agency for Healthcare Research and Quality (AHRQ) for the development and use of clinical registries and clinical data networks that can be used to generate or obtain health outcomes data.[213] AHRQ transferred a portion of these funds to FDA to develop policies, standards, infrastructure, and tools for standardizing clinical study data to enable CER analysis across multiple studies.[214]

It is not FDA policy to require that new drug products or devices submitted for approval be more effective than other approved therapies for the same disease or condition; effectiveness is shown based on clinical data that does not necessarily involve a comparison to another known effective treatment or product.[215] However, in certain circumstances, FDA will consider comparative efficacy; namely when less effectiveness could present a public health danger.[216] Two specific circumstances where a new therapy must be as effective as already approved alternatives are when: 1) the disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack); or 2) the disease to be treated is a contagious illness that poses serious consequences to the health of others (e.g., sexually transmitted diseases).[217] New products developed for particular subpopulations that do not respond to or are unable to tolerate an existing approved therapy require only proof of

---

207 FDCA § 505(d)(3), 21 U.S.C. § 355(d)(3). Manufacturing requirements are discussed more fully in Chapter 9 *supra*.

208 21 C.F.R. § 314.125(b)(1).

209 *Id.* § 314.125(b)(12).

210 FDCA § 505(d)(7), 21 U.S.C. § 355(d)(7); 21 C.F.R. § 314.125(b)(6).

211 21 C.F.R. § 314.125(b)(8). *See* 21 C.F.R. pt. 201 for a detailed description of labeling requirements.

212 Pub. L. No. 111-5, 123 Stat. 115 (2009).

213 *Id.* tit. VIII.

214 *Id.*

215 Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices, Notice, 60 Fed. Reg. 39,180, 39,181 (1995).

216 *Id.*

217 *Id.*

effectiveness in the targeted population and do not need to be as effective as alternative therapies in the broader population.[218]

Advisory Committee Review

Although the primary review of an NDA is, of course, carried out by the appropriate division within CDER, FDA refers many applications to outside advisory committees for their comments and recommendations. These advisory committees, which are composed primarily of prominent research and clinical specialists, review certain critical studies regarding drug products under consideration, as well as proposed labeling.[219] Advisory committees respond to specific questions posed by the agency regarding safety and efficacy, and evaluate whether additional studies are needed to support approval.[220] In addition to advisory committees, FDA also has discretion to consult outside expert reviewers from the scientific community for their views.[221] Under FDASIA, for example, FDA is required to maintain a list of experts who can provide consultation related to the review of drugs and biological products for rare diseases or that are genetically targeted.[222] Advisory committee and outside review recommendations, however, are not binding on the agency.

FDA has typically been more likely to use advisory committee review if the new drug being studied is particularly novel, presents significant new clinical issues, or if review of the drug involves evaluation of complex scientific data. The FDAAA requires FDA to refer any BLA or any NDA for a new chemical entity to an advisory committee for review prior to approval or to summarize in the action letter why it did not do so.[223] In an effort to ensure that advisory committees reflect the most current expert advice, conflict-of-interest rules were amended under FDASIA to improve outside expert recruitment by FDA and to expand the number of experts who can qualify for nomination to serve on an advisory committee.[224]

FDA Action and Time Frames for NDA Review

The FDCA provides that within 180 days after the filing of an NDA "or such additional period as may be agreed" between FDA and the applicant, FDA must either approve the application or give the applicant notice of an opportunity for a hearing as to whether the application is approvable (essentially, a procedural step required before FDA may formally reject an NDA).[225] Because FDA rarely is in a position to reach a final decision on an NDA within 180 days after it is filed, the agency has created a procedural framework that allows it to engage in multiple rounds of review of an NDA that may stretch on much longer than 180 days without running afoul of the statutory deadline.

---

218 *Id.* (citing the approval of atovaquone, although less effective than the standard therapy in the broad population, for the patient group unable to tolerate a widely used therapy for an AIDS-related pneumonia).

219 *Id.*

220 *Id.*

221 *Id.*

222 FDCA § 569(a), 21 U.S.C. § 360bbb (added by FDASIA § 903(a)).

223 FDCA § 505(s), 21 U.S.C. § 355(s) (added by FDAAA § 918).

224 FDCA § 712, 21 U.S.C. § 379d–1 (amended by FDASIA § 1142).

225 FDCA § 505(c)(1), 21 U.S.C. § 355(c)(1).

First, as described above, FDA has by regulation established a 60-day period following actual receipt of the NDA during which the agency decides if the application is sufficiently complete to allow it to be "filed." Only after this determination is made does the statutory "filing clock" start to run.

While the filing step effectively extends the 180-day statutory deadline by 60 days, even this additional amount of time is usually insufficient for FDA to reach a final decision on an application. Accordingly, the primary mechanism by which FDA ensures itself the timing flexibility it needs to complete its review of an application without violating the statutory deadline is to rely on the "or such additional period as may be agreed" language of the statute to create a system in which the NDA applicant in effect agrees to allow the review of the application to continue until FDA is either ready to approve it or makes clear that the application is not approvable in its current form, in which case the applicant typically withdraws the application on its own. (Situations in which an applicant forces FDA to provide a formal hearing on approvability, as the statute contemplates, are quite rare.)

This mechanism in turn is premised on the concept of the review cycle, formerly referred to in FDA regulations as the "review clock." FDA regulations, as amended effective August 11, 2008,[226] state that within 180 days of the receipt of an NDA, FDA will review it and send the applicant either an approval letter or a "complete response" letter describing the deficiencies that must be satisfactorily addressed before the application can be approved.[227] This 180-day period is called the "initial review cycle." Significantly, however, the regulations also provide that the initial review cycle "may be adjusted by mutual agreement between FDA and the applicant or as the result of a major amendment" (amendments to the NDA are discussed below).[228]

A key vehicle for documenting applicants' agreement to extending the initial review cycle is FDA's performance goals under the Prescription Drug User Fee Act (PDUFA), which are negotiated between industry and FDA and formally presented to Congress. First enacted in 1992 with the intent of providing additional resources for FDA drug review and accelerating drug review times, PDUFA is re-authorized on a five-year cycle, with the most recent re-authorization taking place in 2012 as part of the FDASIA. PDUFA applies only to NDAs and BLAs, not to ANDAs;[229] generic drug applications are subject to user fees under the Generic Drug User Fee Amendments (GDUFA), which were enacted as part of FDASIA in 2012.[230]

Under PDUFA, FDA collects a substantial user fee for each NDA (and BLA) it receives, with certain minor exceptions. In exchange, FDA commits to the PDUFA performance goals, which provide for specific review times for NDAs and BLAs. Though not legally binding, these performance goals represent FDA's side of a three-way bargain under which industry agrees to pay the user fees and Congress authorizes FDA to collect the fees and use them

226 *See* 73 Fed. Reg. 39,588 (July 10, 2008).
227 21 C.F.R. §§ 314.100, 314.110.
228 *Id.* § 314.100(c).
229 PDUFA is due for re-authorization in 2017. FDASIA also amended the "generic exception" to state that a prescription product is not subject to a fee if it "is the same product as another product." FDCA § 736(a)(3)(B)(ii) (amended by FDASIA § 103(D)(ii)).
230 FDCA § 744B(b), 21 U.S.C. § 379f (added by FDASIA § 302).

for drug reviews and related tasks. As such, the performance goals are taken seriously by the agency.

In its PDUFA performance goals under the 2012 re-authorization, FDA committed to review and act on 90 percent of standard original NDA and BLA submissions within 10 months of the 60-day filing date, and 90 percent of priority original NDA and BLA submissions (i.e., submissions for drugs that represent significant advances over existing treatments) within six months of the 60-day filing date. Additional performance goals apply to non-NME NDAs, Class 1 and 2 Resubmissions, Original Efficacy Supplements, and Class 1 and 2 Resubmitted Efficacy Supplements.[231] Thus, by signing on to the PDUFA performance goals, industry has effectively agreed to an extension of the statutory review cycle for standard NDA and BLA applications from six months to 10 months.[232]

As noted above, at the conclusion of the initial review cycle, FDA will send the applicant either an approval letter or a complete response letter outlining the additional steps that need to be taken before the application can be approved. Upon receipt of a complete response letter, the applicant must resubmit the application, addressing the deficiencies noted in the letter; withdraw the application; or ask FDA to provide an opportunity for a hearing on the approvability of the application.[233] Under FDA regulations, the applicant that receives a complete response letter automatically agrees to an extension of the statutory review deadline until it takes any of these actions.[234] Failure to take any of the specified actions within one year after the issuance of a complete response letter will be considered a request by the applicant to withdraw the application, unless the applicant has requested an extension.[235] If FDA considers the applicant's failure to take action within one year to be a request to withdraw the application, the agency will give the applicant written notice and a 30-day period in which to explain why the application should not be withdrawn and to request an extension of time to resubmit it.[236]

Resubmissions of an application following receipt of a complete response letter fall into two categories. A "Class 1" resubmission is one that contains relatively minor information such as final printed labeling, draft labeling, certain safety or stability updates, postmarketing study commitments, assay validation data, final release testing on lots used to support approval, or minor re-analyses of previously submitted data.[237] Under FDA's regulations a Class 1 resubmission constitutes an agreement by the applicant to start a new two-month review cycle beginning on the date FDA receives the resubmission.[238] A "Class 2" resubmission is one that includes any item not specified as part of a Class 1 resubmission, including any item that would require presentation to an advisory committee.[239] A Class 2 resubmission

231 PDUFA Performance Goals, *supra* note 72, at 4.

232 Some have claimed to observe an emerging trend toward FDA increasingly failing to meet user fee action dates. Because each re-authorization of the user fee law may involve renegotiation of FDA performance goals, the 2012 goals may be modified upon the next expected re-authorization in 2017.

233 21 C.F.R. § 314.110(b).

234 *Id.* § 314.110(c).

235 *Id.*

236 *Id.*

237 21 C.F.R. § 314.3(b).

238 *Id.* § 314.110(b)(1)(i).

239 *Id.* § 314.3(b).

constitutes an agreement by the applicant to start a new six-month review cycle beginning on the date FDA receives the resubmission. [240]

Submission by the applicant of an amendment to a pending application can also affect the review timelines. If the applicant submits a "major amendment" within three months of the end of a review cycle, FDA's regulations state that this constitutes an agreement by the applicant to extend the review cycle by three months.[241] In its PDUFA performance goals under the 2012 reauthorization, however, FDA noted that a major amendment at any time during the review cycle may extend the goal date by three months.[242] A major amendment may include, for example, a new clinical safety report, reanalysis of a previously submitted study, or the submission of a REMS including elements to assure safe use that were not included in the original application or that were significantly amended.[243] Submission of an amendment that is not major at any time during a review cycle will not extend the cycle, although FDA also may defer review of such an amendment to the next cycle.[244]

Expedited Availability

As discussed above, the history of the FDA drug approval process has been marked by pendular swings between two competing public health goals: ensuring that drugs are as safe and effective as possible before being approved; and avoiding undue regulatory delay in the availability of important new drugs that have the potential to save, extend or improve patients' lives. As the regulatory and scientific burden of meeting FDA's drug approval criteria has increased over the decades, Congress and FDA have recognized the need for, and have established, a variety of mechanisms to speed the availability of especially important and promising drugs. Additionally, in its PDUFA V Commitment Letter, FDA expressed dedication to "advancing and facilitating the development of drugs and biologics for rare diseases."[245] A summary of the options for expedited availability, as discussed herein, is detailed in FDA's 2014 Guidance.[246]

Priority Review

Priority review was established pursuant to the original PDUFA in 1992, where FDA agreed to specific goals for improving the drug review time and created a tiered system for reviewing applications, including faster promised review times for qualifying applications.[247] The program allows for an expedited timeline for the review of the clinical data necessary for approval of an NDA, shortening the clock from 10 months to six months.[248] Generally, to qualify, the drug must treat a serious condition and offer a potentially significant improvement in safety or effectiveness over existing therapies.[249] Sponsors may request

240 *Id.* § 314.110(b)(1)(ii).
241 *Id.* § 314.60(b)(1).
242 PDUFA Performance Goals, *supra* note 72, at 32.
243 *Id.*
244 21 CFR § 314.60(b)(3).
245 *See* PDUFA Performance Goals, *supra* note 72, at 23.
246 *See* FDA, Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.
247 *See* Pub. L. No. 102-571, 106 Stat. 4491 (1992).
248 *See* Expedited Programs Guidance, *supra* note 246, at 8.
249 *Id.* at 7.

priority review, and FDA determines if priority review is appropriate on a case-by-case basis at the time of filing.[250]

Under the FDAAA, a sponsor of a drug approved for the treatment of specified tropical diseases may be granted a "Priority Review Voucher" (PRV), which, among other things, automatically allows an NDA to receive priority review.[251] A recipient of a PRV may use the PRV for a different application, and further may transfer the voucher to another sponsor.[252] In 2012, FDASIA expanded upon priority review by establishing a PRV for "rare pediatric disease" products.[253] A "rare pediatric disease" is defined as a "disease [that] primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents."[254] The program seeks to encourage the development of rare pediatric disease treatments by providing expedited review for drugs containing active ingredients that have not been previously approved.[255] Applicants must notify FDA of their intent to use PRV no later than 90 days prior to application submission,[256] and within five years after approval must report on the estimated population suffering from the disease, the estimated U.S. demand for the product and the actual product distribution.[257]

Fast Track

In FDAMA, Congress added new section 506 to the FDCA[258] leading to the creation of the Fast Track program for drugs intended to treat serious or life-threatening diseases for which there is an unmet medical need. Fast Track is a holistic process whereby FDA takes a much more active and collaborative role throughout the drug development and testing process for designated drugs, in order to "facilitate development and expedite review of drugs to treat serious and life-threatening conditions so that an approved product can reach market expeditiously."[259]

To qualify for Fast Track designation, the drug must be intended for either a life-threatening or serious condition,[260] and must show the potential to address an unmet medical need for such condition.[261] It is not sufficient, however, that the drug be intended for use in patients who have a serious or life-threatening condition. Rather, the drug must be specifically intended to treat the serious condition itself or a serious aspect or sequelae of the condition.[262] Additionally, under the Generating Antibiotics Incentives Now Act (GAIN

---

250 *Id.* at 24.

251 FDCA § 524, 21 U.S.C. § 360n (added by FDAAA § 1102).

252 FDCA § 524(b)(2), 21 U.S.C. § 360n(b)(2); *see also* FDA, Guidance for Industry: Tropical Disease Priority Review Vouchers, at 5 (Oct. 2008), *available at* http://www.fda.gov/downloads/Drugs/Guidances/UCM080599.pdf.

253 FDCA § 529, 21 U.S.C. § 360ff (added by FDASIA § 908).

254 *Id.*

255 FDCA § 529(a)(4)(A)(ii), 21 U.S.C. § 360ff(a)(4)(A)(ii).

256 FDCA § 529(b)(4), 21 U.S.C. § 360ff(b)(4).

257 FDCA § 529(e)(2), 21 U.S.C. § 360ff(e)(2).

258 21 U.S.C. § 356.

259 FDA, Guidance for Industry: Fast Track Drug Development Programs—Designation, Development, and Application Review, at 3 (Jan. 2006) [hereinafter Fast Track Guidance].

260 *Id.* All life-threatening diseases are deemed to be "serious" for Fast Track purposes.

261 *Id.*

262 *Id.*

Act), implemented as part of FDASIA, a drug designated by FDA as a Qualified Infectious Disease Product (QIDP) is eligible for the Fast Track designation.[263]

FDA recommends that sponsors request Fast Track status no later than the date of the sponsor's pre-NDA or pre-BLA meeting with the agency.[264] If the drug is given Fast Track status, the sponsor will have the opportunity to participate in FDA-sponsor meetings that can result in an expedited review process.[265] In addition, FDA may review portions of a drug application prior to submission of the sponsor's complete application.[266] This rolling review process may occur only after FDA conducts a preliminary assessment of the sponsor's clinical data and determines that the drug may be effective.[267] FDA's acceptance of a sponsor's application sections does not, however, obligate the agency to commence its review or to meet its review performance goals prior to receipt of the sponsor's complete application.[268]

The benefits of Fast Track programs include earlier and more frequent meetings between FDA and the sponsor, including broad pre-IND consultation, EOP-1 meetings, EOP-2 meetings, pre-NDA/BLA meetings, and early labeling discussion meetings. As part of a Fast Track program FDA will also provide more frequent, more timely, and more proactive interactions (including meetings and correspondence) on development and clinical trial issues. In addition, Fast Track drug candidate sponsors may be allowed to submit portions of an NDA or BLA as soon as they are ready, without waiting for the full application to be completed and ready for filing. Finally, Fast Track drugs are ordinarily eligible for priority review and also may be eligible for accelerated approval if the sponsor chooses to pursue that approval pathway. Where Fast Track products are approved based on surrogate endpoints, such approval may be conditioned upon postapproval studies and pre-dissemination review by FDA of the company's promotional materials.[269]

Breakthrough Therapy

The breakthrough therapy designation was established under FDASIA to expedite the development and review of a drug, whether alone or in combination with one or more drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.[270] Preliminary clinical evidence may be early evidence of both a clinical benefit and an effect on a mechanistic biomarker (i.e., a biomarker with activity that is conducted through a theoretical mechanism of action for a disease).[271] A clinically significant endpoint for breakthrough therapy purposes will measure an effect on irreversible morbidity or mortality or on serious symptoms.[272]

---

263 *See* FDCA § 505E, 21 U.S.C. § 351 (added by FDASIA § 801-04); 21 U.S.C. § 356(b)(1).
264 Expedited Programs Guidance, *supra* note 246, at 8.
265 *Id.* at 35.
266 *Id.*
267 *Id.*
268 *Id.* at 36.
269 FDCA § 506, 21 U.S.C. § 356(b).
270 FDCA § 506, 21 U.S.C. § 356 (amended by FDASIA § 902).
271 FDCA § 506(a)(1), 21 U.S.C. § 356(a)(1).
272 Expedited Programs Guidance, *supra* note 246, at 12.

A request for breakthrough designation can be made with the submission of an IND or at any time following submission of an application as an amendment to an IND, but should occur no later than the end-of-Phase-2 meeting.[273] A drug that qualifies for designation as a breakthrough therapy will also qualify for Fast Track status. As development and review of a breakthrough therapy may occur over a short period of time when compared to other drug development programs, FDA will likely meet with sponsors on a regular basis to discuss clinical trial designs that will yield the information that is needed to facilitate an accelerated review and approval process.[274]

Accelerated Approval

Unlike priority review and Fast Track, which are intended to expedite the development and review of the clinical data necessary for approval of an NDA, the accelerated approval program is aimed at abbreviating the approval timeline itself by reducing (at least initially) the evidentiary burden needed for drug approval. This procedure, which was adopted in its final form in December 1992,[275] is available only for drugs or biologics that offer meaningful therapeutic benefit compared to existing treatment for serious or life-threatening illnesses. There are two different routes to accelerated approval. Under the first route, FDA may approve a treatment subject to special distribution or use restrictions that address outstanding safety issues.[276] The second route, which is much more significant, provides for approval based on evidence of the drug's effect "on a surrogate endpoint that reasonably suggests clinical benefit or . . . on a clinical endpoint other than survival or irreversible morbidity."[277] Such approval may be conditioned upon the completion of postmarketing clinical studies to "verify and describe the drug's clinical benefit and to resolve remaining uncertainty" about the relationship of the surrogate endpoint to clinical benefit.[278] Drugs and biologics approved under the accelerated procedure are also subject to pre-dissemination review for promotional labeling and advertising, and a streamlined procedure for withdrawal of approval if, among other reasons, a postmarketing clinical study fails to verify clinical benefit.[279]

Postapproval Requirements

The Postapproval Period

An applicant's responsibilities with respect to its NDA do not cease upon the application's approval. The postapproval stage brings with it its own set of obligations for the NDA holder. In particular, in the wake of FDAAA the drug sponsor must reckon with expanded FDA powers over such areas as safety-related labeling changes and the conduct of postmarketing studies.

---

273 *Id.* at 8.
274 *See id.* at 13.
275 21 C.F.R. § 314, subpt. H, as codified at 57 Fed. Reg. 58,942 (Dec. 11, 1992), and amended 64 Fed. Reg. 402 (Jan. 5, 1999).
276 21 C.F.R. § 314.520.
277 *Id.* § 314.510.
278 *Id.*
279 *Id.* §§ 314.550, 314.530.

Changes Affecting an Approved Application

In order to make changes affecting an approved drug that go beyond the conditions established in the NDA, an applicant must address the requirements of the supplemental NDA process. Changes affecting an approved drug are grouped into three categories, each of which carries different procedural requirements. For some changes, the sponsor must submit a supplement to its NDA, and FDA must approve that supplement, before the sponsor can implement the desired changes—the so-called "prior approval" supplement. A second group of changes also requires supplementing the NDA, but the sponsor can implement the changes before FDA takes action on the supplement, subject to the risk that the agency may ultimately not approve the supplement.[280] These supplements are commonly referred to as "changes being effected," or CBE, supplements. A third category of changes need only be listed in the annual report that the sponsor must file with respect to the drug covered by the NDA.

Under FDA's regulation on supplements, prior approval supplements are required for any change to the drug or its manufacturing processes, equipment, or facilities that has "a substantial potential to have an adverse effect" on the drug's identity, strength, quality, purity, or potency as these factors may relate to its safety or effectiveness.[281] On the manufacturing side, this may include changes in the drug's qualitative or quantitative formulation or approved specifications; changes that may affect the sterility assurance of the drug; and changes in the synthesis of the drug substance that may affect its impurity profile or its physical, chemical, or biological properties.[282] And almost all changes in labeling—including new indications, dosing regimens, populations, and the like—require a prior approval supplement, with limited exceptions that will be discussed below.[283]

"Changes being effected" supplements are utilized for changes with only a "moderate" potential for an adverse effect on the performance of the drug. These supplements fall into two subcategories. The first subcategory requires the sponsor to wait 30 days after submitting the supplement before starting distribution of the drug product incorporating the change in question—the so-called "CBE-30."[284] CBE-30s are to be used, for instance, for a change in the drug's container-closure system that does not affect its quality, or for "relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements."[285] When an applicant submits a CBE-30, it may not distribute the drug incorporating the change in question if within the 30-day period following submission FDA informs it that the change requires prior approval or that required information is missing from the supplement.[286] For the second subcategory of CBE changes, the applicant may begin distribution of the affected drug product immediately upon receipt by FDA of the supplement; these CBEs are often referred to as "CBE-0s." CBE-0s may be used for changes involving an addition to a specification or changes in methods or controls to provide increased assurance that the drug will have the

280 For this reason sponsors typically consult informally with FDA before making certain kinds of CBE changes "at risk," particularly safety-related labeling changes.
281 21 C.F.R. § 314.70(b).
282 *Id.* § 314.70(b)(2)(i-iv).
283 *Id.* § 314.70(b)(3), (c)(2).
284 *Id.* § 314.70(c)(1).
285 *Id.* § 314.70(c)(2).
286 *Id.* §314.70(c)(5).

characteristics it purports to possess,[287] or a change in labeling that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens dosage and administration information to increase safe use of the product; or deletes false or misleading information.[288]

Finally, changes in conditions with only a minimal potential for an adverse effect on the drug's performance need only be described in the annual report submitted by the applicant.[289] Examples of such changes include editorial or minor changes in labeling, deletion or reduction of an ingredient that only affects the product's color, and changes in the drug's container size or shape without changes in the closure system (for nonsterile solid dosage forms).[290]

Postmarketing Safety-Related Label Changes

As noted above, the enactment of the FDAAA was preceded by several years of intense public focus on FDA's oversight of postmarketing drug safety. One of the key provisions included in the new law aimed at strengthening FDA's safety oversight powers was new authority to compel a sponsor to make safety-related changes in drug labeling after approval of the drug. Under this new authority, if FDA becomes aware of "new safety information" about a serious drug risk that the agency believes should be included in the drug's labeling, it must promptly notify the sponsor, who then has 30 days to either submit a labeling supplement reflecting the new safety information or explain why the sponsor does not believe a labeling change is warranted.[291] If the agency disagrees with the sponsor's conclusion, it must initiate discussions with the sponsor that may not take more than 30 days from the due date of the sponsor's response, unless extended by the agency. Within 15 days of the conclusion of these discussions, FDA may issue an order requiring the sponsor to make those labeling changes the agency deems appropriate to address the new safety information. Violations of any of these requirements by the sponsor will subject the sponsor to misbranding charges and potential civil money penalties.[292]

In July 2013, FDA issued a final guidance providing details of the agency's interpretation of various aspects of this authority, such as what type of information constitutes "new safety information" that may trigger a labeling change.[293] Information FDA expects to trigger safety-labeling changes includes boxed warnings, contraindications, warnings and precautions, drug interactions, and adverse reactions.[294]

---

287 *Id.* § 314.70(c)(6)(i).

288 *Id.* § 314.70(c)(6)(iii).

289 *Id.* § 314.70(d). The annual report is a document the applicant must submit each year within 60 days of the anniversary date of the NDA's approval date. *Id.* § 314.81(b)(2). This annual report contains various current data about the drug, including a summary of significant new information that might affect the safety, labeling, or effectiveness of the drug product; information about the quantity of the drug distributed; the currently used labeling that accompanies the drug; and changes in chemistry, manufacturing, and controls. *Id.*

290 *Id.* § 314.70(d).

291 21 U.S.C. § 355(o)(4).

292 *Id.*

293 FDA, Guidance for Industry: Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act (July 2013), *available at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf.

294 *Id.*

The process of a safety label change will be initiated upon an FDA notification letter detailing the FDA determination that new safety information should be included in labeling.[295] Upon receipt, an application holder must either 1) submit a supplement[296] with proposed labeling changes to reflect the new safety information; or 2) notify FDA through a rebuttal statement that it does not believe a labeling change is warranted.[297] FDA will either approve an application holder's response or initiate a discussion period[298] for further modifications.[299] Although FDA expresses that it will be a rarity, the agency retains the authority to order a change to product labeling[300] if it concludes that an application holder's proposed labeling changes are inadequate at the end of the discussion period.[301] Further, if the application holder fails to respond, FDA has authority to enforce the section 505(o)(4) requirements through 1) an unapproved new drug charge, 2) a misbranding charge, 3) civil monetary penalties, and/or 4) seizure of the product and injunction.[302]

Adverse Reaction Reporting

"Adverse drug experiences" are somewhat circularly defined under FDA's regulations as any adverse events associated with the use of a drug in humans.[303] An applicant holding an approved NDA or ANDA must promptly review reports of adverse drug experiences associated with its drug, regardless of the source from which such reports were obtained.[304] If a reaction is both serious (e.g., fatal, life-threatening, or permanently disabling) and unexpected (not listed in labeling, or differing from reactions listed in the labeling due to greater severity or specificity), it must be reported in an "alert report" within 15 calendar days of the applicant's receipt of the information.[305] Finally, all adverse reactions that are not serious and unexpected must be reported at quarterly intervals for three years after an application is approved, and annually thereafter.[306]

The FDAAA did not amend the adverse drug event reporting system *per se*. However, with the extensive new safety authorities provided to FDA under the FDAAA to respond to newly reported safety information—including the power to impose a REMS, to mandate safety-related labeling changes, and to require postmarketing studies—the potential consequences of adverse event information submitted to FDA under the existing system have obviously increased dramatically. FDASIA, however, added a requirement that drug discontinuances and interruptions with supply additionally be reported.[307]

---

295 *See id.* at 6.

296 FDA will communicate whether a prior approval supplement or changes-being-effected supplement should be submitted. *See id.* at 6-7.

297 *Id.* at 9. *See also* FDCA § 505(o)(4)(B)(i)-(ii).

298 *See* FDCA § 505(o)(4)(C).

299 Labeling Changes Guidance, *supra* note 293, at 8.

300 *See* FDCA § 505(o)(4)(E).

301 *See* Labeling Changes Guidance, *supra* note 293, at 10. FDA has implemented its authority under section 505(o)(4) in a number of cases including Advair Diskus, Aranesp, Epogen and Procrit, Geodon, Propylthiouracil, Symbicort, Symbyax, Vasotec, and Zyprexa. *See* FDA, Safety Labeling Change Orders, *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm189280.htm.

302 *See* Labeling Changes Guidance, *supra* note 293, at 14-15.

303 21 C.F.R. § 314.80(a).

304 *Id.* § 314.80(b).

305 *Id.* § 314.80(c)(1)(i).

306 *Id.* § 314.80(c)(2).

307 FDCA § 506C(a), 21 U.S.C. § 356c (amended by FDASIA § 1001(a)).

Sentinel Program

In May 2008, FDA launched the Sentinel Initiative to develop and implement a proactive, national electronic system for monitoring the safety of FDA-approved drugs and other medical products.[308] This was in response to section 905 of the FDAAA, which mandates FDA to develop an enhanced ability to monitor the safety of drugs after these products reach the market.[309]

The Sentinel Initiative is a new approach to postmarket risk identification and adverse event surveillance that requires FDA to "develop methods to obtain access to disparate data sources," in order to implement a "post-market risk identification and analysis system" capable of linking and analyzing safety data from these aggregate sources.[310] The initiative directs FDA collaboration with public, academic, and private entities[311] in a long-term effort to augment the agency's existing and largely passive postmarket safety surveillance systems, including the CDER's Adverse Event Reporting System (AERS).[312] The envisioned active surveillance would enable FDA to actively request information from Sentinel System data partners when a safety question arises about a medical product.[313]

Withdrawal of NDA Approval

Although FDA rarely invokes its authority to withdraw NDAs under section 505(e) of the FDCA, there are several circumstances under which the agency can take such action.[314] As might be expected, the conditions for NDA withdrawal generally relate to serious problems with the drug or the application. For instance, FDA can withdraw an NDA if the drug is unsafe for use under the conditions of use for which the application was approved.[315] Similarly, FDA can use its withdrawal authority if new clinical evidence shows that the drug is not safe under approved conditions, or if the drug is not effective.[316] Additionally, FDA can seek withdrawal of an application if the drug's labeling is false or misleading, or if there are inadequate assurances that the drug's quality, strength and purity are as claimed.[317] The agency can also withdraw an NDA if the sponsor fails to file required patent information in a timely manner, or if the NDA contains false statements of material fact.[318]

---

308 *See* The Sentinel Initiative July 2010 Report, *available at* www.fda.gov/downloads/.../FDAsSentinelInitiative/UCM233360.pdf.

309 *See id.* ("FDAAA set goals that FDA's new safety monitoring system must be able to access data from 25 million people by July 2010 and 100 million people by July 2012"; FDA met the July 2010 goal and continues to work toward the goal for 2012).

310 FDCA § 505(k)(3).

311 FDCA § 505(k)(4).

312 *See* The Sentinel Initiative Report, *supra* note 308 (FDA's passive safety surveillance has involved gathering risk information from external sources in reporting suspected adverse reactions; whereas, the active surveillance instituted through the Sentinel program will enable FDA to initiate its own safety evaluations utilizing available electronic healthcare data to investigate the safety of drugs and other medical products.).

313 *See id.* ("Data partners will include organizations such as academic medical centers and healthcare systems with electronic health record systems, and health insurance companies with administrative claims data.").

314 FDCA § 505(e), 21 U.S.C. § 355(e); 21 C.F.R. § 314.150.

315 *Id.* § 505(e)(1), 21 U.S.C. § 355(e)(1); 21 C.F.R. § 314.150(a)(2)(i).

316 *Id.* § 505(e)(2)-(3), 21 U.S.C. § 355(e)(2)-(3); 21 C.F.R. § 314.150(a)(2)(ii)-(iii).

317 21 C.F.R. § 314.150(b)(2)-(3).

318 FDCA § 505(e)(4)-(5), 21 U.S.C. § 355(e)(4)-(5). A complete list of grounds for NDA withdrawal is set forth in 21 C.F.R. § 314.150.

If FDA seeks to withdraw an NDA, normally it must give the applicant notice and the opportunity for a hearing.[319] If the drug in question presents an "imminent hazard," however, the Secretary of DHHS can summarily suspend approval of the application and give the applicant the opportunity for an expedited hearing.[320] The Secretary cannot delegate the authority to summarily suspend NDAs in this fashion, but can and has delegated to FDA the authority to hold the expedited hearing.[321] Historically, FDA rarely invoked its authority to withdraw or summarily suspend approval of NDAs.

More recently, however, FDA has taken several high-profile actions to withdraw drug approvals, including a proposal to withdraw the breast cancer indication for Avastin, securing the voluntary withdrawal of the weight loss drug Meridia after a tie vote by an FDA Advisory Committee on whether the drug should be involuntarily withdrawn, a proposal to withdraw approval of the low blood pressure drug Midodrine due to a failure of the sponsor to conduct required postapproval studies, and the withdrawal of the approval of propoxyphene products based on FDAAA-mandated postmarket safety studies.

Postmarketing Studies

Although clinical studies are generally thought of as a prerequisite to approval, there are also clinical studies that take place after approval—the so-called postmarketing or "Phase 4" studies. Such studies can be designed for a variety of purposes, including to 1) obtain additional safety data; 2) obtain additional efficacy data; 3) detect new uses for or abuses of a drug; or 4) determine effectiveness for labeled indications under conditions of widespread usage.

There are at least two reasons FDA may be interested in Phase 4 studies. First, such studies allow FDA to grant approval of a new drug on the condition that the applicant complete studies that resolve remaining questions about the drug's safety and efficacy. Using Phase 4 studies to implement a conditional approval of this sort avoids delaying approval of drugs with apparent therapeutic importance. Phase 4 studies can also be used to facilitate FDA's postapproval monitoring of an approved drug when concerns about its safety or efficacy arise.

The FDAAA added to FDA's postmarketing study toolkit new authority to require a sponsor to complete a previously agreed postmarketing study or to impose a new requirement to conduct and complete a postmarketing study on a marketed drug either to 1) assess a known serious risk related to use of the drug; 2) assess signals of serious risk related to use of the drug; or 3) identify an unexpected serious risk when available data indicate the potential for such risk.[322] This new authority comes with several restrictions. For example, FDA cannot require a postmarketing study unless adverse event reporting and active surveillance would not be sufficient to fulfill the purpose of the study, and the agency cannot require a clinical trial unless a less burdensome kind of study (e.g., a patient registry or an epidemiological

[319] FDCA § 505(e), 21 U.S.C. § 355(e); 21 C.F.R. § 314.150(a).

[320] 21 U.S.C. § 355(e)(5).

[321] *Id.*; *see also* 21 C.F.R. § 314.150(a)(1).

[322] 21 U.S.C. § 355(o)(3). In April 2011, FDA issued a final guidance on the implementation of this authority. FDA, Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (April 2011).

study) would be inadequate. Failure to comply with a postmarketing study requirement imposed under this new authority carries with it a potential misbranding charge and substantial civil monetary penalties.[323]

Looking Ahead

As we have seen, over the long term FDA's approach to new drug approvals has involved a constant effort to balance the inherent tension between earlier access to new treatments and rigorous evidentiary standards for product approvals. This balancing process has not always been smooth, as multiple stakeholders, from patient advocacy groups to product sponsors to healthcare payors, have sought to influence the direction of the process, often forcefully. In recent years, questions of value have also emerged as important considerations in this equation, as the healthcare system looks for its own balance between affordability and effective patient care. As a result, the challenges and complexities for drug sponsors continue to mount. The ultimate effects of this trend on industry's ability to deliver innovative treatments to patients remain to be seen.

[323] *Id.*