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FDA's Expedited Approval Mechanisms for New Drug Products

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"Discovery is seeing what everybody else has seen, and thinking what nobody else has thought."
—Albert Szent-Gyorgi

MODERN MEDICINE AND SCIENCE have made incredible strides in improving and extending lives. Nonetheless, many diseases and conditions still lack adequate therapies. According to a report issued by the President's Council of Advisors on Science and Technology (PCAST) in September 2012 on Propelling Innovation in Drug Discovery, Development, and Evaluation, roughly 30 million Americans suffer from 7,000 rare diseases, but only 350 therapies are approved as treatments.[1] Indeed, "[96] percent of orphan diseases, including rare cancers, lack effective therapies."[2] Other conditions demand improved therapies as well. For example, "[h]eart disease and stroke remain leading causes of mortality."[3] The public health need for continued research and development of new drug and biologic products for significant diseases is clear and compelling.

But beyond these important health reasons for stimulating research and development of new compounds, there are ancillary and supportive economic considerations for propelling innovative research and development. According to the Pharmaceutical Research and Manufacturers of America (PhRMA),[4] the United States' biopharmaceutical industry contributes substantially to the U.S. economy. PhRMA reports that the industry directly employs over 800,000 workers in well-paid jobs and diverse fields, and supports an additional 2.5 million jobs across the country.[5] Moreover, PhRMA asserts that it supports over $789 billion in total economic output.[6] For several years, though, the increased time and money necessary to develop a new compound, the failure rate of prospective products, and a decrease in venture capital investments, among other strains on the industry, have propelled concerns that innovative research in the U.S. might wither, stop, or move to other nations or regions, decreasing the potential short term access for U.S. patients to some new products, potentially leaving others unexplored entirely, and hurting a significant segment of the U.S. economy.

As a result, Congress, the Food and Drug Administration (FDA), and the pharmaceutical industry have sought to nurture an "ecosystem" conducive to the development of innovative, safe, and effective new compounds in the U.S. Among the mechanisms developed are four expedited approval mechanisms, the most recent of which—the Breakthrough Therapy designation—Congress created in 2012 through

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[1]Executive Office of the President, President's Council of Advisors on Science and Technology, "Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation," (Sept. 2012) at vi and n.1 (hereinafter PCAST Report).
[2]*Id.* at vi.
[3]*Id.* at vi and n.1.
[4]PhRMA represents the country's leading biopharmaceutical researchers and biotechnology companies. *See* PhRMA, *About PhRMA*, PHRMA.ORG, *available at*: <http://www.phrma.org/about> (last visited Mar. 29, 2014).
[5]PhRMA, *Economic Impact*, PHRMA.ORG, *available at*: <http://www.phrma.org/economic-impact> (last visited Mar. 29, 2014).
[6]PhRMA, *Biopharmaceutical Impact on the U.S. Economy*, PHRMA.ORG, <http://www.phrma.org/sites/default/files/pdf/US-FACT-SHEET-Battelle-Jobs-2013-07-19.pdf> (last visited Mar. 29, 2014) (*citing* Battelle Technology Partnership Practice, The Economic Impact of the U.S. Biopharmaceutical Industry, Report prepared for PhRMA, July 2013).

the Food and Drug Administration Safety and Innovation Act (FDASIA). Sponsors of new drug and biologic products (sponsors) have embraced the new Breakthrough Therapy designation: as of roughly December 2014, FDA reported having received 260 requests for Breakthrough Therapy designation, of which it granted 74 and denied 139.[7] Of the 41 designated compounds, four have been approved for marketing.

This article seeks to discuss the development of these mechanisms and describe when a sponsor may use each mechanism and what benefits that mechanism will provide. It argues that the four mechanisms each apply in slightly different circumstances and provide slightly different benefits. But the new Breakthrough Therapy designation essentially establishes a hierarchical layer over the Fast Track designation for a subset of compounds that appear especially promising, most likely through medical and scientific advances in targeted therapies. In addition to the tools already available through the Fast Track mechanism—which may include a high likelihood of receiving Priority Review—a Breakthrough Therapy designation focuses agency resources on product review primarily through the commitment of personnel.

This article is organized into four parts. The first part provides background information on the standard requirements and process for approving a new drug for marketing.[8] This section includes an explanation of the standard every new drug product must meet for approval, a description of the traditional clinical trial phases and endpoints, and general trends in the time and finances required to develop successfully a new drug product. The second part describes the historical development of expedited approval mechanisms for new drug products. It describes the FDA's original prioritization classification system that was formalized during the 1970s up to and including the most recent Breakthrough Therapy designation. The third part explains each of the four expedited approval mechanisms currently used by FDA, while the fourth part goes one step further by comparing and contrasting the similarities and differences of the older expedited approval mechanisms with the Breakthrough Therapy designation.

BACKGROUND ON THE FDA APPROVAL PROCESS FOR A NEW DRUG PRODUCT

A. History of the FDA approval process

The modern safety and efficacy requirements that govern FDA's review and approval of a new drug[9] product evolved out of a series of legislative enactments, beginning in 1938 with the Federal Food, Drug and Cosmetic Act of 1938 (the FDCA), after the tragic deaths of more than 100 people from a poisonous ingredient in Elixir Sulfanilamide.[10]

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[7]U.S. Department of Health & Human Services, Food and Drug Administration, "Frequently Asked Questions Breakthrough Therapies," *available at*: <http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentsofthefdcact/fdasia/ucm341027.htm> (last visited Jan. 7, 2015).

[8]The Breakthrough Therapy designation applies to biological products, as well. This article focuses primarily on drugs, but may include references to biological product provisions in some instances.

[9]The definition of "drug" has remained the same since 1938. It is:

> articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary;…and articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals; and articles intended for use as a component of any articles specified in [these] clauses.

21 U.S.C. § 321(g)(1). *See also* 21 C.F.R. § 202.128. The Public Health Services Act (PHSA) defines

> [t]he term "biological product" [as] a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

42 U.S.C. §262(i)(1). In other words, it is a product that is isolated from a living organism (such as a human, an animal, or a microorganism) and used in the prevention, treatment, or cure of human disease. Biological products include vaccines, blood and blood components, tissues, and recombinant therapeutic proteins, among other things. *See also* 21 C.F.R. § 600.3 (2014); U.S. Department of Health and Human Services, Food and Drug Administration (FDA), *What are Biologics Questions and Answers*, FDA.GOV, (Apr. 14, 2009), *available at*: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm> (last visited Mar. 25, 2014). Many biological products meet the definition of a drug; for a comparison between drugs and biological products *see* Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Mechanism for Follow-On Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 559–61 (Spr. 2008).

[10]Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1802 (Nov. 1996); Martin S. Lipsky and Lisa K. Sharp, *From Idea to Market: The Drug Approval Process*, 14.5 J. AM. BD. FAMILY PRAC. 362 (2001).

The law overhauled the regulatory system that had existed for almost 30 years. Recognizing that post-marketing monitoring alone was insufficient to protect the public's health from dangerous drugs, the FDCA required manufacturers to apply to FDA to market a new drug.[11] If a specified period of time passed without action by FDA, the law deemed the application to be approved.[12] The law also required a manufacturer to show that a new product was safe.[13]

In October 1962, following the tragic discovery that a drug marketed as a sleeping pill led to substantial malformations in thousands of newborns in Western Europe, Congress expanded the pre-market requirements for manufacturers of new drug and biologic products through the Kefauver-Harris Drug Amendments to the FDCA.[14] The amendments replaced the automatic approval provisions if FDA failed to act with a requirement for affirmative FDA approval.[15] The law further mandated that manufacturers demonstrate substantial evidence of efficacy for a new drug, laying the foundation for the current system of development and clinical trial phases.[16] Numerous acts have amended the FDCA since 1962, but the heart of these two requirements remains the same.

B. The safety and efficacy standards for new drug product approval

To receive approval for marketing, a sponsor must show that a new drug is safe[17] and

[11] *See* Federal Food, Drug, and Cosmetic Act (FDCA), Pub. L. No. 75-717, 52 Stat. 1040 (1938); A "new drug," was defined in § 201(p), 21 U.S.C. § 321(p), as "a drug (i) which has not become generally recognized by qualified experts as safe for use under the conditions of use indicated in its labeling (excepting any drug previously subject to the Act as regards conditions of use for which it then had been represented) or (2) which has been found safe in investigations but which has not been actually used for a material extent or time under the conditions of use indicated." *See* David F. Cavers, *The Food, Drug, and Cosmetic Act, Its Legislative History and Substantive Provisions*, LAW AND CONTEMPORARY PROBLEMS, at 32 n.166, *available at*: <http://scholarship.law.duke.edu/cgi/viewcontent.cgi?article=1937&context=lcp> (last visited Mar. 1, 2014).

Under the current law, the term "new drug" means "any drug…the composition of which is such that such drug is 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" or one which had become generally recognized as safe but "which [had] not been used to a material extent or for a material time." 21 U.S.C. § 321(p); *see also* Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA CONSUMER MAGAZINE (Jan.–Feb. 2006), *available at*: <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/> (last visited Apr. 15, 2014).

[12] *See* Meadows, *supra* note 11.

[13] *See* Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938); *see also* Testimony of FDA Commissioner George Larrick, "Drug Safety," Hearings Before a Subcommittee of the House Committee on Government Operations, 88th Congress 2d Session (1964), *reprinted in part in* Peter Barton Hutt and Richard A. Merrill, FOOD AND DRUG LAW: CASES AND MATERIALS, 3d ed. at 877–78 (hereinafter the Cases and Materials book (alone) is Hutt & Merrill), at 695. FDA required information on effectiveness for some products used in the treatment of conditions that were life-threatening or that presented "grave risks" so that the FDA could assess their safety, but for many products, FDA lacked authority to require any evidence of efficacy. *Id.*

[14] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962), *available at*: <http://www.gpo.gov/fdsys/pkg/STATUTE-76/pdf/STATUTE-76-Pg780.pdf> (last visited Apr. 29, 2014); Meadows, *supra* note 11. One FDA Medical Officer, Frances O. Kelsey, MD, PhD, had delayed introduction of Thalidomide to the market in the United States based on her concerns over it. *Id. See also* Frances O. Kelsey, *Thalidomide Update: Regulatory Aspects*, 38.3 TERATOLOGY 221 (1988).

[15] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 § 102(d) (1962), *available at*: <http://www.gpo.gov/fdsys/pkg/STATUTE-76/pdf/STATUTE-76-Pg780.pdf> (last visited Apr. 29, 2014); *see also* Meadows, *supra* note 11.

[16] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 § 102 (1962), *available at*: <http://www.gpo.gov/fdsys/pkg/STATUTE-76/pdf/STATUTE-76-Pg780.pdf> (last visited Apr. 29, 2014); Jennifer Kulynych, PhD, *Will FDA Relinquish the ''Gold Standard'' for New Drug Approval? Redefining ''Substantial Evidence'' in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L.J. 127, 131–35 (1999).

[17] Specifically, § 505(b) of the FDCA requires the FDA to reject a new drug application if it does:

> (1) … not include 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; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) … upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, [the Secretary] has insufficient information to determine whether such drug is safe for use under such conditions …

21 U.S.C. § 355(d). The law provides for other reasons for rejecting marketing approval for a new drug, as well, related to efficacy, patent information, and labeling, *Id.*

effective.[18] To establish effectiveness, the sponsor must present "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."[19] "Substantial evidence" is:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.[20]

By its terms, § 505(d) of the FDCA permits FDA to find that data from one adequate and well-controlled clinical investigation and confirmatory evidence constitutes substantial evidence of effectiveness,[21] but FDA has typically only applied this provision where the lone study was statistically significant at a very high level or for products addressing orphan diseases, where more than one trial is not logistically feasible.[22] In determining whether an

[18] *Id.* While only the FDCA governs the regulation of drugs, both the Public Health Service Act (PHSA), 42 U.S.C. § 201, et seq., Pub. L. 78-410, 58 Stat. 682, 702 (1944), and the FDCA govern the regulation of biological products, Gitter, 35 Fla. St. U. L. Rev. at 563–64. The overlap of authorities arises from several factors. Many biologics satisfy the statutory definition of a drug as well as biologic; additionally, Congress included a provision in § 505 of the PHSA providing that "Nothing contained in this Act shall be construed as in any way affecting, modifying, repealing, or superseding the provisions of the Federal Food, Drug, and Cosmetic Act …" based on the belief at the time that the FDCA applied to biological products. *Id.* at 563–64 n.40 (*citing* 42 U.S.C. § 262(g) and United States Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) Responsibilities Questions and Answers (Apr. 14, 2009), *available at*: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133072.htm>). *See also* Hutt & Merrill, *supra* note 13, at 877–78. Finally, another provision in § 505(j) of the PHSA provides that "The Federal Food, Drug, and Cosmetic Act, including the requirements under sections 505(o), 505(p), and 505-1 of such Act, applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act." 42 U.S.C. § 262(j). For marketing approval under the PHSA, a sponsor must demonstrate in a biological licensing application (BLA) that the biological product is "safe, pure, and potent;" the BLA also must establish that the facility in which the product is "manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent" and that the applicant "consents to inspection of [its] facility." 42 U.S.C. § 262(a)(2)(B); *see also* 21 C.F.R. § 601.2(d) (2014) ("Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products.") Despite the different statutory language, "[l]icensing of biologic products under the [PHSA] is very similar to the new drug approval process for human drugs." United States Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) Responsibilities Questions and Answers (Apr. 14, 2009), *available at:* <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133072.htm>. *See also* Hutt & Merrill, *supra* note 13, at 891; Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 Food & Drug L.J. 123, 129, and n.50 (1995) (*citing* 21 C.F.R. § 601.25; 37 Fed. Reg. 16,679 (1972) (proposal to review safety, efficacy, and labeling of biological products); 38 Fed. Reg. 4319 (1973) (final regulation)).

[19] 21 U.S.C. § 355(d).

[20] *Id.*

[21] *Id.*

[22] *See* Hutt & Merrill, *supra* note 13, at 690–91. *See also* U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, at 3 and 13 (May 1998) (explaining that "[w]ith regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness" and that "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible," while providing examples of a few other instances that one trial might meet the efficacy standard) (*citing* Final Decision on Benylin, 44 Fed. Reg. 51512, 518 (Aug. 31, 1979); *Warner-Lambert, Co. v. Heckler*, 787 F.2d 147 (3d Cir. 1986); S. Rep. No. 87-1744 (1962)); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007), at 2–3 (hereinafter "Clinical Trial Endpoints Guidance"); PCAST Report, *supra* note 1, at 68 n.157. A guidance outlines FDA's "current thinking" on a topic, but "does not create or confer any rights for or on any person and does not operate to bind FDA or the public." *See* Clinical Trial Endpoints Guidance, at 1.

investigation is adequate and well-controlled, FDA considers specific characteristics, including whether the study design permits a valid comparison between the investigational drug and the control to permit quantitative assessment of the drug's effect and whether the recruitment, allocation to treatment arms, observation of patients, and method of analysis permit inference, by, for example, limiting bias and assuring comparability.[23]

A sponsor must also establish safety "for use under conditions prescribed, recommended, or suggested in the proposed labeling."[24] Neither the statutes nor regulations governing marketing approval define safety. To assess safety, FDA uses a risk-benefit framework.[25] This analysis weighs the benefits against the risks of approving a new compound and considers all of the evidence submitted regarding safety and efficacy, the type and severity of the condition the new compound addresses, other available therapies for that condition, and risk management tools that potentially could ensure the benefits outweigh the risks.[26]

C. Clinical trials and phases of drug development

To develop the evidence necessary to satisfy the FDCA's safety and efficacy requirements, sponsors use a series of pre-clinical and three pre-marketing human clinical trial phases.[27] Each phase builds on data from the prior phases and examines a different component of the drug's mechanisms, safety, and efficacy.[28] While the three human clinical trial phases are theoretically distinct experiments, some modern investigations have blurred the lines between them or excluded components altogether.[29]

The process begins with preclinical research through *in vitro* (test tube) tests, tissue cell cultures, computer driven data analysis, and/or live animal models to obtain basic information about the new drug's toxicity, pharmacodynamics, and pharmacokinetics.[30] If these studies appear sufficiently promising, the manufacturer files an Investigational New Drug (IND) Application to obtain an exemption from the FDCA's prohibition against shipping experimental drugs without FDA approval in interstate commerce and to allow FDA to assess the safety of the study.[31]

After the submission of an IND, the investigator introduces the investigational drug to humans for the first time in Phase 1.[32] These trials are small, typically composed of about twenty to eighty healthy individuals, and are not controlled.[33] The investigator seeks to assess the safety (including significant short-term side-effects), toxicity, dosage

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[23]21 C.F.R. § 314.126.

[24]21 U.S.C. § 355(d)(1).

[25]FDA, *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA V Implementation Plan—February 2013, Fiscal Years 2013-2017*, FDA.GOV, at 1, *available at*: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf> (last visited Mar. 25, 2014).

[26]*Id. See also* Testimony of FDA Commissioner George Larrick, "Drug Safety," Hearings Before a Subcommittee of the House Committee on Government Operations 88th Congress 2d Session 150, 153, 154 (1964) (describing three-step operation for decision making), *reprinted in part in* Hutt & Merrill, *supra* note 13, at 695.

[27]The FDCA's provisions address the standard of evidence required for approval; they do not expressly require this series. *See* 53 Fed. Reg. 41516-01 (Oct. 21, 1988).

[28]U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Guidance for Industry: MC (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (Jan. 2010), at 3 (hereinafter Nonclinical Safety Studies Guidance).

[29]Lawrence M. Friedman, *et al.*, FUNDAMENTALS OF CLINICAL TRIALS, 3D ED. at 5 (1998) (hereinafter Friedman). *See also* Nonclinical Safety Studies Guidance, at 3 (noting that "there is a growing trend to merge phases of clinical development").

[30]*See generally* Nonclinical Safety Studies Guidance, at 3–9. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies (Jan. 2006), at 8 (hereinafter Exploratory IND Studies Guidance). *See also* Blanchard Randall IV, CRS REPORT FOR CONGRESS: THE U.S. DRUG APPROVAL PROCESS: A PRIMER (Congressional Research Service, the Library of Congress, June 1, 2001), at 7 (hereinafter Randall).

[31]21 U.S.C.A. §§ 331, 355; 21 C.F.R. §§ 312.20, 312.22, 312.23, 312.40; Exploratory IND Studies Guidance, at 7–8. Michael Dickson and Jean Paul Gagnon, *Key Factors in the Rising Cost of New Drug Development*, 3 NATURE 417, 418 (May 2004), *available at*: <http://www.nature.com.ezp-prod1.hul.harvard.edu/nrd/journal/v3/n5/pdf/nrd1382.pdf> (last visited Mar. 2, 2014) (hereinafter Dickson & Gagnon). Friedman, *supra* note 29, at 3. Unlike an NDA or BLA, an IND becomes effective if FDA does not initiate a clinical hold within a specified time period. *See also* 21 C.F.R. § 312.40; 21 C.F.R. § 312.42.

[32]*See* Exploratory IND Studies, at 2 (*citing* 21 C.F.R. § 312.23(a)(8)). The application may be filed at other stages in some cases depending on where and how the development process is conducted.

[33]21 C.F.R. § 312.21; Friedman, *supra* note 29, at 4.

range, and the pharmacokinetics of the investigational drug.[34] Some studies may have an extension component, in which the optimal dose determined from a dose escalation series is tested without controls in a group of study participants.

For those investigational drugs that survive Phase 1, the investigator then generally conducts a randomized, controlled trial of 80 to 200 subjects who have the disease or condition the drug is intended to treat.[35] Phase 2 trials provide more information on safety, and, by testing on patients with the disease or condition of interest, these trials present the first data on the efficacy of the investigational drug and any dose-response relationships.[36] The success of Phase 2 relies on the adequacy of the design of Phase 1. For example, if Phase 1 provided inadequate information on dosage levels, Phase 2 may test the investigational drug "for activity at too low or [too] high a dose."[37]

In the usual case, the safety and efficacy data from these two phases do not in themselves satisfy FDA's requirements of "adequate tests by all methods reasonably applicable to show whether or not such drug is safe" and of "substantial evidence" of efficacy, making Phase 3 trials necessary.[38] Phase 3 clinical trials are expanded controlled and uncontrolled studies.[39] Phase 3 trials involve significantly more patients (on the order of hundreds to thousands of patients) and apply stricter exclusionary criteria to the patients who may enroll than Phase 2 trials.[40] These trials provide more extensive data on safety and efficacy, including any side effects associated with long-term use, to enable FDA "to evaluate the overall benefit-risk relationship of the drug …"[41]

One particularly important component of Phase 3 trials is the primary endpoint used to measure the benefit from a drug product.[42] Under the regular approval mechanisms, FDA approves New Drug Applications (NDAs) based on either a direct clinical efficacy endpoint or a validated surrogate endpoint.[43] A clinical endpoint "is a characteristic or variable that directly measures a therapeutic effect of a drug—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives."[44] A clinical benefit "is a positive therapeutic effect that is clinically meaningful in the context of a given disease. The clinical benefit must be weighed against a treatment's risks to determine whether there is an overall benefit for patients (i.e., positive benefit-risk profile)."[45] Quintessential primary clinical efficacy endpoints include improved overall survival and symptomatic improvement (such as time to progression of cancer symptoms).[46]

An intermediate clinical endpoint is a measure of how a patient feels or functions, but is not the ideal endpoint that a drug product seeks to affect.[47] A surrogate endpoint is an alternative endpoint that measures the effect of a drug product on a distant biological marker that is predicted to relate with some degree of certainty to a clinical efficacy endpoint.[48] A validated surrogate endpoint "is known

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[34]*Id.* Jaime L. Aldes, *Note: The FDA Clinical Trial Process: Effectuating Change in the Regulatory Framework Governing Clinical Trials to Account for the Historical Shift from ''Traditional'' to ''New'' Phase I Trials*, 18 HEALTH MATRIX 463 (Summer 2008). *See also* FDA: ClinicalTrials.gov-Clinical Trial Phases, U.S. National Institutes of Health, National Library of Medicine, *available at*: <http://www.nlm.nih.gov/services/ctphases.html> (last visited Mar. 2, 2014) (hereinafter FDA: ClinicalTrials.gov-Clinical Trial Phases).

[35]21 C.F.R. § 312.21; Michael D. Greenberg, PhD, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U.J. LEGIS. & PUB. POL'Y 295 (1999–2000), at 304 (hereinafter Greenberg).

[36]*Id. See also* FDA: ClinicalTrials.gov-Clinical Trial Phases, *supra* note 34.

[37]Friedman, *supra* note 29, at 4.

[38]Greenberg, *supra* note 35, at 305. The requirement for larger more rigorous clinical trials has been criticized, nonetheless. *See id.* and n.50 (*citing* National Cancer Institute, Final Report of the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS 2 (1990)).

[39]21 C.F.R. § 312.21.

[40]Friedman, *supra* note 29, at 5. Greenberg, *supra* note 35, at 304.

[41]21 C.F.R. § 312.21; Greenberg, *supra* note 35, at 304. *See also* FDA ClinicalTrials.gov-Clinical Trial Phases, *supra* note 34.

[42]Thomas R. Fleming, *Surrogate Endpoints and FDA's Accelerated Approval Process: The Challenges Are Greater Than They Seem*, 24.1 HEALTH AFFAIRS 67–78, at 67 (2005).

[43]Hutt & Merrill, *supra* note 13, at 710. Fleming, *supra* note 42, at 67–68.

[44]U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014), at 17 (hereinafter Final Guidance). *See also* Clinical Trial Endpoints Guidance, *supra* note 22, at 2, 3. Fleming, *supra* note 42, at 67. PCAST report, *supra* note 1, at 37.

[45]Final Guidance, at 17. Clinical Trial Endpoints Guidance, *supra* note 22, at 2, 3. Friedman, *supra* note 29, at 67.

[46]Clinical Trial Endpoints Guidance, *supra* note 22, at 4.

[47]PCAST report, *supra* note 1, at 37.

[48]U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Guidance for Industry: E9 Statistical Principles for Clinical Trials (Sept. 1998), at 9, 43. Friedman, *supra* note 29, at 71. PCAST report, *supra* note 1, at 37 n.108.

to predict clinical benefit" for a certain disease state and for a certain type of intervention.[49] It has been suggested that to be a validated surrogate endpoint, the biological marker "must be correlated with the clinical endpoint" and "must fully capture the net effect of the intervention on the clinical-efficacy endpoint" for a specific disease setting and class of interventions.[50] Blood pressure reduction, for example, is a validated surrogate for risk of stroke in patients with cardiovascular disease for well-studied classes of antihypertensive agents such as beta-blockers and low-dose diuretics with known favorable safety profiles.[51]

Following Phase 3 trials, a sponsor may submit an NDA seeking approval to market the compound. A sponsor also may conduct Phase 4 studies after FDA approves an NDA and the new drug enters the market. Phase 4 studies seek "to gather information on the drug's effect in various populations and any side effects associated with long-term use."[52]

At various points during this development process, FDA and the sponsor of a new drug product may meet to discuss questions and issues that arise. For any type of new drug product, a sponsor may request meetings at the end of Phase 2 (EOP2 meeting) to discuss the safety of proceeding to Phase 3, the Phase 3 plan and protocol, and any additional information needed to support a marketing application, among other topics; they may also seek to meet with FDA prior to the submission of a NDA (pre-NDA meeting) to discuss any major unresolved problems, statistical analysis methods, and the best approach to formatting and presenting the data in the NDA.[53]

D. Pressures on drug development and innovation: time and cost of full marketing approval for a new drug product

The length and cost of the traditional development and approval process varies between products, and comparisons of the length of the development process across time periods are complicated by different methods of analysis and different data. But, there is nonetheless evidence and an accepted belief that both have been increasing.[54] According to some estimates, in the 1960s and 1970s, clinical development of a new compound through marketing approval took respectively 7.9 years and 8.2 years, on average.[55] Although one study assessing data for the 1980s and 1990s estimated that it had decreased to approximately 7.5 years, much of this reduction may have been due to shorter FDA approval times in the 1990s following the passage of the Pharmaceutical Development User Fee Act of 1992 (PDUFA), which established time goals for

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[49]Final Guidance, at 17.

[50]Friedman, *supra* note 29, at 71 (2005) (*citing* R.L. Prentice, *Surrogate Endpoints in Clinical Trials: Definition and Operational Criteria*," 8.4 STATISTICS IN MEDICINE 431–440 (1989)). As Fleming explains, not all biomarkers correlated with a clinical efficacy endpoint meaningfully affect it. An intervention by a drug or biological product could have a positive affect on a biomarker but not on the clinical efficacy endpoint if they are on different causal chains. In addition, an intervention could have a mechanism of action that affects the clinical endpoint that is independent of the mechanism of action observed to affect the biological marker. Fleming, *supra* note 42, at 68–71.

[51]Friedman, *supra* note 29, at 74 (2005). *See also* Clinical Trial Endpoints Guidance, *supra* note 22, at 2.

[52]FDA: ClinicalTrials.gov-Clinical Trial Phases, *supra* note 34.

[53]21 C.F.R. § 312.47 (2014). Historically, FDA classified meetings as A, B, or C. Type B meetings include EOP2 meetings and pre-NDA/pre-BLA meetings. Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants, rev. 1 (May 2009) (expiration date Aug. 31, 2012, but still available on FDA.gov) (hereinafter Formal Meetings Guidance). Center for Drug Evaluation and Research, Manual of Policies and Procedures, MAPP 6025.6, "Good Review Practice: Management of Breakthrough Therapy Designated Drugs and Biologics" (hereinafter MAPP 6025.6). Food and Drug Administration, Center for Biologics Evaluation and Research, Biologics Procedures (SOPPs), SOPP 8101.1, "Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants, v.5 (Oct. 15, 2012) (hereinafter SOPP 8101.1). FDA and the sponsor may also meet to discuss a clinical hold on an IND application, for a special protocol assessment, or for dispute resolution. The Food and Drug Administration Modernization Act (FDAMA) of 1997 created the Special Protocol Assessment Agreement, which involves a binding, written agreement between FDA and a sponsor that a particular Phase 3 trial outcome will be sufficient for marketing approval. PCAST report, *supra* note 1, at 47. These agreements are available in a few other instances. The SPA provides certainty for a sponsor, but may require multiple rounds of discussions over a long period of time, may be discouraged by some FDA divisions, and generally is not used for adaptive trials. *Id.* at 47–48 (*citing* Food and Drug Administration, Draft Guidance on Adaptive Design Clinical Trials for Drugs and Biologics). 21 C.F.R. §§ 10.75, 312.48, and 314.103; Formal Meetings Guidance, *supra* this note. For additional information on the process, *see* CDER 21st Century Review Process Desk Reference Guide, *available at*: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm> (last visited Jan. 6, 2015).

[54]PCAST report, *supra* note 1, at 14.

[55]Dickson & Gagnon, *supra* note 31, at 418 (estimating an average of 7.9 years in the 1960s). J.A. DiMasi, *et al.*, *Cost of Innovation in the Pharmaceutical Industry*" 10(2) J. HEALTH ECON. 107–142, 123 (1991) (estimating an average of 8.24 years).

regulatory approval.[56] Indeed, the length of the period between the start of clinical testing and submission of an NDA or biological licensing application (BLA) with FDA was on average six years (72.1 months) in the 1980s and early 1990s, 3.5 months longer than the same period in the 1970s and early 1980s.[57] Another analysis suggested that the average development time from patent filing through market launch in the U.S. and 15 European Union countries spanned 9.7 years for products launched in the 1990s and increased to 13.9 years for those which began marketing in 2000 or later.[58]

In addition to an increase in the length of clinical trials, the cost of developing new compounds has risen dramatically. According to one study led by DiMasi, the average out-of-pocket cost to develop a new compound that receives marketing approval by FDA, taking into account the costs of other failed research over the same time period, was $403 million (in 2000 U.S. dollars), or $802 million capitalized, for drugs first tested in humans between 1983 and 1994 and receiving marketing approval on or about 1997.[59] The estimated total capitated cost was more than twice as high as that calculated by the author in an earlier study for drugs first tested in humans a decade earlier (between 1970 and 1982) and receiving marketing approval on or around 1984, which itself was more than twice as high as figures calculated for new compounds generally approved in the 1970s.[60] Notably, evidence suggests that costs associated with time accounted for half of these total costs.[61] Moreover, evidence indicates that clinical testing expenses significantly drive the increased costs of developing a new compound to marketing approval.[62]

II. HISTORY OF FDA PRIORITIZATION AND EXPEDITED APPROVAL SCHEMES

The length and cost of developing and obtaining approval of a new product, as well as improved scientific understanding of diseases and conditions, have spurred numerous mechanisms to facilitate expedited approval of new drug products. These include: the prioritization matrix formalized by FDA in 1974, Priority Review, Accelerated Approval, Fast Track designation, and Breakthrough Therapy designation.

A. The original prioritization matrix

Following the Kefauver-Harris Amendments, FDA internally began to use a matrix of chemical type and therapeutic potential to classify and prioritize the review of INDs and NDAs. The matrix was formalized in 1974, and a version of it was utilized until January 1, 1992.[63] The chemical classification represented a "fixed, objective rating that describe[d] FDA's assessment of the drug's relationship to active moieties already marketed and approved in the U.S."[64]

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[56]DiMasi, *supra* note 55, at 164–65. Pharmaceutical Research and Manufacturers of America (PhRMA) has reported an average drug development time of 14.2 years in the 1980s and 1990s, Dickson & Gagnon, *supra* note 31 at 418, but as DiMasi *et al.* discuss, the data presented by PhRMA do not accurately reflect that period.

[57]DiMasi, *supra* note 55, at 164–65.

[58]Fabio Pammolli, *et al.*, *The Productivity Crisis in Pharmaceutical R&D*, 10 NATURE REVIEWS 428–438 (June 2011). *See also* Dickson & Gagnon, *supra* note 31, at 419 (estimating average drug development and approval time to be between 9 to 12 years). Janet Woodcock and Raymond Woosley, *The FDA Critical Path Initiative and Its Influence on New Drug Development*, 59 ANNU. REV. MED. 1, 2 (2008) (explaining that expectations that the drug development program would obtain information on more topics than had been addressed between the 1960s to 1980s, such as dose-response information, long-term use data, and data on women participants, led to larger and more expensive clinical trials). All of the figures are illustrative of a general trend, but direct comparisons between the development times between different studies are limited by numerous factors, including different analytical methodologies.

[59]DiMasi, *supra* note 55, at 166. This estimate does not include estimated post-marketing expenses. DiMasi estimates the total capitated cost with post-marketing expenses to be roughly $900 million (in 2000 United States dollars).

[60]*Id.* at 167, 181. In DiMasi's study, the real cost of the entire clinical testing phase for a new compound, on average, had increased five fold over those estimated in his prior study for new compounds first tested in humans between 1970 and 1982, while the cost of long-term animal testing had only risen by 60 percent. The authors used similar methodologies in the three analyses, allowing comparisons between them. However, differences in the sampling periods for the studies and changes in the average length of the development process limit these comparisons. *Id.* at 167.

[61]*Id.* at 166.

[62]*Id.* at 162.

[63]Hutt & Merrill, *supra* note 13, at 529, 531. Food and Drug Administration, Center for Drug Evaluation and Research, Staff Manual Guide, CDER 4820.3, "Drug Classification and Priority Review Policy," n.1 (Jan. 22, 1992) (hereinafter CDER 4820.3).

[64]CDER 4820.3. A type 1 compound was a new molecular entity, such as a drug that had not yet been approved or marketed in the United States, either alone, in a combination product, or as part of a mixture of stereoisomer. A type 2 compound used an already approved or marketed active moiety, but contained a new salt, ester, or non-covalent derivative of an existing drug, while a type 3 compound was a new dosage form or formulation of an existing drug with either the same or a new indication. New combinations of ingredients, duplicates of drugs already on the market by another firm, new indications received a designation of types 4, 5, or 6.

Chemical types were identified with a number ranging from one, for a new molecular entity, to six, for already marketed drug seeking a new indication. Although generally mutually exclusive, some compounds received more than one type of chemical classification.[65]

Therapeutic classification was a subjective rating of the drug's therapeutic value, which could change during drug development based on the evidence before FDA.[66] Initially, compounds were assigned a mutually exclusive Therapeutic Potential designation of A, B, or C, based on whether the compound would provide important, modest, or little to no therapeutic gains over existing products. Important gains included "effective therapy or diagnosis (by virtue of greatly increased effectiveness or safety) for a disease not adequately treated or diagnosed by any marketed drug" and "improved treatment of a disease through improved effectiveness or safety (including decreased abuse potential)."[67] A modest therapeutic gain entailed real gains, which ranged from greater convenience to a large reduction in cost or usefulness for a subpopulation.[68] If a compound "essentially duplicate[d] the medical importance and therapeutic usage" of something already on the market in the U.S, it was classified as Type C.[69] The therapeutic system also provided for the inclusion of other important information, such as a drug's status as an orphan drug, its likely use in children, or the existence of important toxicity problems.[70]

The higher the therapeutic classification, the greater the precedence a reviewer would give the NDA.[71] High classifications also provided other benefits to a sponsor. The classification system was a factor "in determining which drugs [would] be submitted to advisory committee review and which [would] be candidates for 'End of Phase II' conferences and priority review."[72] New "[d]rugs which [met] the criteria for priority review [also could] make an early submission of NDA manufacturing and controls information."[73]

The classification matrix reportedly reduced review times for some applications.[74] In 1978, for example, FDA approved the 21 NDAs that it had classified as new molecular entities, on average, in 21 months; at that time, FDA generally required 32 months, on average, to approve an NDA.[75]

B. The AIDS epidemic

In the 1980s, a new tragedy—one that "typifies the diseases of the future: slow, subtle, complex, and rooted in lifestyles and genes"—propelled changes in the new drug regulatory scheme to enable faster approval for certain new products.[76] A series of cases of homosexual men suffering from rare diseases that typically afflicted the elderly led the medical community to identify a new syndrome, the Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS).[77] For several years following this initial discovery period (roughly 1981 to 1984), HIV/AIDS patients had no scientifically established or FDA-approved treatments to halt the progression of the virus, leading society to view HIV/AIDS as lethal.[78] Those suffering from the syndrome had a significantly lower risk threshold than the average American; in other words, sufferers were willing to take greater risks in the safety of treatments in the hopes of obtaining any therapeutic benefit.[79] Patients began seeking out any therapy that had anecdotal evidence of benefit, joining black market buying clubs and cooking medicine themselves.[80]

These patients and the pharmaceutical industry increasingly criticized FDA as being far too slow, conservative, and risk-averse in the circumstances.[81] Indeed, the demands of the FDCA drug development process added significant challenges to the marketing approval of a new drug compound for HIV/AIDS. Individuals lived with HIV/AIDS for years without knowing of their infection until symptoms developed leading to a diagnosis.[82] Under the traditional developmental framework, potential therapies, like zidovudine (better known now as AZT) could not meet the risk-benefit requirements, or show the lack of long-

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[65] *Id.*
[66] *Id.*
[67] Food and Drug Administration, Staff Manual Guide BD4820.3 (undated), *reprinted in part in* Hutt & Merrill, *supra* note 13, at 530.
[68] *Id.*
[69] *Id.*
[70] *Id.*
[71] *Id.*
[72] *Id. See also Providing a Breakthrough for Drugs with Promise*, 13 FDA Consumer, July–Aug. 1979, at 25.
[73] CDER 4820.3.
[74] *Providing a Breakthrough for Drugs with Promise*, *supra* note 72, at 26.
[75] *Id.*
[76] Peter W. Huber, The Cure in the Code: How 20th Century Law is Undermining 21st Century Medicine (2013), at 80 (hereinafter Huber).
[77] Greenberg, *supra* note 35, at 308. Huber, *supra* note 76, at 79, 90.
[78] Greenberg, *supra* note 35, at 310–11. Huber, *supra* note 76, at 90.
[79] Greenberg, *supra* note 35, at 309, 311.
[80] Greenberg, *supra* note 35, at 311. Huber, *supra* note 76, at 94.
[81] Greenberg, *supra* note 35, at 309, 312.
[82] Huber, *supra* note 76, at 83.

term toxic side effects quickly enough given the progression to mortality rate of HIV/AIDS.[83] Ultimately, FDA collaborated with the sponsor to facilitate a focused development and review program that led to the approval of zidovudine in approximately two years.[84]

C. Creation of Priority Review, Accelerated Approval, and Fast Track designation

The activism of the often socially marginalized HIV/AIDS patients ultimately produced several reforms by FDA and Congress.[85] FDA promulgated Subpart E in 1988, modeled on the zidovudine clinical development process.[86] The regulations recognized the need for the "broadest flexibility in applying the statutory standards" and the altered risk-benefit threshold of patients with life-threatening and seriously debilitating diseases.[87] They provided for early and close consultation between FDA and the drug product's sponsor, listing "procedures such as pre-IND and end of Phase 1 meetings as methods to improve the efficiency of preclinical and clinical development, and focus on efforts…to reach early agreement on the design of major clinical efficacy studies …"[88] They further provided for the use of medical risk-benefit judgment in the approval decision, including the consideration of the severity of the disease and the lack of a satisfactory alternative.[89]

By January 1992, FDA also had amended its internal prioritization system, combining the Type A and B classifications into a Type P ("Priority Review, therapeutic gain") category, and renaming Type C as Type S ("Standard Review, substantially equivalent").[90] In addition to these two mutually exclusive classifications, FDA retained two additional classifications created in 1988.[91] One was a specific top priority classification, Type AA, for a drug "indicated for the treatment of AIDS or HIV-related disease."[92] The other was a broader category Type E ("Subpart E drug") for a drug developed and/or evaluated under 21 CFR Part 312 Subpart E."[93]

In response to the AIDS epidemic, Congress also looked into the allegations of a "drug lag."[94] Recognizing that the delay arose in part from FDA's dearth of resources, in October 1992, Congress passed the Prescription Drug User Fee Act of 1992 (PDUFA).[95] PDUFA established a system of

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[83]Huber, *supra* note 76, at 83. Greenberg, *supra* note 35, at 312.

[84]While drafting new rules, FDA permitted a trial of ziduvidine in patients with fungal pneumonia, a common lethal coinfection in patients with full-blown AIDS. FDA consulted closely with the sponsor and the National Institutes of Health to streamline the development process to two to four weeks of preclinical animal testing and Phase 1 and 2 clinical testing. Based in part on the overwhelming evidence of its superiority to the placebo, FDA approved ziduvidine for marketing in roughly two years in 1987, with an agreement for post-marketing Phase 4 trials; the approval expanded to early-stage treatment in or around 1990. Huber, *supra* note 76, at 83–84. 53 Fed. Reg. 41516-01 (Oct. 21, 1988).

[85]Greenberg, *supra* note 35, at 310.

[86]53 Fed. Reg. 41516-01. *See also* 21 C.F.R. § 312.80, et seq. FDA modeled the Subpart E procedures on the development of ziduvidine (AZT). *See* 53 Fed. Reg. 41516-01.

[87]21 C.F.R. § 312.80; 53 Fed. Reg. 41516-01.

[88]21 C.F.R. §§ 312.80, 312.82; *see also* 53 Fed. Reg. 41516-01.

[89]21 C.F.R. §§ 312.80, 312.84 (2008); *see also* 53 Fed. Reg. 41516-01.

[90]CDER 4820.3.

[91]*Id.*

[92]*Id.* Henry Grabowski and Y. Richard Wang, *Do Faster Food and Drug Administration Drug Reviews Adversely Affect Patient Safety? An Analysis of the 1992 Prescription Drug User Fee Act*, 51 J. Law and Economics 377, 380 (May 2008) (hereinafter Grabowski & Wang). *See also* 53 Fed. Reg. 41516-01.

[93]CDER 4820.3. Grabowski & Wang, *supra* note 92, at 380.

[94]James T. O'Reilly, Food and Drug Administration, 3d ed., Vol. 1, at 14–49 (2012).

[95]Prescription Drug User Fee Act of 1992, Pub. L. 102-571, 106 Stat. 4491 (1992). *See also* The Library of Congress, Thomas, Bill Summary and Status, 102nd Congress (1991–1992), H.R. 6181, *available at*: <http://thomas.loc.gov/cgi-bin/bdquery/z?d102:HR06181:@@@L&summ2=m&> (last visited Mar. 18, 2014). Congress must renew PDUFA every five years. The fifth and most recent renewal was in 2012 through the FDASIA. The components of the program, such as the amount of the user fees and the timeframes for regulatory decisions, are renegotiated with each renewal. *See also* Statement of Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, Before the Committee on Health, Education, Labor And Pensions, Unites States Senate, "FDA User Fee Agreements: Strengthening FDA and the Medical Products Industry for the Benefit of Patients" (Mar. 29, 2012) (hereinafter Woodcock 3/29/12 Statement) (noting that prior to PDUFA, the review process was understaffed, unpredictable and slow due to insufficient resources).

user fees paid by manufacturers to FDA for the review of NDAs. The funds were dedicated to hiring new personnel.[96] In exchange, FDA committed to review timetables in which to complete its analysis of applications.[97] As part of that scheme, PDUFA codified two of FDA's prioritization categories of NDAs: Priority Review and Standard Review.[98]

In December 1992, FDA also created the Accelerated Approval mechanism for full NDA approval through regulations.[99] This mechanism applied to the approval of new drug products for serious or life-threatening conditions that provide meaningful therapeutic benefit to patients over existing treatments.[100] It permitted the sponsor to show efficacy through clinical trials demonstrating an effect on an unvalidated surrogate endpoint that, nonetheless, was "reasonably likely to predict clinical benefit," rather than a validated surrogate endpoint or clinical efficacy endpoint.[101] For example, a study might evaluate the effect of a treatment on progression-free survival (PFS) rather than mortality.[102] The use of a surrogate marker may substantially shorten the duration of a trial where the disease would take a long time to progress to the ultimate clinical efficiency endpoint, such as mortality.[103]

The Fast Track designation evolved out of the Subpart E regulations and was codified in 1997 when Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA).[104]

Finally, Congress created the Breakthrough Therapy designation in 2012 through the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA).[105] In addition to creating this new designation, FDASIA authorized a broader use of Accelerated Approval.[106]

D. Development of Breakthrough Therapy designation

The concept of the Breakthrough Therapy mechanism arose from several factors, including the dramatic advances in science and economic pressures on the pharmaceutical industry. Prior to 1981, when HIV/AIDS was uncovered, scientists developed the vast majority of new therapies from the disease itself or from substances found in nature, through a trial-and-error process, rather than

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[96]Randall, *supra* note 30, at 2. Until 2007, the PDUFA agreement between the pharmaceutical industry and FDA limited the use of the user fees to new drug reviews rather than other FDA tasks. Thereafter, FDA could also use the funds for other activities aimed at improving FDA's ability to review expeditiously applications, such as updating FDA's information technology. Grabowski & Wang, *supra* note 92, at 380.

[97]*Id.* at 318. Initially, FDA committed to reviewing and issuing one of three outcome letters for 90 percent of standard applications within 12 months and 90 percent of priority applications within 6 months. *Id.*

[98]*Id.*

[99]57 Fed. Reg. 58942-60 (1992). 21 C.F.R. §§ 314.500, 601.41 (2014). *See also* Clinical Trial Endpoints Guidance, *supra* note 22, at 2.

[100]21 C.F.R. §§ 314.500, 601.41 (2014). *See also* FDA Website, *Speeding Access to Important New Therapies, For Consumers: Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review*, FDA.GOV, *available at*: <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm#summary> (last visited Feb. 1, 2014).

[101]21 C.F.R. §§ 314.510, 601.41. Accelerated Approval also permitted FDA to approve an effective drug that could only be used safely if its distribution or use were restricted. 21 C.F.R. §§ 314.520, 601.42 (2014).

[102]Clinical Trial Endpoints Guidance, *supra* note 22, at 5, 8. PFS is "the time from randomization until objective tumor progression or death." *Id.* at 8.

[103]Indeed, 26 of the 35 cancer therapies approved for marketing by FDA using the Accelerated Approval mechanism between 1992 and 2010 completed Phase 4 conventional clinical trials; those trials "required a median time of almost four more years of investigation"—a substantial time for patients with cancer. Huber, *supra* note 76, at 90.

[104]Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, 111 Stat. 2295 (1997), *available at*: <http://www.gpo.gov/fdsys/pkg/PLAW-105publ115/html/PLAW-105publ115.htm> (last visited Apr. 29, 2014). *See also* Huber, *supra* note 74, at 100–01. Grabowski & Wang, *supra* note 92, at 380 n.6. In enacting the FDAMA, Congress sought to authorize broader application of expedited approval and approval from HIV/AIDS and cancer to any serious or life-threatening disease. Food and Drug Administration Modernization Act of 1997, S. Rep. 105-43 (1997), *available at*: <http://www.gpo.gov/fdsys/pkg/CRPT-105srpt43/pdf/CRPT-105srpt43.pdf> (last visited May 4, 2014). The FDAMA consolidated Subpart E and Accelerated Approval in the Fast Track program. Grabowski & Wang, *supra* note 92, at 380 n.6. Senate Report 105-43 clearly delineated Fast Track and Accelerated Approval as two programs, however.

[105]Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No. 112-144, 126 Stat. 993 § 902 (2012), *available at*: <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf> (last visited May 4, 2014). For a concise discussion of FDASIA, *see generally* Daniel B. Kramer and Aaron S. Kesselheim, *User Fees and Beyond—The FDA Safety and Innovation Act of 2012*, 367.14 N. ENG. J. MED. 1277 (2012).

[106]*See* 21 U.S.C. § 356. FDASIA, Pub. L. No. 112-144, 126 Stat. 993 § 901 (2012).

through intentional design.[107] The core of the modern drug and biological product regulatory system developed against this backdrop. In 1981, however, FDA licensed a revolutionary new product, the first ACE inhibitor, which was modeled to fit a specific protease enzyme.[108] Gradually, scientists embarked on a process of designing therapeutic compounds with an increasing understanding of biochemistry, pharmacology, and genetics. "The advent of genomic sciences, rapid DNA sequencing, combinatorial chemistry, cell-based assays, and automated high throughput screening (HTS)…led to a 'new' concept of drug discovery."[109] The completion of the human genome in 2001 has likely contributed to that new direction.[110] Indeed, one of the most notable new scientific advancements in drug development is the increase in molecularly targeted therapies, which target "subgroups of patients (within the larger population with a given disease) who are predicted to benefit from them."[111] The increased specificity and potential for substantially greater benefits over other therapies provide great promise, but also may lead to tension between the regulatory requirements and ethics, time, costs, and patient perspectives.[112]

One drug in particular epitomized this tension. Roche and Plexxikon, Inc. developed a new product intended to treat metastatic melanoma (vemurafenib)[113] by targeting a specific gene mutation that reportedly occurs in 40 to 60 percent of metastatic melanoma patients.[114] In a Phase 1 dose-escalation clinical trial in 2008 and 2009, over 80 percent of the 32 extension patients with metastatic melanoma and the gene mutation benefited clinically through tumor shrinkage.[115] In the context of cancer, where the standard of care treatments slowed the growth of tumors in only 10 to 20 percent of metastatic melanoma patients, and the average survival for one of the treatments was less than eight months, these early clinical results were compelling.[116]

Although some suggested that Roche and Plexxikon, Inc. apply for Accelerated Approval, the companies decided to complete a small Phase 2 clinical trial and a traditional randomized, controlled Phase

[107]Huber, *supra* note 76, at 26–27.

[108]*Id*. at 27–28.

[109]Jurgen Drews, *Drug Discovery: A Historical Perspective*, 287 SCIENCE 1960, 1961 (2000). *See also* FDA, *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*, FDA.GOV (October 2013), *available at*: <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275048.htm> (last visited Nov. 6, 2014).

[110]L.J. Lesko and J. Woodcock, *Pharmacogenomic-guided Drug Development: Regulatory Perspective*," 2 PHARMACOGENOMICS J. 20 (2002) (hereinafter Lesko & Woodcock).

[111]Rachel E. Sherman, *et al.*, *Expediting Drug Development—The FDA's New ''Breakthrough Therapy'' Designation*, 369.10 N. ENG. J. MED. 1877–1880, 1877–78 (Nov. 14, 2013).

[112]*See, generally, id*. (discussing the use of pharmacogenomics and pharmacogentics in drug development, its promise, and the regulatory issues that it raised). The authors noted that they were not aware of any standard definitions of pharmacogenomics and pharmacogenetics. As used in their article, they defined pharmacogenomics as the "global science of using genetic information from an individual or population for the purpose of: (1) explaining interindividual differences in pharmacokinetics (PK) and pharmacodynamics (PD); (2) identifying responders and non-responders to a drug; and (3) predicting the efficacy and/or toxicity of a drug." *Id.* at 20–21. Similarly, they defined pharmacogenetics as "a scientific subset of [pharmacogenomics] in which there are genetic variations…to drug doses and dosing regimens that result in different systemic drug exposure patterns (PK) in individuals or populations." *Id.* at 21.

[113]Vemurafenib has also been known as PLX4032 (RG7204).

[114]Center for Drug Evaluation and Research, Summary Review for Application No. 202429Orig1s000, *available at*: <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202429Orig1s000SumR.pdf> (last visited May 4, 2014) (hereinafter Vemurafenib Summary Review). Amy Harmon, *New Drugs Stir Debate on Rules of Clinical Trials*, N.Y. TIMES, Sept. 18, 2010, *available at*: <http://www.nytimes.com/2010/09/19/health/research/19trial.html?pagewanted=all&_r=0> (hereinafter Harmon (9/18/10)). Letter from Abigail Alliance for Better Access to Developmental Drugs to Margaret O. Hamburg, Commissioner, Food and Drug Administration, dated Oct. 15, 2010, at 1, *available at*: <http://abigail-alliance.org/docs/abigailletter.pdf> (hereinafter Abigail Alliance Letter). Vemurafenib (PLX4032) targets the V600E mutation of the BRAF kinase gene. *Id.*

[115]Vemurafenib Summary Review, *supra* note 114, at 3. *See also* Keith T. Flaherty, *et al.*, *Inhibition of Mutated, Activated BRAH in Metastatic Melanoma*, 363.9 N. ENG. J. MED. 809–819 (hereinafter Flaherty); Amy Harmon, *A Roller Coaster Chase for a Cure*, N.Y. TIMES, Feb. 21, 2010, *available at*: <http://www.nytimes.com/2010/02/22/health/research/22trial.html?pagewanted=all> (describing the early research and develop of Vemurafenib (PLX4032)). Harmon (9/18/10), *supra* note 114 (also noting that "[t]he reprieve was all too brief: most saw their tumors begin to grow again within the year."). Abigail Alliance Letter, *supra* note 114, at 1.

[116]Flaherty, *supra* note 115, at 810. *See also* Harmon (9/18/10), *supra* note 114. At the time Roche and Plexxikon, Inc. were developing PLX4032, the only FDA approved drug for treatment of metastatic melanoma was dacarbazine, which FDA approved for that indication in May 1975. Abigail Alliance Letter, *supra* note 114, at 2.

3 clinical trial.[117] The performance of these trials in which many patients were randomly given a treatment that early clinical evidence had shown to be dramatically inferior to the investigatory drug, and the general advances in science, pharmacogenetics, and pharmacogenomics, prompted debates in the scientific community and popular press on whether the traditional regulatory framework fit the new scientific methods and whether its use was ethical.[118]

Concerns about the economics of modern drug development, supply chain security if development efforts migrated outside the United States, and job security also contributed to the public debate over the requirements of the regulatory process.[119] Since the passage of PDUFA, FDA reported tremendous progress in shortening review times and reversing the drug lag in FDA review of NDAs in comparison to other regulatory agencies.[120] Nonetheless, concern existed over the unpredictability, financial costs, and length of the drug development and approval process.[121] In a report issued shortly after the passage of FDASIA, a group of experts concluded that developing a new compound still required more time and money than in the past, in part because of the inefficiency of the clinical trial system and the need for large and long trials to establish the necessary safety and efficacy data.[122] Ominously, it also found that resources available for new compound development were dwindling, due to the loss of revenue of many pharmaceutical companies as a large segment of drugs lost their patent exclusivity (without any new compounds to replace the lost revenue) and a decline in venture capital investment, reportedly due to concerns over unfavorable returns on investment.[123] A high rate of candidate compound failure and regulatory uncertainty further complicated the innovation ecosystem, according to the report.[124] The basic concern was that these factors would cause venture capitalists to decrease their investments in small biological and pharmaceutical companies and lead established manufacturers to withdraw from certain fields of

[117]Vemurafenib Summary Review, *supra* note 114, at 2, 3. *See also* Flaherty, *supra* note 115, at 819; Abigail Alliance Letter, *supra* note 114, at 4. Information on the Phase 3 trial, the BRIM3 trial, is available in Vemurafenib Summary Review, *supra* note 114, at 3, and at clinicialtrials.gov. The Phase 3 trial number is NCT01006980. Ultimately, FDA gave vemurafenib (or Zelboraf) "a Fast-Track designation because it had the potential to improve overall survival in patients with melanoma, the most dangerous type of skin cancer. Because of convincing early findings with this drug, FDA scientists worked proactively with the sponsor during drug testing to encourage early submission of the application. FDA approved Zelboraf in 2011 to treat patients with late-stage (metastatic) or unresectable (cannot be removed by surgery) melanoma." Woodcock 3/29/12 Statement, *supra* note 95, at 7; *see also* U.S. Department of Health and Human Services, Food and Drug Administration, About FDA, Notable FY 2011 Approvals, *available at*: <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276413.htm> (last visited May 4, 2014).

[118]Clinical research requires a state of clinical equipoise—"a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Should the investigator discover that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment." Benjamin Freedman, *Special Article: Equipoise and the Ethics of Clinical Research*, 317 N. ENG. J. MED. 3, 141 (1987). Clinical trials also may raise ethical considerations in the delay they cause sick patients who are not enrolled in the clinical trials, in obtaining access to a treatment that may be significantly more effective than that available on the market. For metastatic melanoma, for example, the five-year survival-rates for patients with stage IIIC or IV cancer are 40 percent and 15 to 20 percent, respectively. *See* American Cancer Society, *Melanoma Skin Cancer, What Are the Survival Rates for Melanoma Skin Cancer by Stage?* CANCER.ORG, *available at*: <http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-survival-rates> (last visited Mar. 8, 2014).

[119]Bennet, M, 158 Cong. Rec. S3400-02, 2012 WL 1858787 (May 22, 2012) (discussing the benefits of the bill that became the FDASIA for cancer patients, the pharmaceutical industry employees, and the supply chain's stability).

[120]*See, e.g.*, Woodcock 3/29/12 Statement, *supra* note 95. According to Dr. Woodcock, between 1992 and 2012, FDA had reduced the approval phase length from 2 years on average to 1.1 years on average "more recently." *Id.* Dr. Woodcock also reported that in fiscal year 2011, FDA met the PDUFA deadlines in 34 out of 35 cases for groundbreaking new medicines and that in 24 of those approvals (or 70 percent of cases) FDA did so before any other regulatory agency. *Id. See also* Harkin, T, 158 Cong. Reg. S3389-05 (citing a study from the *New England Journal of Medicine* regarding the favorable performance of the FDA in approving new compounds in comparison to Canada's regulatory agency).

[121]General Accountability Office, GAO-07-49, "New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts, at 5, 25 (Nov. 2006); *see* Upton, F, 158 Cong. Rec. H3825-01. PCAST Report, *supra* note 1.

[122]PCAST Report, *supra* note 1, at 11, 13–14. The report noted that the inefficiencies of clinical trials could be alleviated in part through trials that targeted a specific subset of patients who would most likely benefit from the compound based on the presence of some validated biomarker or through innovative new ways of designing trials using modern statistical techniques. *Id.* at 21.

[123]*Id.* at 9–10.

[124]*Id.* at 12, 14.

development due to diminished financial incentives. Such losses risked not only the public health but also threatened the U.S. economy. Pharmaceutical products represent one of the most significant exports for the United States, and the industry employs a significant number of workers directly and indirectly.[125]

The Breakthrough Therapy mechanism originated during a discussion at a conference co-hosted by Friends of Cancer Research and the Brookings Institute in 2011 regarding potential new approaches to speed up the FDA approval process for certain promising new drugs.[126] A panel of experts that included Janet Woodcock, the Director of the Center for Drug Evaluation and Research (CDER) at FDA, identified a potential development and full approval strategy for obtaining reliable information on safety and efficacy for new therapies that demonstrated large treatment effects early in the development process by considering three new compounds, including vemurafenib.[127]

In the spring of 2012, after Friends of Cancer Research advocated before Congress for updated mechanisms to respond to the rapid advancement of science, including the Breakthrough Therapy designation,[128] members of Congress introduced two bills in the Senate and House, which sought to amend the FDCA to add a new breakthrough therapy designation,[129] and which were ultimately incorporated into the Food and Drug Administration Safety and Innovation Act. FDASIA made two significant and general changes to the expedited approval mechanisms then-available for drug products. First, it authorized FDA to apply the Accelerated Approval mechanism more broadly.[130] Second, it created an altogether new mechanism, the Breakthrough Therapy designation.[131]

III. OVERVIEW OF FOUR CURRENT FDA ACCELERATED APPROVAL MECHANISMS

Following the enactment in 2012 of the FDASIA and the issuance of a Final Guidance by FDA, four expedited approval mechanisms exist for new drugs seeking full marketing approval.

A. Priority Review

Under the two-tier Priority Review framework, FDA classifies all original NDAs, original BLAs, and efficacy supplements for either priority or standard review, whether or not the sponsor requests a specific designation.[132] Under FDA's Guidance and the updated CDER MAPP 6020.3, to receive Priority Review, the new product must treat a serious or life-threatening condition and "provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies," if approved.[133] FDA determines whether a new drug product represents a significant improvement on a case-by-case basis,

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[125]*Id.*

[126]Thomas Fleming, *et al.*, Issue Brief: Panel 4—Development Paths for New Drugs with Large Treatment Effects Seen Early, Conference on Clinical Cancer Research (Nov. 2011), *available at*: <http://www.focr.org/sites/default/files/Panel4FINAL11411.pdf> (hereinafter Issue Brief Panel 4). Friends of Cancer Research, 2012 Annual Report, at 10, *available at*: <http://www.focr.org/sites/default/files/annual-report/FOCR-AR12.pdf> (hereinafter FOCR 2012 Ann. Rpt.).

[127]Issue Brief Panel 4, *supra* note 126, at 2.

[128]FOCR 2012 Ann. Rpt., *supra* note 126, at 4, 6, 8.

[129]On March 26, 2012, Senator Michael F. Bennett (D-CO), Senator Orrin Hatch (R-UT), and Senator Richard Burr (R-NC), introduced the "Advancing Breakthrough Therapies for Patients Act" in the Senate. The Library of Congress, Thomas, Bill Summary and Status 112th Cong., All Information on S. 2236, "Advancing Breakthrough Therapies for Patients Act of 2012", *available at*: <http://thomas.loc.gov/cgi-bin/bdquery/D?d112:1:./temp/~bdHDqW:@@@L&summ2=m&|/home/LegislativeData.php?n=BSS;c=112|> (last visited Mar. 5, 2014). In May 2012, Congresswoman Diana DeGette (D-CO) and Congressman Brian Bilbray (R-CA) introduced a bill "To amend chapter V of the Federal Food, Drug, and Cosmetic Act to expedite the development and review of breakthrough therapies," in the House of Representatives. The Library of Congress, Thomas, Bill Summary and Status 112th Cong., All Information on H.R. 5334, "To amend chapter V of the Federal Food, Drug, and Cosmetic Act to expedite the development and review of breakthrough therapies," *available at*: <http://thomas.loc.gov/cgi-bin/bdquery/z?d112:HR05334:@@@L&summ2=m&|/home/LegislativeData.php?n=BSS;c=112|> (last visited Mar. 5, 2014).

[130]21 U.S.C. § 356(c). FDASIA, Pub. L. No. 112-144, 126 Stat. 993 § 901 (2012).

[131]21 U.S.C. § 356(a). FDASIA, Pub. L. No. 112-144, 126 Stat. 993 § 902 (2012).

[132]MAPP 6020.3, at 2.

[133]*Id.*; *see also* SOPP 8405 (ver. 4); Final Guidance, at 24. Certain applications automatically receive priority review. These include, but may not be limited to, (1) "Supplemental applications that propose labeling changes pursuant to a final pediatric study report …", (2) "Applications submitted in response to a written request under the Best Pharmaceuticals for Children Act …", (3) "Applications or supplements for a drug designated as a qualified infectious disease drug under section 505E(d) of the [FDCA] …", (4) "Applications or supplements submitted with a priority review voucher …" MAPP 6020.3, at 3. Priority review vouchers are granted to sponsors "of applications for drugs for the treatment or prevention of certain tropical diseases, as defined in section 524(a)(3) and (4) of the FD&C Act, and for treatment of rare pediatric diseases, as defined in section 529(a)(3) of the FD&C Act." Mapp 6020.3, at 3 n.5.

but it may consider evidence of increased effectiveness, elimination or substantial reduction of a treatment-limiting adverse reaction, improved patient compliance that is expected to improve a serious outcome, or evidence of safety or effectiveness in a new subpopulation.[134]

Although FDA expects the source of this evidence to be randomized superiority trials, comparing the new drug product to the currently available therapy, FDA has some flexibility in the types of evidence that will establish a significant improvement.[135] It notes in its Final Guidance on the four expedited approval mechanisms, for example, that a trial that demonstrates effective treatment of a subpopulation using an historical control may be persuasive.[136]

FDA independently decides whether to give Priority Review to a new drug product whether or not specifically requested, but a sponsor may request Priority Review when it submits its original NDA or efficacy supplement.[137] All original NDAs and efficacy supplements that do not meet the criteria for Priority Review receive the Standard Review designation.[138]

The primary benefit of receiving Priority Review is a reduction of four-months in the projected review time by FDA. FDA aims to complete review of an NDA for a compound with a Priority Review designation within six months; the goal for a compound with a Standard Review designation is to complete review within ten months.[139] In addition, FDA intends "to direct overall attention and resources to the evaluation of applications for" Priority Review drug products.[140]

B. Accelerated Approval

For a new compound to qualify for Accelerated Approval[141] following the enactment of FDASIA, it must address a serious or life-threatening condition and demonstrate an effect on a surrogate endpoint or an intermediate clinical endpoint other than a direct measure of mortality or survival.[142] The surrogate endpoint or intermediate clinical endpoint must be "reasonably likely to predict" the clinical benefit or an effect on irreversible morbidity or mortality.[143]

In its Final Guidance, FDA has interpreted an intermediate clinical endpoint to be "a measurement of a therapeutic effect that can be measured earlier than an effect on IMM [irreversible morbidity and mortality] and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit."[144] FDA appears to anticipate that most studies using an intermediate clinical endpoint to demonstrate clinical benefit would be a basis for traditional approval, leaving only a narrow slice of circumstances for accelerated approval.[145] It believes that Accelerated Approval based on an intermediate clinical endpoint may be appropriate where "[a] study demonstrates a relatively short-term clinical benefit in a chronic disease setting…[and] the short-term benefit is considered reasonably likely to predict long-term benefit or where '[a] clinical endpoint demonstrates a clinical benefit that is reasonably likely to predict an effect on IMM…[where] it is essential to confirm the effect on IMM'" for example, "because available therapy has established effects on IMM."[146]

FDA defines a "surrogate endpoint" in its Final Guidance as "a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit."[147] As examples, FDA highlights "[c]learance

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[134]MAPP 6020.3, at 6–7; *see also* SOPP 8405; Final Guidance, at 24–25.
[135]Final Guidance, at 25.
[136]*Id.*
[137]*Id.* at 33. Likewise, a sponsor may request priority review when it submits its original BLA. *Id.*
[138]MAPP 6020.3; *see also* SOPP 8405.
[139]MAPP 6020.3, at 2; Final Guidance, at 25. Review designation may change during the course of FDA's review of an original NDA, original BLA, or efficacy supplement, due to the approval of other drugs, the availability of new information, or advisory committee recommendations, among other things. MAPP 6020.3. at 4. However, a re-designation does not alter the review timeline during the first review cycle. MAPP 6020.3, at 4; Final Guidance, at 34.
[140]MAPP 6020.3. at 2; Final Guidance, at 24.
[141]FDA has approved over 80 new products under the Accelerated Approval mechanism since its establishment. Of that group, "29 drugs [] treat cancer, 32 [compounds] treat HIV, and 20 [] treat other conditions, such as pulmonary hypertension, Fabry disease, and transfusion-dependent anemia." Woodcock 3/29/12 Statement, *supra* note 93, at 7.
[142]21 U.S.C. § 356(c)(1)(A). Final Guidance, at 15. In enacting the FDASIA, Congress expanded the Accelerated Approval mechanism in several ways that provide FDA with more flexibility. Final Guidance, at 15. *See also* Stearns, C., 158 Cong. Rec. H3825-01.
[143]21 U.S.C. §356(c)(1)(A). Final Guidance, at 15.
[144]Final Guidance, at 18.
[145]*Id.* at 18 and 19.
[146]*Id.* at 18. In its Final Guidance, FDA provides two examples of intermediate clinical endpoints found to support accelerated approval. The first involved evidence of "a large therapeutic effect on relapse rate through approximately 13 months of treatment" for multiple sclerosis, "where there was uncertainty about the durability of the observed effect." The second involved "a demonstration of delay in delivery" by a treatment for preterm labor, where FDA required the sponsor to "demonstrate improved long-term postnatal outcomes" in postmarketing studies. *Id.* at 18–19.
[147]Final Guidance, at 17.

of bacteria from the blood stream as evidenced by a laboratory measurement of bacteria in the blood" for clinical resolution of infection, "[o]utcomes of 6-month follow-up treatment (i.e., sputum culture status and infection relapse rate" for pulmonary tuberculosis resolution, "[d]ecrease in iron stores for patients with iron overload caused by thalassemia" for "a decrease in transfusion-related adverse events caused by iron overload in the body," and "[r]adiographic evidence of tumor shrinkage (response rate) in certain cancer types" as a prediction of "improvement of overall survival."[148]

The type of evidence a sponsor can rely on to establish the necessary relationship between the surrogate or intermediate endpoint and the clinical efficacy endpoint includes "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools,"[149] although "[e]vidence of pharmacologic activity alone is not sufficient."[150]

In addition, unlike the FDA regulations, § 506(c) of the FDCA does not expressly require that a new drug product provide meaningful therapeutic benefit to patients over existing treatments.[151] Rather, it permits FDA to take into account "the availability or lack of alternative treatments," as well as "the severity, rarity, or prevalence of the condition."[152] In its Final Guidance, however, FDA explains that it interprets § 506(c) as broadening the use of Accelerated Approval in several ways.[153] These include providing (1) "additional flexibility concerning the implications of available therapy on eligibility for accelerated approval," (2) clarifying "the use of [intermediate] clinical endpoints…as a basis for accelerated approval," (3) explicitly allowing FDA "to consider pharmacologic or other evidence developed using biomarkers or other scientific methods or tools, in conjunction with other data," in determining whether to approve a product, and (4) "indicating that FDA should take into account, "… the severity, rarity, or prevalence of the condition …"[154]

Further, § 506(c) of the FDCA permits, but does not require, FDA to hinge Accelerated Approval on verifying the predicted effect on irreversible morbidity or mortality or other clinical benefit through post-approval studies.[155] Nonetheless, FDA appears to continue to require confirmatory post-approval trials, "completed with due diligence."[156]

FDA may withdraw approval in several circumstances, including if the sponsor does not "conduct a required postapproval study of the drug with due diligence,"[157] the study "fails to verify and describe" the "predicted effect on irreversible morbidity or mortality or other clinical benefit,"[158] "[o]ther evidence demonstrates that the product is not shown to be safe or effective under the conditions of use,"[159] or "[t]he applicant disseminates false or misleading promotional materials relating to the product."[160]

The Accelerated Approval mechanism benefits a sponsor or manufacturer by facilitating shorter clinical trials. Rather than waiting for data on a clinical endpoint, Accelerated Approval permits a sponsor or manufacturer to utilize an event that may occur earlier in time.[161]

C. Fast Track approval

An investigational new drug product is eligible for Fast Track designation if "it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition …"[162] The type of evidence required may be nonclinical or clinical and varies with

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[148] *Id.* at 18.

[149] 21 U.S.C. § 356(c)(1)(B) (2014); Final Guidance, at 19. The act expands on the list provided for in the regulations to explicitly permit consideration of pharmacologic evidence. *See* 21 U.S.C. § 356(c)(1)(B) (2014); 21 C.F.R. §§ 314.510, 601.41.

[150] Final Guidance, at 19 (*citing* 57 Fed. Reg. 58942).

[151] 21 U.S.C. § 356(c)(1)(A). *See also* 21 C.F.R. §§ 314.500, 601.40. FDASIA also de-coupled Accelerated Approval from Fast Track designation.

[152] 21 U.S.C. § 356(c)(1)(A).

[153] Final Guidance, at 15.

[154] *Id.* at 15 (internal citations omitted).

[155] 21 U.S.C. § 356(c)(2)(A). *See also* 21 C.F.R. §§ 314.510, 601.41.

[156] Final Guidance, at 15, 22.

[157] 21 U.S.C. § 356(c)(3)(A).

[158] 21 U.S.C. § 356(c)(3)(B).

[159] Final Guidance, at 23.

[160] *Id.* For an example of the withdrawal of approval of an indication for a product that was approved under Accelerated Approval, *see* Decision of the Commissioner, Department of Health and Human Services, Food and Drug Administration, on the Proposal to Withdraw Approval for the Breast Cancer Indication for AVASTIN (Bevacizumab) (November 18, 2011), Docket No. FDA-2010-N-0621, *available at*: < http://www.fda.gov/downloads/NewsEvents/Newsroom/UCM280546.pdf > (last visited May 1, 2014) (withdrawing accelerated approval of Avastin with paclitaxel in the treatment of metastatic breast cancer).

[161] Final Guidance, at 15–16.

[162] 21 U.S.C. § 356(b)(1). Fast Track approval is also available to a drug designated by FDA as a qualified infectious disease product under Title VIII of the FDASIA, which is called "Generating Antibiotic Incentives Now" (GAIN). *Id.*; *see also, generally,* FDASIA, Pub. L. 112-144, 126 Stat. 993 §§ 801–806 (2012); Final Guidance, at 9.

the stage of development of the product; it could include "theoretical rationale, mechanistic rationale (based on nonclinical data) or evidence of nonclinical activity …"[163] A sponsor may request Fast Track designation when the sponsor files an IND application or any time thereafter prior to the receipt of marketing approval.[164] If a new drug product meets these criteria, Fast Track designation is mandatory. However, FDA may rescind the designation if emerging data no longer supports it.[165]

Fast Track designation provides several benefits to a sponsor. Section 356(b)(1) of the FDCA requires FDA to "facilitate the development and expedite the review of" a Fast Track drug product.[166] The statute itself provides one such benefit explicitly. Rolling review of a Fast Track product's NDA may be possible if FDA finds that a "fast track product may be effective" based on a "preliminary evaluation of clinical data submitted by the sponsor," and other administrative criteria[167] are met.[168] This enables FDA to review "portions of[] an application for the approval of the product before the sponsor submits a complete application," potentially expediting the review process.[169]

In addition, Fast Track designation permits frequent interaction between a sponsor and the FDA review team. Meetings are possible prior to submitting an IND application, at the end of Phases 1 and 2 and at other times, as appropriate.[170] They may cover topics such as "study design, extent of safety data required to support approval, dose-response concerns, [] use of biomarkers,…accelerated approval, the structure and content of an NDA, and other critical issues … ."[171]

D. Breakthrough Therapy designation

The fourth expedited approval mechanism—the Breakthrough Therapy designation—applies to a new drug product if it "is intended, alone or in combination with 1 or more other 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 1 or more clinically significant endpoints."[172]

In its Final Guidance, FDA has interpreted "preliminary clinical evidence" to mean evidence "sufficient to indicate that the drug may demonstrate substantial improvement in effectiveness or safety over available therapies, but in most cases is not sufficient to establish safety and effectiveness for purposes of approval."[173] This generally will require more than data from *in vitro* studies or animal models.[174] FDA expects preliminary clinical evidence to come from Phase 1 or 2 clinical trials.[175] Data from human clinical trials "should involve a sufficient number of patients to be considered credible," though the data may not be definitive at the time of a Breakthrough Therapy designation.[176] The strongest preliminary clinical evidence would come from a study, comparing the new compound to an available therapy or placebo (where no therapy exists) or the new compound with the standard of care to the standard of care alone; clinical data showing a large difference between a new compound and an historical control may be persuasive, as well.[177] In addition to evidence of clinical benefit, nonclinical evidence could be supportive.[178]

According to FDA's Final Guidance on its four expedited approval mechanisms, "substantial improvement" generally means a "clear advantage over available therapy" and depends on both the size of the treatment effect and "the importance of the observed effect to the treatment of the serious condition or serious aspect of the condition."[179] FDA has interpreted a "clinically significant endpoint" relatively broadly. It "generally [] refer[s] to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) [,] on symptoms that represent serious consequences of the disease," or "on findings that suggest an effect on IMM or

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[163]Final Guidance, at 9, 11.
[164]21 U.S.C. § 356(b)(2); Final Guidance, at 28.
[165]Final Guidance, at 8, 30.
[166]21 U.S.C. § 356(b)(1).
[167]Section 356(d)(1) requires that a sponsor "provide[] a schedule for submission of information necessary to make the application complete; and pay[] any fee that may be required under section 379h" of Title 21. 21 U.S.C. § 356(d)(1).
[168]21 U.S.C. § 356(d)(1). *See also* Final Guidance, at 10, 35–36.
[169]21 U.S.C. § 356(d)(1). The review time commitments by FDA for priority and standard review, discussed above, do not begin, however, until the date the NDA or BLA is complete. *Id; see also* Final Guidance, at 36.
[170]Final Guidance, at 9.
[171]*Id.*
[172]21 U.S.C. § 356(a). *See also* Final Guidance, at 11.
[173]Final Guidance, at 11.
[174]Rachel E. Sherman, *et al.*, *Expediting Drug Development—The FDA's New ''Breakthrough Therapy'' Designation*," 369 N. Eng. J. Med. 20, 1877–1880, at 1877 (Nov. 14, 2013) (hereinafter Sherman).
[175]Final Guidance, at 11.
[176]*Id.*
[177]*Id.*
[178]*Id.*
[179]*Id.* at 12. FDA presents examples of how a sponsor might demonstrate a substantial improvement over available therapy through preliminary clinical evidence. *Id.* at 11–12.

serious symptoms…"[180] Among other findings, these could be an effect on a surrogate or intermediate clinical endpoint that meets the Accelerated Approval requirements or on a pharmacodynamics biomarker that "strongly suggests the potential for a clinically meaningful effect on the underlying disease."[181]

A sponsor may apply for the Breakthrough Therapy designation when it files an IND application or anytime thereafter.[182] If the sponsor's application satisfies the Breakthrough Therapy designation requirements, designation of the new drug product as a breakthrough therapy is mandatory. The designation entitles a sponsor to "appropriate actions [by FDA] to expedite the development and review of an application for approval of a breakthrough therapy."[183] FDASIA lists several examples of potential actions that FDA may take. These focus on creating a collaborative and close process between FDA and the sponsor through the commitment of timely communication and meetings, experienced and senior FDA personnel, an FDA employee responsible for coordinating the review within FDA, and efforts by FDA to make the trials as efficient and small as practicable.[184] In its Final Guidance, FDA has reiterated these benefits and added that a Breakthrough Therapy product may obtain rolling review and "could be eligible for priority review if supported by clinical data at the time of BLA, NDA, or efficacy supplement submission."[185]

IV. COMPARISON OF THE BREAKTHROUGH THERAPY DESIGNATION WITH FAST TRACK DESIGNATION, PRIORITY REVIEW, AND ACCELERATED APPROVAL

The Breakthrough Therapy designation does not provide a new expedited mechanism to a new category of disease and illnesses. Rather, all four expedited approval mechanisms target a particular category of therapies—those intended to treat a serious aspect of a condition or a serious condition (hereinafter "serious diseases").[186] In addition, FDA preliminarily has interpreted all four expedited approval mechanisms as requiring that a new compound address an unmet medical need, "a condition whose treatment or diagnosis is not addressed adequately by available therapy."[187]

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[180] *Id.* at 12.

[181] *Id.* at 11.

[182] 21 U.S.C. § 356(a)(2). *See also* Final Guidance, at 30, FDA opines that "in most cases breakthrough therapy designation requests should be submitted as an amendment to the IND" because sponsors should not request breakthrough therapy designation "until they have [the necessary] preliminary clinical evidence …". FDA also advises that sponsors submit applications prior to the start of "clinical trial(s) intended to serve as the primary basis for demonstration of efficacy" so that the sponsor can obtain most of the designation's benefits. *Id.*

[183] 21 U.S.C. § 356(a)(1) and (3)(A).

[184] 21 U.S.C. § 356(a)(3)(B). For a detailed description of the actions CDER will take between granting a Breakthrough Therapy designation and the submission of a marketing application, *see generally* MAPP 6025.6.

[185] Final Guidance, at 13–14.

[186] 21 U.S.C. § 356(a)–(c); MAPP 6020.3; SOPP 8405. *See also* Final Guidance, at 2, 3. FDA explains in its Final Guidance that it "intends to interpret the term *serious* as it has done in the past for the purposes of accelerated approval and expanded access to investigational drugs for treatment use." Final Guidance, at 2, 3. It has been defined as:

> … a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Id. n. 7 (*citing* 21 C.F.R. § 312.300(b)(1)). FDA has found cystic fibrosis, various forms of cancer, hepatitis C, acute heart failure, lysosomal acid lipase deficiency, hypophosphatasia, Duchenne's muscular dystrophy, sporadic inclusion-body myositis, and Lambert-Eaton myasthenic syndrome to be serious diseases. 21 C.F.R. § 312.300; Final Guidance, at 2–3; Sherman, *supra* note 158, at 1878 (listing drugs with an announced Breakthrough Therapy Designation as of Sept. 30, 2013). Many other conditions may qualify as serious.

[187] Final Guidance, at 4. *See also* 21 U.S.C. § 356(c); 21 C.F.R. §§ 314.500, 601.40. Serious conditions that lack any therapy clearly constitute an unmet medical need. Where there is a therapy available, an unmet medical need may exist if the new compound impacts a serious aspect of the disease not effected by the existing therapy or has an improved effect on a serious outcome over available therapy; "[h]as an effect on a serious outcome of the condition in patients who are unable to tolerate or failed to respond to available therapy"; "[c]an be used effectively with other critical agents that cannot be combined with available therapy"; avoids certain toxicities of available treatment or reduces "the potential for harmful drug interactions" while providing comparable efficacy; has a "documented benefit…that is expected to lead to an improvement in serious outcomes" while providing comparable "safety and efficacy to those of available therapy"; or "[a]ddresses an emerging or anticipated public health need, such as a drug shortage." Final Guidance, at 5.

Thus, a new compound might qualify for multiple mechanisms.

A. Breakthrough Therapy and Fast Track designations

FDASIA creates a hierarchy, placing the Breakthrough Therapy designation at a level above the Fast Track designation, but only for a subset of Fast Track products. To receive the Breakthrough Therapy designation, the evidentiary requirements are stricter at an earlier point in the development process than Fast Track. For both designations, a sponsor may request the designation as early as with the filing of the IND application. Whether a sponsor requests Breakthrough Therapy designation at the IND stage or some later point, a sponsor always must present clinical evidence of improvement over existing therapies.[188] In contrast, while FDA will likely require available clinical data to accompany a request for Fast Track designation later in the development process, at an early developmental stage, a sponsor may be able to obtain a Fast Track designation with "evidence of activity in a nonclinical mechanism, a mechanistic rationale, or pharmacologic data."[189] Moreover, for Breakthrough Therapy designation, the improvement demonstrated must be substantial, while Fast Track designation requires only the potential for improvement.[190]

The subset of new drug products that qualify for the Breakthrough Therapy designation also receive more benefits than Fast Track products. First, the sponsors of Breakthrough Therapy products enjoy a closer, more-collaborative relationship with FDA. FDA has specifically identified in its Final Guidance possible meetings for Fast Track products that are earlier in the development process than for non-expedited products: these include pre-IND and EOP1, at which the sponsor may discuss the design of studies, data required by FDA, use of biomarkers, and other issues.[191] FDASIA, the Final Guidance, and CDER's Good Review Practice on Management of Breakthrough Therapy-Designated Drugs and Biologics provide for even greater, more-frequent meetings for Breakthrough Therapy products. As FDA explains in its Final Guidance, "FDA will seek to ensure that the sponsor … receives timely advice and interactive communications in order to help the sponsor design and conduct a development program as efficiently as possible" and this communication can occur "throughout drug development."[192] Indeed, FDA suggests that sponsors of Breakthrough Therapy products have an initial comprehensive multidisciplinary breakthrough therapy meeting with all relevant FDA disciplines[193] to discuss "the overarching, high-level plan for drug development" and topics such as "planned clinical trials and endpoints, plans for expediting the manufacturing development strategy, and studies that potentially could be completed after approval."[194] Further, FDA anticipates subsequent discipline-specific meetings outside of the critical IND milestone meetings.[195] These meetings provide a forum to discuss important issues "at different development phases."[196] And, importantly, the sponsor and FDA can determine their frequency in a unique communication plan.[197] Critical IND milestone meetings also can occur earlier than in other cases.[198] Thus, a Breakthrough Therapy designation appears to permit the opportunity for earlier meetings and FDA's assurance of timely advice and interactions on a much-more-continuous basis throughout development than Fast Track products receive.

Second, Breakthrough Therapy products also may receive greater access and coordination from FDA personnel. These products may have the commitment (where appropriate) of intensive involvement

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[188] 21 U.S.C. § 356(a).
[189] Final Guidance, at 9.
[190] 21 U.S.C. § 356. According to Janet Woodcock, MD, "Failure of the preliminary clinical data to suggest a 'substantial' benefit over existing therapy has been a major reason for denial." She explains that "in situations where some standard-of-care therapy exists, a distinction between small, 'incremental' improvements and game-changing effects must be made." Janet Woodcock, *Drug Development in Serious Diseases: The New 'Breakthrough Therapy' Designation*, 95.5 Clinical Pharmacology & Therapeutics 483–485, at 484 (2014) (hereinafter "Woodcock 2014"). Dr. Woodcock also explains that "the value of various end points used to evaluate efficacy has been a significant area of discussion." *Id.* She states that other issues leading to denial of a Breakthrough Therapy designation are where hope has triumphed over evidence "for example, cases in which no clinical advantage over existing therapy had been shown or the sponsor was not being permitted by the FDA to proceed with further clinical testing because of safety concerns." *Id.*
[191] Final Guidance, at 9. *See also* 21 C.F.R. § 312.82. These meetings occur earlier than meetings between a sponsor and FDA in non-expedited cases. *See* 21 C.F.R. §§ 312.82, 312.47.
[192] Final Guidance, at 13; *see also* 21 U.S.C. § 356(a)(3)(B).
[193] MAPP 6025.6, at 9.
[194] *Id.*
[195] *Id.*
[196] *Id.*
[197] *Id.*
[198] *Id.* at 10.

of "senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review."[199] Breakthrough Therapy products also have a FDA cross-disciplinary project lead for the FDA review team.[200] The project lead facilitates an efficient review of the development program and serves as a scientific liaison between the review team and the sponsor.[201] This level of coordination within FDA is not available for other products.[202] In discussing the communication issues between FDA and sponsors, the PCAST report notes that "no single individual has authority and accountability for integrating the input, resolving conflicting opinions within the FDA, and communicating informally in a timely ongoing manner."[203] Rather, many staff across divisions and offices participate in the review, leading potentially to communications to sponsors from different individuals, variable and unpredictable timeframes for reviews of applications and clinical holds, and possibly conflicting opinions within FDA on issues.[204] The addition of experienced and senior FDA personnel and an internal project lead provides a valuable asset to Breakthrough Therapy products because of the chance of significantly greater efficiency in the review and communications to the sponsor.[205]

Third, FDA may permit both Fast Track and Breakthrough Therapy products to undergo Rolling Review.[206]

Whether the additional meetings and commitment of senior and experienced FDA personnel meaningfully adds to the efficiency and quality of the development program depends on how FDA implements it, but Janet Woodcock, MD, reports that "Sponsors of designated products have remarked on the degree of FDA involvement and have also stated that their timelines for filing a market application have been accelerated as a result."[207] Altogether, the Breakthrough Therapy designation has additional benefits available to its products that may facilitate the development and review process to a greater extent than for Fast Track products.[208]

B. Breakthrough Therapy and Priority Review

A hierarchical relationship also exists between Breakthrough Therapy and Priority Review.

Differences exist between the two mechanisms, stemming largely from their different goals. Priority Review focuses on the review component of the pre-market phase of a new drug product, setting a shorter goal for completing review and providing greater resources. Breakthrough Therapy designation seeks to streamline the pre-review development process.[209] Thus, a sponsor requests these designations at different times. The evidence required to qualify for Breakthrough Therapy must exist far earlier in the development process than for Priority Review. Further, although not definitive, the clinical evidence must show a substantial improvement on a clinical endpoint for the Breakthrough Therapy designation, while a Priority Review drug must only show a significant improvement in effectiveness or safety.[210]

Overall, Breakthrough Therapy designation likely provides a greater chance of reducing the length (and potentially cost) of the entire pre-market process than Priority Review alone, because development currently demands the greatest amount of time

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[199]Final Guidance, at 14.
[200]*Id.*
[201]*Id.*
[202]*See* PCAST Report, *supra* note 1, at 46; Peggy Eastman, *New FDA 'Breakthrough' Designation Likely to Speed Cancer Drug Approvals*, Oncology Times (Nov. 17, 2012), *available at*: <http://journals.lww.com/oncology-times/blog/onlinefirst/pages/post.aspx?PostID=578> (*quoting* Robert Temple, MD, Deputy Center Director for Clinical Science, FDA, Center for Drug Evaluation and Research, as saying that the Breakthrough Therapy designation provides an important change, because it "makes [FDA] think collectively in a systematic way about this. We are going to be held accountable; that is a change. Fast-track didn't quite do that.").
[203]PCAST Report, *supra* note 1, at 46.
[204]*Id.*
[205]The cross-disciplinary project lead will not resolve all communication issues. For example, FDA holds the position that it is not legally permitted to share information with a sponsor that comes up because of its review of another sponsor's application or protocol submission. *See id.*, at 47 and n.134 (*citing* 21 C.F.R. §§ 20.61, 312.130, 314.430; 18 U.S.C. § 1905; 22 U.S.C. § 331(j)).
[206]21 U.S.C. § 356 (d)(1); Final Guidance, at 10, 13–14, 35–36.
[207]Woodcock 2014, *supra* note 191, at 484.
[208]For another view on the benefits of the Breakthrough Therapy designation, *see* Jonathan J. Darrow, Jerry Avorn, and Aaron S. Kesselheim, *New FDA Breakthrough-Drug Category—Implications for Patients*, 370.13 N. Eng. J. Med. 1252 (2014).
[209]Breakthrough Therapy designation may affect the review time through Rolling Review, but Rolling Review does not require FDA to begin its review before receiving a complete application nor does it alter the goal for action on the NDA or BLA. 21 U.S.C. § 356(d)(2); 21 C.F.R. §§ 314.101, 601.2; Final Guidance, at 36.
[210]21 U.S.C. § 356(a)(1); MAPP 6020.3; Final Guidance, at 24; *see also* SOPP 8405.

during the pre-market process and because in many cases a Breakthrough Therapy product may qualify for Priority Review as well. Indeed, 11 of the 13 compounds with a Breakthrough Therapy designation that have been approved by FDA for marketing received Priority Review.[211]

C. Breakthrough Therapy and Accelerated Approval

The Breakthrough Therapy designation has more differences relative to Accelerated Approval than to the Fast Track designation or Priority Review. Nonetheless, a subtle hierarchy exists between the two mechanisms. Accelerated Approval primarily aids a

[211] As of November 5, 2014, FDA has approved for marketing 14 compounds that had a Breakthrough Therapy designation: (1) Gazyva on Nov. 1, 2013; (2) Imbruvica on Nov. 13, 2013; (3) Solvadi on Dec. 6, 2013; (4) Kalydeco on Feb. 21, 2014; (5) Arzerra on Apr. 17, 2014; (6) Zykadia on Apr. 29, 2014; (7) Zydelig on July 23, 2014; (8) Imbruvica on July 28, 2014; (9) Promacta on Aug. 26, 2014; (10) Keytruda on Sept. 4, 2014; (11) Harvoni on Oct. 10, 2014; (12) Ofev on Oct. 15, 2014; (13) Esbriet on Oct. 15, 2014; and (14) Trumenba on Oct. 29, 2014. All but two of these compounds—Arzerra and Imbruvica—also received Priority Review. In addition, six of the products received Accelerated Approval. Another compound, Arzerra, was on the market for one indication, when the manufacturer Glaxo Group Limited (d/b/a GlaxoSmithKline) pursued and received a Breakthrough Therapy designation for a new indication as a first line therapy; FDA concluded that the clinical trials supporting approval of Arzerra as a first line therapy also supported the post-marketing obligations under the Accelerated Approval program for the prior indication. Four products, at least, also received Fast Track designation; notably, at least two of these products—Ofev and Esbriet—both obtained this designation prior to receiving the Breakthrough Therapy designation. Finally, eight compounds were given another designation as an Orphan Product. Of the 14 compounds with a Breakthrough Therapy designation approved by FDA, 13 are drugs and one (Trumenba) is a biologic. *See* FDA, *Regulatory Information, Frequently Asked Questions: Breakthrough Therapies*, FDA.GOV, *available at*: <http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm341027.htm> (last visited Oct. 22, 2014); FDA, *FDA News Release: FDA Approves Ofev to Treat Idiopathic Pulmonary Fibrosis*, FDA.GOV (Oct. 15, 2014), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418994.htm> (last visited Oct. 22, 2014); Boehringer Ingelheim, Press Release, Biehringer Ingelheim's Investigational Therapy Nintedanib Receives First FDA Breakthrough Therapy Designation in IPF, BOEHRINGER-INGELHEIM.COM (July 16, 2014), *available at*: <http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2014/16_july_2014_ipf.html> (last visited Oct. 28, 2014); *U.S. FDA Accepts NDA Filing for Boehringer Ingelheim's Nintedanib for Idiopathic Pulmonary Fibrosis*, DRUGS.COM (July 2, 2014), *available at*: <http://www.drugs.com/nda/nintedanib_140702.html> (last visited Oct. 27, 2014) (noting the FDA granted Fast Track designaton to Ofev in June 2013); *Boehringer Ingelheim's Investigational Therapy Nintedanib Receives FDA Breakthrough Therapy Designation*, DRUGS.COM (July 16, 2014), *available at*: <http://www.drugs.com/nda/nintedanib_140716.html> (last visited Oct. 27, 2014); FDA, *FDA News Release: FDA Approves Esbriet to Treat Idiopathic Pulmonary Fibrosis*, FDA.GOV (Oct. 15, 2014), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418991.htm> (last visited Oct. 22, 2014); InterMune: Investors News Release (July 17, 2014), *available at*: <http://investor.intermune.com/phoenix.zhtml?c=100067&p=irol-newsArticle&ID=1948523&highlight=> (last visited Oct. 28, 2014); *FDA Advisory Committee Recommends Approval of InterMune's Esbriet (pirfenidone) for Idiopathic Pulmonary Fibrosis*, PRNEWSWIRE (Mar. 9, 2010), *available at*: <http://www.prnewswire.com/news-releases/fda-advisory-committee-recommends-approval-of-intermunes-esbrietr-pirfenidone-for-idiopathic-pulmonary-fibrosis-87151342.html> (last visited Oct. 28, 2014); Check Orphan, *FDA Grants Priority Review of Pirfenidone NDA for the Treatment of Patients with IPF*, CHECK ORPHAN (Jan. 7, 2010), *available at*: <http://www.checkorphan.org/grid/news/treatment/fda-grants-priority-review-of-pirfenidone-nda-for-the-treatment-of-patients-with-ipf> (last visited Oct. 28, 2014); FDA, *FDA News Release: FDA Approves First Combination Pill to Treat Hepatitis C*, FDA.GOV (Oct. 10, 2014), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418365.htm> (last visited Oct. 22, 2014); FDA, *FDA News Release: FDA Approves Keytruda for Advanced Melanoma*, FDA.GOV (Sept. 4, 2014), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm412802.htm> (last visited Oct. 23, 2014); GSK, *GSK Receives FDA Approval of an Additional Promacta® (eltrombopag) Indication for Use in Patients with Severe Aplastic Anaemia (SAA) Who Have Had an Insufficient Response to Immunosuppressive Therapy (IST)*, GSK.COM (Aug. 26, 2014), *available at*: <http://www.gsk.com/en-gb/media/press-releases/2014/gsks-promacta-eltrombopag-receives-fda-approval-of-an-additional-indication/> (last visited Oct. 23, 2014); FDA, *FDA News Release: FDA Approves Imbruvica to Treat Chronic Lymphocytic Leukemia*," FDA.GOV (Feb. 12, 2014), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm385764.htm> (last visited Oct. 22, 2014); FDA, *FDA News Release: FDA Approves Zydelig for Three Types of Blood Cancers*," (July 23, 2014), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm406387.htm> (last visited Oct. 23, 2014); FDA, *FDA News Release: FDA Approves Zykadia for Late-stage Lung Cancer*, (Apr. 29, 2014), *available at*: <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm395299.htm> (last visited Oct. 22, 2014); FDA, *Drugs: Ofatumumab*, FDA.GOV, *available at*: <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm393823.htm> (last visited Oct. 22, 2014); FDA, *Drugs: Ofatumumab*, *available at*: <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm393823.htm> (last visited Oct. 22, 2014); FDA, *FDA News Release: FDA Approves Kalydeco to Treat Rare Form of Cystic Fibrosis*, FDA.GOV (Jan. 31, 2014), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm> (last visited Oct. 22, 2014); FDA, *FDA News Release: FDA Approves Solvadi for Chronic Hepatitis C*, FDA.GOV (Dec. 6, 2013), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm377888.htm> (last visited Oct. 22, 2014); FDA, *FDA News Release: FDA Approves Imbruvica for Rare Blood Cancer*, FDA.GOV (Nov. 13, 2013), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm374761.htm> (last visited Oct. 22, 2014); FDA, *FDA News Release: FDA Approves Gazyva for Chronic Lymphocytic Leukemia*, FDA.GOV (Nov. 1, 2013), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm373209.htm> (last visited Oct. 22, 2014); Sue Sutter, *Pink Sheet—Pfizer's Meningitis B Vaccine*

sponsor by permitting it to use an endpoint that is expected to occur more quickly than the true primary clinical endpoint of interest. This concrete tool can reduce the length of clinical trials, but does so through one design component. The Breakthrough Therapy designation provides for a close collaboration between the sponsor and FDA to discuss the overall design of the trials. This could potentially include Accelerated Approval and the use of a surrogate marker or intermediate clinical endpoint in trials to develop evidence to support marketing approval. But, it does not guarantee any concrete design elements or any design elements not otherwise available to any other product.

Further, because Accelerated Approval primarily benefits a sponsor by reducing the time to the endpoint of the trial, the products receiving Accelerated Approval generally address conditions with a long disease course and an extended period of time before clinical benefits can be measured.[212] The Breakthrough Therapy designation is not so limited.

Finally, FDA generally requires a sponsor to conduct post-marketing trials to confirm the relationship between the surrogate or intermediate clinical endpoint and the clinical benefit.[213] Under Accelerated Approval, FDA may withdraw approval of a drug or biological product in an accelerated manner under certain circumstances, including post-marketing trials that do not verify the expected benefit.[214] While FDA may require any new drug or biological product, including a Breakthrough Therapy product, to complete post-marketing studies, they may be required less often than for Accelerated Approval products. Thus, the Breakthrough Therapy designation potentially enables greater efficiency in the development phase of new product than does Accelerated Approval.

V. CONCLUSION

Accelerated Approval, Priority Review, Fast Track, and Breakthrough Therapy each have the potential to shorten the pre-market process. But, the Breakthrough Therapy designation may provide additional benefits to a qualifying compound above those already available through the other three expedited approval mechanisms, primarily by increasing the quantity and quality of the interaction between FDA and a sponsor. Notably, the pharmaceutical industry is embracing the new designation, outstripping FDA's expectations.[215] Yet, it remains to be seen whether FDA implements

Trumenba is CBER's First ''Breakthrough'' Approval, FOCR.ORG (Oct. 30, 2014), *available at*: <http://www.focr.org/news/pink-sheet-pfizer's-meningitis-b-vaccine-trumenba-cber's-first-'breakthrough'-approval> (last visited Nov. 5, 2014); *FDA News Release, First Vaccine Approved by FDA to Prevent Serogroup B Meningococcal Disease*, FDA.GOV (Oct. 29, 2014), *available at*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm420998.htm> (last visited Nov. 4, 2014); Pfizer, *Press Release—Pfizer Receives FDA Accelerated Approval for Trumenba® (Meningococcal Group B Vaccine) for the Prevention of Invasive Meningococcal B Disease in Adolescents and Young Adults*, PFIZER.COM (Oct. 29, 2014), *available at*: <http://www.pfizer.com/news/press-release/press-release-detail/pfizer receives_fda_accelerated_approval_for_trumenba_meningococcal_group_b_vaccine_for_the_prevention_of_invasive_meningococcal_b_disease_in_adolescents_and_young_adults> (last visited Nov. 4, 2014); Friends of Cancer Research, *Breakthrough Therapies*, FOCR.ORG, *available at*: <http://www.focr.org/breakthrough-therapies> (last visited Nov. 5, 2014). For a discussion of drug and biologic approvals under the different mechanisms, *see* Saurabh Rob Aggarwal, *A Survey of Breakthrough Therapy Designations*, 32.4 NATURE BIOTECHNOLOGY 323 (2014).

[212]Final Guidance, at 15.

[213]21 U.S.C. § 356(c)(2); 21 C.F.R. §§ 314.510. 601.41; Final Guidance, at 22. FDA may require the manufacturer to conduct a Phase 4 clinical trial after beginning to market the new drug or biological product. This is an important distinction when a new drug or biological product shows substantially greater efficacy than the standard of care or when no other treatment exists. As Roche articulated in its decision to pursue Phase 3 clinical trial of PLX4032, "with patients already begging doctors for the drug, it seemed unlikely that anyone would join a trial with only a 50-50 chance of getting PLX4032 once it was already on the market." Harmon (9/18/10), *supra* note 110. "Unless the trial was conducted before approval, it seemed, there would be no chance to get definitive data on its effectiveness." *Id.* The chance that FDA might only approve PLX4032 for a limited population, such as those who had previously tried another treatment—the population in the Phase 1 enrichment trial—further motivated Roche to conduct a pre-approval Phase 3 randomized controlled clinical trial. If Roche were unable to enroll sufficient patients for a Phase 4 clinical trial, not only might Roche be unable to definitively prove effectiveness, but also it might be unable to obtain approval to market to a larger population. Given concern over the ability to conduct a randomized controlled clinical trial *after* a drug reaches the market through the Accelerated Approval mechanism, the use of that mechanism and the likelihood of it accomplishing its goal are greatly diminished. In this circumstance, the Breakthrough mechanism does fill a gap vis-à-vis the Accelerated Approval mechanism—adding flexibility and increased coordination between FDA and a manufacturer. *Id. See also* Abigail Alliance Letter, *supra* note 110, at 8.

[214]21 U.S.C. § 356(c)(3); 21 C.F.R. §§ 321.530, 601.43; Final Guidance, at 23.

[215]Woodcock 2014, *supra* note 191, at 484.

the tools in a way that adds efficiency to the process, while maintaining the standards of safety and effectiveness. Should many of these applications qualify for the Breakthrough Therapy designation, FDA may again face a significant resource strain, which itself could undermine the overall value of the new mechanism and devalue the other mechanisms. Regardless, the Breakthrough Therapy designation is just one of many reforms needed to harmonize the current innovation ecosystem, as the PCAST Report and other articles assert.

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