

**NDA Approval Under FDCA Section 505(b)(1) Based on Effectiveness Data from One Clinical Trial**

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*“In the area of drugs, the law codifies the agency’s current practice of allowing in certain circumstances one clinical investigation as the basis for product approval. The act, however, does preserve the presumption that, as a general rule, two adequate and well-controlled studies are needed to prove the product’s safety and effectiveness.”*

FDA Backgrounder, The FDA Modernization Act of 1997 (Nov. 21, 1997).

*“The law does not seem to allow us to act on the basis of a single study without [confirmatory evidence], but we have anyway.”*

Dr. Robert Temple, FDA Center for Drug Evaluation & Research Associate Director for Medical Policy, quoted in Better Phase II Could Allow for More Single-Trial Approvals, THE PINK SHEET, Jan. 21, 2002, at 23.

For a new drug to be approved under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), the Food and Drug Administration (FDA) must find “substantial evidence” of effectiveness. 21 U.S.C. § 355(d).<sup>2</sup> Section 505(d) defines substantial evidence as evidence consisting of “adequate and well-controlled investigations.” Since 1963, FDA has interpreted the plural “investigations” in section 505(d) ordinarily to require two or more clinical trials. FDA has explained that replication is necessary to rule out bias, chance, and other problems that might undermine the integrity of study results.

In 1997, Congress amended section 505(d) explicitly to authorize FDA to find “substantial evidence” of effectiveness without data from two trials. Section 115(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA) provided:

If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence . . . .

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<sup>2</sup> A new drug must also be found “safe” within the meaning of FDCA section 505 before it can be approved. 21 U.S.C. § 355(d). Under the statute, safety is assessed using data from “adequate tests by all methods reasonably applicable,” not just clinical trials. *Id.* This analysis therefore focuses exclusively on the evidentiary standard applicable to a determination of effectiveness.

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Prior results described herein do not guarantee a similar outcome.

21 U.S.C. § 355(d). For more than ten years, therefore, FDA has had explicit statutory authority to find a new drug effective based on data from a single trial plus “confirmatory evidence.”

FDA has not issued guidance specifically addressing FDAMA section 115(a), but has issued guidance on the characteristics of a clinical trial that make it “sufficient to establish effectiveness” under section 505(d). FDA has also emphasized that reliance on data from a single trial to find effectiveness is appropriate only for a drug with an effect on mortality, irreversible morbidity, or a disease with potentially serious outcomes, so that confirmation of the results in an additional trial would be practically or ethically impossible. FDA has further asserted that finding effectiveness based on data from a single trial would generally not be appropriate for a drug that provides only symptomatic benefit.

FDA had approved drugs on the basis of one trial even before FDAMA was enacted. Indeed, portions of the legislative history for section 115(a) indicate that it primarily codified FDA’s practice regarding approval based on a single clinical trial and preserved the agency’s discretion to determine when such approvals would be appropriate. Some of the legislative history and comments of legislators both during and after enactment, however, suggest that FDAMA was intended to change FDA’s practice and make approval based on one clinical trial more routine. In particular, a House report on the legislation states that FDAMA section 115(a) was intended to apply to all drugs, including those that are not for serious or life-threatening diseases. The agency nevertheless has asserted that, as a general rule, data from two clinical trials are still necessary to demonstrate effectiveness under section 505.

To evaluate the frequency with which FDA approves new drugs based on effectiveness data from one clinical trial, we researched the relevant statutory background and FDA guidance, and also reviewed new drug approvals since FDAMA was enacted to determine how many were based on effectiveness data from one clinical trial. Out of 394 products approved from 1998 to 2011, 30 were approved on the basis of effectiveness data from only one clinical trial.

## **I. STATUTORY BACKGROUND**

### **A. THE SECTION 505(d) REQUIREMENT FOR “SUBSTANTIAL EVIDENCE” OF EFFECTIVENESS**

FDA was first given explicit statutory authority to review new drugs for effectiveness with the Drug Amendments of 1962. See Pub. L. No. 87-781, § 102, 76 Stat. 780, 781 (1962). As amended by this legislation, section 505(d) of the FDCA requires FDA to find “substantial evidence” of a new drug’s effectiveness before it can be marketed. See 21 U.S.C. § 355(d). The statute defines “substantial evidence” as:

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.

Id. FDA has defined the characteristics of “adequate and well-controlled” investigations, which include “a clear statement of the objectives of the investigation” and a description of the proposed and actual methods of analysis; “a design that permits a valid comparison with a control”; methods to assure that appropriate subjects are selected; and methods to minimize bias. See 21 C.F.R. § 314.126(b).

**B. FDA’S INTERPRETATION OF SECTION 505(d) “ORDINARILY” TO REQUIRE DATA FROM TWO OR MORE TRIALS**

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In the first regulations promulgated under amended section 505(d), FDA interpreted the provision “ordinarily” to require data from two or more clinical trials to show efficacy:

Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintain [sic] adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls.

28 Fed. Reg. 6377, 6378 (June 20, 1963) (then codified at 21 C.F.R. § 130.4(c)(1)(ii)) (emphasis added).<sup>3</sup>

In congressional testimony in the 1970s, FDA’s Chief Counsel construed this language to mean that two clinical trials were ordinarily required, but also stated that “two clinical trials is not a rigid requirement.” Use of Advisory Committees by the Food and Drug Administration: Hearings Before the Subcomm. on Intergovernmental Relations of the H. Comm. on Gov’t Operations, 93d Cong. 122 (1974) (statement of Peter Barton Hutt, Chief Counsel, FDA). Similarly, when FDA revised its procedures for hearings available to applicants whose new drug applications (NDAs) were denied, it provided that hearings would be denied on a summary basis only when “no adequate and well-controlled clinical investigations . . . showing effectiveness have been identified.” 39 Fed. Reg. 9750, 9763 (Mar. 13, 1974) (emphasis added) (then codified at 21 C.F.R. § 130.14(g)(1)); see also 21 C.F.R. § 314.200(g)(1) (current regulation).

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<sup>3</sup> This language remained part of the regulations when they were reorganized and renumbered in 1974, but was eliminated when they were revised as part of the “NDA rewrite” in 1985. See 39 Fed. Reg. 11680, 11718 (Mar. 29, 1974) (renumbering 21 C.F.R. § 130.4 as § 314.1); 50 Fed. Reg. 7452, 7494 (Feb. 22, 1985) (renumbering § 314.1 as § 314.50). FDA might have construed the language referring to “more than one . . . investigator” to require more than one trial because most clinical trials at the time involved only one investigator. See FDA, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998) [hereinafter Clinical Evidence of Effectiveness Guidance], available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf>.

At the same time, however, FDA indicated that it might change its policy to require data from two trials in all cases. The preamble to the revised hearing procedure regulations explained:

The Commissioner is considering whether the regulations should be changed to require, in all instances, at least two studies by independent investigators . . . before a drug may be regarded as proved effective. Pending any such requirement, the submission of a single study showing effectiveness . . . will be sufficient to preclude immediate summary judgment.

39 Fed. Reg. at 9755 (emphasis added).

In 1979, FDA referred to plural “investigations” in section 505(d) as the statutory basis for its general “requirement” of data from at least two trials to demonstrate effectiveness. 44 Fed. Reg. 51512, 51518 (Aug. 31, 1979). This reference came in the context of the agency’s ruling that the nonprescription drug Benylin (diphenhydramine hydrochloride) had not been shown to be effective in part because the drug manufacturer had not submitted data from two clinical trials in the target population. *Id.* at 51516-20. Since the Benylin order was issued, FDA has continued to refer to the term “investigations” as the source of its authority to require data from two or more trials to demonstrate effectiveness. *See, e.g., The Regulation of New Drugs by the Food and Drug Administration: The New Drug Review Process: Hearings Before the Subcomm. on Intergovernmental Relations of the H. Comm. on Gov’t Operations, 97th Cong. 437 (1982) [hereinafter The Regulation of New Drugs by the FDA] (statement submitted by Dr. Arthur Hayes, Comm’r, FDA); Clinical Evidence of Effectiveness Guidance, supra note 3, at 3.<sup>4</sup>*

FDA’s position was expressly grounded in the principle of replication. In the Benylin order, FDA stated that its policy was “founded upon a basic proposition of science that an experiment must be reproducible in order for the results to be considered valid.” *See* 44 Fed. Reg. at 51518. In 1982, FDA Commissioner Dr. Arthur Hayes appeared before the House of Representatives and submitted a statement that further described this rationale:

As a general rule, FDA policy requires at least two adequate and well-controlled studies to support the effectiveness of an approved indication for a new drug. This policy is based on the established scientific principle that experimental data usually need to be replicated in order to be credible. Replication helps assure that the experimental findings are not simply attributable to chance, and are not dependent upon particular conditions imposed by a particular experimental situation or investigator.

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<sup>4</sup> We have identified no reported case involving the validity of FDA’s position that data from two trials are generally required to support new drug approval under FDCA section 505. Several cases have affirmed other aspects of FDA’s interpretation and application of the FDCA’s standard for effectiveness. *See, e.g., Weinberger v. Hynson, Westcott & Dunning Inc.*, 412 U.S. 609, 617-19 (1973) (upholding FDA’s regulations defining “adequate and well-controlled investigations”); *Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 154-155 (3d Cir. 1986) (“The Act does not define ‘effectiveness,’ thus leaving the task of deciding how effective a new drug must be to the agency to which Congress delegated enforcement. . . . The Commissioner’s interpretation of the statute as requiring a showing of clinical significance, rather than merely statistical significance, is persuasive . . .”).

The Regulation of New Drugs by the FDA, *supra*, at 437. Since then, FDA has often referred to the need for independent substantiation of experimental results (sometimes as a principle of “good science”) as the reason that data from two or more clinical trials are typically required to demonstrate effectiveness. *See, e.g.*, FDA, Guideline for the Format and Content of the Clinical and Statistical Sections of an Application 15 (July 1988) [hereinafter Clinical and Statistical Guidance]; 57 Fed. Reg. 58942, 58948 (Dec. 11, 1992); 60 Fed. Reg. 39180, 39181 (Aug. 1, 1995); Revitalizing New Product Development from Clinical Trials through FDA Review: Hearing Before the S. Comm. on Labor and Human Resources, 104th Cong. 13, 30 (1996) (testimony of Dr. David Kessler, Comm’r, FDA, and Dr. Janet Woodcock, Dir., Ctr. for Drug Evaluation and Research (CDER), FDA); Clinical Evidence of Effectiveness Guidance, *supra* note 3, at 4.

### **C. FDA’S ARTICULATION OF CIRCUMSTANCES IN WHICH DATA FROM ONE TRIAL ARE SUFFICIENT**

In the 1980s and early 1990s, FDA clarified the circumstances in which it would find data from one clinical trial sufficient to demonstrate effectiveness. According to a statement submitted by Commissioner Hayes to the House of Representatives in 1982:

The Agency does not believe that the law requires more than one study in every conceivable case . . . and FDA has recognized the narrow exceptions to a strict two-study policy when compelling circumstances arise. For example, last November FDA approved the drug timolol for the prevention of cardiovascular death in patients who had recovered from acute myocardial infarction (heart attack). In that instance, the Agency was presented with data from a large multi-center but, nonetheless, single trial. The study appeared to be well conducted, involved almost 2,000 patients, and had clear cut results which were highly statistically significant. Because the drug was intended to prevent death, and because ethical problems would have been presented had additional controlled studies been required, FDA believed the available data from the single study constituted substantial evidence of effectiveness for the indication.<sup>5</sup>

The Regulation of New Drugs by the FDA, *supra*, at 437; *see also* Clinical and Statistical Guidance, *supra*, at 15 (the timolol trial demonstrated a “major effect on mortality” and “was very persuasive because of excellent design, minimal or no problems during execution of the study, and a high degree of statistical significance”); Clinical Evidence of Effectiveness Guidance, *supra* note 3, at 12 (the timolol trial was a “particularly persuasive (low p-value), internally consistent, multicenter study that demonstrated a major effect on mortality and reinfarction rate” and “[f]or ethical reasons, . . . was considered unrepeatabe”).

FDA subsequently rejected a request to find a drug effective under section 505

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<sup>5</sup> Commissioner Hayes appears to have been referring to the approval of Blocadren (timolol maleate) in November 1981. It appears, however, that another timolol product—Timoptic (timolol maleate)—had already been approved in August 1978, so that there might have been more clinical trial data demonstrating timolol’s effectiveness than are referred to here. *See* FDA, Drugs@FDA, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>.

based on data from one trial where the drug was intended for relief of symptoms. In a 1985 decision withdrawing NDA approvals for a number of oral proteolytic enzyme drugs, FDA stated:

There have been a few drugs approved on the basis of one adequate and well-controlled study. . . . [T]hese approvals have been limited to situations where (1) the disease is very rare and it is extremely difficult to obtain subjects for two studies; (2) the disease process is expensive to study experimentally; (3) the study conducted is very large and multi-centered; and (4) the disease is rapidly fatal and there is no alternative therapy.

Commissioner's Final Decision Withdrawing Approval of New Drug Applications for Five Oral Proteolytic Enzymes, FDA Docket No. 75N-0139, slip op. at 24 (May 30, 1985). FDA ruled that there was "no reason to relax the two study requirement" for the drugs at issue because they were labeled to treat inflammation, edema, ecchymosis (bruising), and pain, which conditions were "clearly not rare, rapidly fatal, or expensive to study," and because no trial submitted was large or multi-centered. Id.; see also Deprol®; Final Decision Following Formal Evidentiary Public Hearing, 58 Fed. Reg. 50929, 50936 (Sept. 29, 1993); Cyclospasmol®; Final Decision on Proposed Withdrawal of Approval of New Drug Application, 61 Fed. Reg. 64099, 64101 (Dec. 3, 1996).

Public scrutiny of FDA's approach to the drug approval process increased around this time, prompted in part by concerns that the agency was approving drugs for AIDS and cancer too slowly. See generally S. REP. NO. 105-43, at 6-10 (1997). FDA responded with internal reforms, including regulations allowing "accelerated approval" of certain new drugs for serious or life-threatening illnesses. See 57 Fed. Reg. at 58942. In the preamble to those regulations, FDA specifically addressed the situations in which effectiveness could be established on the basis of data from one trial. FDA reiterated that the FDCA and "good science" typically "require" at least two trials, but noted that drugs had been approved on the basis of one trial in circumstances like those described by Commissioner Hayes in 1982. Specifically, FDA noted that approval based on one trial had occurred where "the study was of excellent design, showed a high degree of statistical significance, involved multiple study centers, and showed some evidence of internal replicability, e.g., similar effects in major study subsets." Id. at 58948.

FDA made a similar statement three years later in response to "the assertion, by some industry officials, that the act not be interpreted as requiring multiple clinical studies when one 'pivotal' study could suffice. 60 Fed. Reg. at 39181. FDA stated that replication of results could be accomplished "in some instances . . . within one large, well-designed, multi-center study," but also emphasized that "this approach can be successful only when results are strong. . . . A statistically marginal result, even in a very large study, cannot provide convincing evidence without replication." Id. FDA again cited timolol as an example of a drug approved on the basis of one trial, as well as dornase alfa for the treatment of cystic fibrosis and zidovudine (commonly referred to as AZT) for AIDS. Id.

Throughout this period, FDA continued to emphasize that data from two trials would "ordinarily" be required. See id.; Clinical and Statistical Guidance, supra, at 15. In the 1988 Clinical and Statistical Guidance, FDA stated that data from a "particularly persuasive" trial could be accepted as evidence of effectiveness in some cases, but such cases "are unusual

and an applicant seeking to invoke these exceptional circumstances must provide strong support for this position.” Clinical and Statistical Guidance, supra, at 15.

**D. ENACTMENT OF FDAMA SECTION 115(a)**

**1. Consideration of FDA Reform Legislation in the 104th Congress**

Industry groups and others sought comprehensive legislative reform in the mid-1990s and proposed, among other things, amendments to FDCA section 505(d) expressly to permit new drug approval on the basis of one clinical trial. See generally Formulary Decisions, DUR Results and Shareholder Communications Would Be Beyond FDA Reach in BIO Draft Bill for FDA Reform Submitted to Sen. Kassebaum, THE PINK SHEET, Apr. 24, 1995, at 3; First Republican FDA Reform Bill Resembles PhRMA Proposal, THE PINK SHEET, July 3, 1995, at 23; FDA Clarification of Efficacy Requirements Falls Short of “Re-Go”, THE PINK SHEET, Nov. 6, 1995, at 7.

Bills based on these proposals were introduced in both the House of Representatives and the Senate during the 104th Congress. Two of the bills would have added a sentence to the end of section 505(d) providing that substantial evidence could consist of data from “one well-controlled clinical investigation . . . and confirmatory evidence.” Food and Drug Administration Performance and Accountability Act of 1995, S. 1447, 104th Cong., 1st Sess., § 602 (1995); Life Extending and Life Saving Drug Act, H.R. 1995, 104th Cong., 1st Sess., § 6 (1995). According to the report on the Senate bill, this language was intended to provide FDA with “statutory flexibility” and to “confirm[] the current FDA interpretation that substantial evidence may, as appropriate, consist of data from one adequate and well-controlled clinical investigation and confirmatory evidence.” S. REP. NO. 104-284, at 4, 38 (1996).

One of the House bills would have changed the definition of “substantial evidence” to mean evidence from “one or more” clinical trials. See Drug and Biological Products Reform Act of 1996, H.R. 3199, 104th Cong., 2d Sess., § 5(1) (1996). The bill, as well as the Senate bill, would have also given FDA discretion to waive the requirement for adequate and well-controlled investigations altogether. Id. § 5(2); S. 1447 § 602.

In testimony before the Senate and the House, Dr. Carl Peck, former CDER Director, stated that FDA had made a “logical and appropriate advance . . . in response to public epidemics of life-threatening and rare diseases” by approving drugs for AIDS, cancer, and other serious or life-threatening conditions on the basis of “fewer trials and more extensive evaluation of all of the information contained in the NDA.” Revitalizing New Product Development from Clinical Trials through FDA Review, supra, at 155-56 (prepared statement submitted by Carl Peck, MD, Dir., CDDS, Georgetown Univ. Med. Ctr.); see also FDA Reform Legislation: Hearing Before the Subcomm. on Health & Env’t of the H. Comm. on Commerce, 104th Cong. 304-05 (1996) (same). Dr. Peck also asserted, however, that these actions had generated controversy and that FDA needed “statutory authority expressing the will of Congress to ratify non-traditional procedures.” See Revitalizing New Product Development from Clinical Trials through FDA Review, supra, at 155. According to him, a rigid requirement of two trials was “scientifically out of place” because the need to develop drugs to treat “desperate conditions” was as important as protecting the public against possibly harmful drugs. Id. at 156.

FDA expressed concern over the “one or more” language. In a prepared statement, FDA Commissioner Kessler wrote:

The Agency’s current presumption is that, for pharmaceuticals, ordinarily, replicated evidence is expected, but FDA, in particular circumstances (i.e., where a single study offers internal evidence of consistency of the product’s effectiveness), may rely on a single adequate and well-controlled trial. The [proposed legislation], on its face, does not appear to change that presumption. However, we understand that its purpose is to create a presumption that one adequate and well controlled trial will be sufficient for purposes of approving a new drug.

The Agency strongly opposes a change that would eliminate the replication requirement for drug approval. It is a basic tenet of science that data can be considered reliable only if, when an experiment is run for the second time, it produces the same findings and observations that it produced the first time. The American public deserves to receive drugs that have been tested according to well accepted scientific principles.

FDA Reform Legislation, supra, at 36-37.

In testimony, Dr. Kessler emphasized that “the real issue is whether there is reproducibility in the trial. . . . [T]he issue is not one or two, because trials today are developed in complex ways, and they are multicentered.” Revitalizing New Product Development from Clinical Trials through FDA Review, supra, at 13 (testimony of Dr. Kessler); see also id. at 30 (testimony of Dr. Woodcock) (“Efficacy can be proven by a single trial in some cases where there is a definitive result and where it is replicated across many centers.”). One representative from a patient advocacy organization also testified that FDA’s current policy was sufficient and that a change to the statutory standard was unnecessary. See id. at 76, 179-80 (testimony of and prepared statement submitted by Derek Link, Assistant Dir., Gay Men’s Health Crisis).

Ultimately, none of the proposed legislation passed in the 104th Congress.

## **2. Passage of FDA Reform Legislation in the 105th Congress**

Industry and Congress continued to show interest in broad-ranging agency reform during the 105th Congress, including codification of the agency’s authority to approve new drugs on the basis of efficacy data from one trial. See PhRMA FDA Reform Proposal for 1997 Drops Summary Data & Default Approval Provisions, THE PINK SHEET, Jan. 7, 1997, at 3; PhRMA and BIO Continue to Seek Independence of FDA Advisory Committees in Reform Proposal, THE PINK SHEET, Apr. 14, 1997, at 5.

In Congressional hearings, an industry representative took the position that FDA routinely accepted data from one trial with adequate supporting evidence for approval of biological products, but required two trials for drugs, and that there was “no justification in science or logic for this difference.”<sup>6</sup> Addressing the FDA’s Performance, Efficiency, and Use of

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<sup>6</sup> In response to this criticism, FDA employees have asserted that the standards of approval for both



Resources: Hearings Before the S. Comm. on Labor & Human Resources, 105th Cong. 147, 186 (1997) (testimony of and prepared statement submitted by Gordon Binder, Chairman & CEO, Amgen Inc.). He acknowledged that the agency had recently issued a draft guidance on the issue, but also stated: “FDA still generally interprets the law to require two or more pivotal Phase III studies to provide substantial evidence of effectiveness, regardless of the scientific adequacy of the data.” Addressing the FDA’s Performance, Efficiency, and Use of Resources, *supra*, at 187.

New bills were then introduced in the House and Senate that again included provisions to amend section 505(d). See Drug and Biological Products Modernization Act of 1997, H.R. 1411, 105th Cong. § 5(1) (Apr. 23, 1997); Food and Drug Administration Modernization and Accountability Act of 1997, S. 830, 105th Cong. § 409(b) (June 5, 1997). As originally introduced, the Senate bill, which was titled the Food and Drug Administration Modernization and Accountability Act of 1997 (FDAMAA), would have added a sentence at the end of section 505(d) providing:

If the Secretary determines that only one investigation is required, then the Secretary may require appropriate supporting scientific evidence obtained prior to or after such investigation. The Secretary shall establish a mechanism to ensure the fair and consistent application of this provision to new drugs.

See S. 830 § 409(b).

The Clinton Administration, Ranking Minority Member of the Senate Committee on Labor and Human Resources Edward Kennedy, and patient groups expressed concern that this language would overly weaken FDA’s standard for effectiveness by diluting its requirement for confirmatory trials. See “Substantial Evidence” Definition Likely to Be Debated at Labor Cmte. FDA Reform Mark-Up June 18, THE PINK SHEET, June 16, 1997, at 3 [hereinafter “Substantial Evidence” Definition Likely to Be Debated]. Senator Kennedy therefore proposed language intended to retain “two clinical investigations as the presumptive evidentiary standard” while clarifying the opportunity for “flexibility” in approving new drugs on the basis of one trial. Id. (quoting committee summary of proposed amendments).

In contrast, Committee Chairman James Jeffords proposed a substitute that would have changed the definition of “substantial evidence” to require “one or more” clinical investigations, with “appropriate supporting scientific evidence” also required at the agency’s discretion. Id. Committee member Bill Frist also supported an amendment intended to discourage the presumption that multiple trials are necessary for new drug approval. Id.

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drugs and biological products are the same. In 1998, Dr. Woodcock asserted that “the perception that CBER products might require only a single trial comes from the fact that many of these are very serious or life threatening diseases . . . or perhaps they have been vaccines which is a very different situation.” See NIH/FDA Clinical Trials Database to Include Industry Trials by 2000—FDAer, THE PINK SHEET, Sept. 21, 1998, at 13 (omission in original) (also quoting Rebecca Devine, PhD, Assoc. Dir. for Policy, Ctr. for Biologics Evaluation and Research (CBER)); see also Clinical Evidence of Effectiveness Guidance, *supra* note 3, at 11 (“In the case of preventative vaccines, one adequate and well-controlled clinical trial may be supported by compelling animal challenge/protection models, human serological data, passive antibody data, or pathogenesis information.”).

In response, Secretary of Health and Human Services Donna Shalala wrote to Chairman Jeffords, expressing her concern that his proposed language “would undermine the public health protections that the American people now enjoy, by . . . lowering the review standard for marketing approval.” Letter from Donna E. Shalala, Sec’y of Health & Human Servs., to Hon. James M. Jeffords, Chairman, Comm. on Labor & Human Res., U.S. Senate (June 11, 1997), available at 143 CONG. REC. S9817 (1997).

Following committee debate, a revised version of the legislation was referred to the Senate, which included language similar to that supported by Senator Frist:

Substantial evidence may, as appropriate, consist of data from 1 adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation), if the Secretary determines, based on relevant science, that such data and evidence are sufficient to establish effectiveness.

See S. 830, 105th Cong. § 409(b) (July 1, 1997); “Substantial Evidence” Definition Likely to Be Debated, supra. When introducing the amended bill, Chairman Jeffords explained that the change in language had been made to address Secretary Shalala’s concerns. He said:

Key changes have been made . . . to assure that there is not a presumption of less than two well-controlled and adequate investigations, while guarding against the rote requirement of two studies. We made it very clear you don’t have to do two, although it is quite acceptable for you to do two, but you shouldn’t look at as being required. It is not necessary.

143 CONG. REC. at S8163; see also id. at S8879, S8894-95 (statements of Sen. Jeffords) (“FDA would retain total discretion to require a sufficient number of trials to show safety and efficacy.”). The trade press also reported that the new language was adopted at Kennedy’s insistence that FDA retain discretion to determine when one trial is sufficient. HHS Clinical Trial Databank Would Exempt Industry from Disclosures Interfering with Enrollment Under Dodd Amendment, THE PINK SHEET, June 23, 1997, at 13.

In the report accompanying the revised legislation, the committee described the new language as a “clarification” that “confirmed” FDA’s current interpretation of the substantial evidence requirement:

The committee believes that the science and practice of drug development and clinical evaluation have evolved significantly in the past 35 years, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. Modern clinical trial design often utilizes multiple investigators, multiple study sites, randomization, large enrollment numbers, statistical power, controls, clinical endpoints and other mechanisms that can demonstrate the reproducibility underlying FDA’s request for two or more separate studies for each new drug and/or indication. Therefore, it is the

committee's understanding that independent substantiation is the scientific basis underlying FDA's substantial evidence requirements.

The FDA usually interprets the requirement to demonstrate substantial evidence of effectiveness to require two adequate and well-controlled clinical studies, but has shown flexibility and approved some drugs on the basis of one adequate and well-controlled clinical study. Given scientific advancement in the past 35 years and the promise of further advancement, it is the committee's belief that the structure of a particular clinical protocol and the quality of the data underlying a new drug application should guide FDA's substantiation requirements. Therefore, the legislation confirms the current FDA interpretation that substantial evidence may, as appropriate, when the Secretary determines, based on relevant science, consist of data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained either before or after the investigation).

S. REP. NO. 105-43, at 30; see also id. at 82 ("Section 409 . . . add[s] a new sentence to 505(d) giving the Secretary discretion to approve drugs under certain conditions on the basis of one adequate and well-controlled investigation with confirmatory evidence . . .").

Committee member Patty Murray expressed concern about the provision in an additional view provided in the report:

Despite the many positive improvements, the current draft of the pending legislation has some serious flaws and I am concerned that in an effort to reform and revitalize the FDA, we weaken their role as a public health agency. Despite modifications, I am still concerned about some of the proposed changes on substantial evidenc [sic]—we simply cannot and should not act to limit the ability of the FDA to require comprehensive clinical trials. I believe that the current Guidance Document that governs FDA practices does offer each investigator the "guidance" necessary to determine the number of clinical trials necessary—I am still not convinced that the proposal before us today will actually clarify, but rather limit the ability of FDA to require two trials in order to replicate science.

S. REP. NO. 105-43, at 105.

Agreement on the provision was eventually reached and the bill passed the Senate. See 143 CONG. REC. at S9156 (statement of Sen. Dodd); id. at S9850 (rollcall vote); S. 830, 105th Cong. § 408(b) (Sept. 24, 1997). Shortly thereafter, the House then replaced the text of the bill with that of its own version and passed the bill. See 143 CONG. REC. at H8482, H8500. The House version included new language to be added to the end of section 505(d):

If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and

confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

Food and Drug Administration Regulatory Modernization Act of 1997, S. 830, 105th Cong. § 110(a) (Oct. 7, 1997).

In the report accompanying the bill, the House Committee on Commerce explained that this language was largely intended to “codify” FDA’s current practice. The report also emphasized, however, that FDA’s approval standard should be the same for drugs that “are and are not for serious and life-threatening disease”:

[Revised section 505(d)] authorizes the FDA, in its discretion, to approve an NDA on the basis of one adequate and well-controlled clinical investigation and confirmatory evidence . . . . The FDA will also retain its inherent administrative discretion to waive this requirement completely, as it has done in the past, where it would be unethical or unnecessary.

The FDA has itself recognized in recent guidance that substantial evidence of effectiveness may consist of one adequate and well-controlled investigation and confirmatory evidence consisting of earlier clinical trials, pharmacokinetic data, or other appropriate scientific studies. The Committee agrees that the quality of the data and information available about a drug, rather than the number of studies performed, should determine the standard for FDA approval of a new drug. Authorizing the FDA to approve a drug on the basis of one well-controlled investigation will reduce the number of patients required to undergo clinical trials and the possibility of receiving a placebo; reduce the cost of drug development, and thus, the ultimate cost of a new drug to the public; reduce the total time needed to obtain FDA approval of a new drug; increase the number of new drugs that can be investigated; and thus speed the development and availability of important new drugs to help improve the public health.

The codification applies to all drugs, including those that are and are not for serious and life-threatening disease. Each disease is important to those who suffer from it, and every disease has a debilitating effect both on the patient and on the family and caretakers. This statutory standard will assure that the rights of all patients are recognized in the development of new drugs intended to alleviate their suffering. There is no scientific or public health basis for imposing different standards for approval of drugs for different categories of diseases.

H.R. REP. NO. 105-310, at 67-68 (1997) (emphasis added).

The differences between the House and Senate versions were then resolved in conference. No additional changes were made to the proposed language to be added to

section 505(d), and there was no further reference to the provision in the conference report. See H.R. REP. NO. 105-399 (1997). The language introduced in the House became section 115(a) of the final version approved by both houses and signed into law by President Clinton in November 2007. See Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 115(a), 111 Stat. 2296, 2313 (1997).

### **3. Statements of Legislators After Enactment**

In contrast to the Senate and House reports, Senator Jeffords said several months after FDAMA was passed that section 115(a) was intended to change agency practice and to make acceptance of data from a single clinical trial for approval routine. According to the trade press, he said, “We expect that FDA will move away from the rote assumption that every product application must have two clinical trials. . . . [The message of the FDAMA provision] must be reflected by a change in the day-to-day functioning of the agency.” Single Pivotal Trial Provides Adequate Approval Basis—Jeffords, THE PINK SHEET, June 15, 1998, at 24.

Similarly, several years after FDAMA was passed, Representative Richard Burr wrote that FDA had not implemented section 115(a) aggressively enough. He wrote that FDA should “intensify implementation” of the provision, noting that “there continues to be a lack of consistency between and within FDA centers regarding the definition of confirmatory evidence as it relates to single clinical trial approvals. The lack of consistency leads to mixed messages to the industry which in turn dulls the goals of Section 115(a).” See Burr Criticizes FDA for Not Using Single Trials to Approve Drugs, FDA WEEK, Jan. 18, 2002; Five Years After FDAMA, Experts Still Debate Single Trial Issue, FDA WEEK, Jan. 18, 2002.

## **II. FDA GUIDANCE**

Just before the FDA reform legislation was introduced in the 105th Congress, FDA had issued a draft guidance for industry titled, “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.” See 62 Fed. Reg. 13650 (Mar. 21, 1997). The draft guidance identified characteristics of a single trial that could make it sufficient to demonstrate effectiveness, similar to those articulated by Commissioners Hayes and Kessler in their congressional testimony in 1982 and 1996. The four characteristics were: large size with a multicenter design; multiple “studies” in a single study (such as prospective stratifications or identified analytic subsets based on variables such as disease severity, geographic residence, or demographic characteristics); use of multiple endpoints involving beneficial but different effects; and statistically very powerful findings. FDA, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products 13-15 (Draft March 1997), available at <http://web.archive.org/web/19970505100418/http://www.fda.gov/cder/guidance/evidence.pdf>. The guidance also noted that reliance on a single study would generally be limited to situations involving an effect on mortality or irreversible morbidity, or prevention of a disease with potentially serious outcomes, such that confirmation of the results in a second trial would be ethically difficult or impossible. Id. at 13.

Shortly after FDAMA section 115(a) became law, FDA finalized the guidance. See 63 Fed. Reg. 27093 (May 15, 1998). In the guidance, FDA reiterated that section 505(d) originally was intended to require data from at least two adequate and well-controlled trials and

reaffirmed that it had relied on one trial to support approval “generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.” Clinical Evidence of Effectiveness Guidance, supra note 3, at 3.

The guidance also states that the “usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results.” Id. at 4. It also lists several problems with clinical trials that are addressed by independent substantiation:

- Unanticipated, undetected, systematic biases that might lead to flawed conclusions;
- Inherent variability in biological systems that might produce a positive trial result by chance alone;
- Site- or investigator-specific factors such as disease definition, concomitant treatment, and diet that might lead to results that are not generalizable to the intended population; and
- Rare instances of scientific fraud.

Id. at 4-5. The guidance recognizes that statistical, methodological, and other safeguards can mitigate these problems, but asserts that such safeguards are “often inadequate” to address them in a single trial. Id. at 5. “Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.” Id. The guidance also provides that “replication” might not be the best term for the type of substantiation needed because “[p]recise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design.” Id.

The guidance also recognizes, however, that the “science and practice of drug development and clinical evaluation have evolved significantly since the effectiveness requirement for drugs was established, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases.” Id. at 2. The guidance specifically addressed the situation “in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a new drug is effective.” Id. at 6. FDA noted that “reliance on a single study of a given use . . . leaves little room for study imperfections or contradictory (non-supportive) information. In all cases [addressed by the guidance], it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and the results reflect a clear prior hypothesis documented in the protocol.” Id.

Like the draft, the final guidance identifies several characteristics of a single trial

that can make it sufficient to demonstrate effectiveness. The final guidance expands on the list of characteristics to include five instead of four:

- Large size and multicenter design with (1) no single site providing an unusually large fraction of patients, and (2) no single investigator or site disproportionately responsible for the favorable effect seen;
- Consistency across key patient subsets, such as study populations that differ with respect to prior therapy, disease stage, age, gender, or race;
- Multiple studies in a single study, such as separate demonstrations of drug effectiveness as monotherapy and in combination with another drug;<sup>7</sup>
- Use of multiple, important, prospectively identified primary or secondary endpoints, each representing a beneficial but different effect; and
- Statistically very persuasive findings.

Id. at 13-15. The guidance emphasizes that no one of these characteristics is necessarily determinative, but the presence of one or more in a trial might make it adequate to support an effectiveness claim. Id. at 13.

Also like the draft guidance, the final guidance emphasizes that reliance on a single trial is generally appropriate in situations involving mortality, irreversible morbidity, or a disease with a potentially serious outcome. The final guidance also states that approval based on data from a single trial would generally not be appropriate for a drug that provides only symptomatic benefit:

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparable persuasive study. For this reason, reliance on 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. For example, sequential repetition of strongly positive trials that demonstrated a decrease in post-infarction mortality, prevention of osteoporotic fractures, or prevention of pertussis would present

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<sup>7</sup> Another FDA guidance notes that dose-response studies—which allow observations of benefits and risks at different doses—“can, in some cases, be particularly convincing and can include elements of internal consistency that, depending on the size of the study and outcome, can allow reliance on a single clinical efficacy study as evidence of effectiveness.” FDA, Guidance for Industry: Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications 4 (April 2003), [available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf).

significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

Id. The guidance also states that reliance on a single trial might not be appropriate when other data suggest that the drug is not effective. Id. at 15-16.

More recently FDA issued a draft guidance that specifically addresses when a single “non-inferiority” trial—a trial intended to show that a new treatment is not inferior to an active control—may be adequate to demonstrate effectiveness. Consistent with FDA’s general guidance, the draft notes that two or more non-inferiority trials will “usually” be necessary to support effectiveness. But, “[w]hen the trials needed are very large (to have adequate statistical power) . . . this may become a significant problem and it is worth considering what might make a single trial persuasive.” FDA, Guidance for Industry: Non-Inferiority Clinical Trials 14 (Draft Mar. 2010) available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf>. According to the draft, a single trial may be adequate where there is sufficient prior information about the new drug, or the trial generates statistically persuasive results. With respect to the first of these considerations, the draft guidance states that a single trial “might” be acceptable if the new drug is pharmacologically similar to the active control, there is a “very persuasive” biomarker confirming similar activity of the drug, or the drug has been shown to be effective in closely related clinical setting or related subpopulations (such as pediatric versus adult patients). With respect to the second consideration, a non-inferiority trial can be statistically persuasive if, for example, the new drug’s effectiveness is shown to be very close to or superior to that of the active control. Id. at 14-15, 38-39.

For two specific types of drugs, FDA has indicated that one trial might be more routinely used to obtain approval: cancer drugs and certain antimicrobial drugs. For cancer, FDA’s Oncologic Drug Products Division Director Dr. Richard Pazdur has said that one trial is “generally” used as a basis for approval.<sup>8</sup> Oncologic Accelerated Approval Best Based on Pivotal Trial Interim Analysis, THE PINK SHEET, June 26, 2006 (also noting that one trial in the oncology context “really represents multiple trials because it does usually have multiple endpoints” such as survival, time-to-progression, and response rate); see also Casodex SNDA “Not Approvable”, THE PINK SHEET, June 24, 2002, at 7 (attributing to Dr. Pazdur statement that approval based on one global trial is the ultimate goal for oncology). For antimicrobial drugs to treat streptococcal infections, FDA has issued a draft guidance stating, “A statistically adequate and well-controlled multicenter trial should be performed establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product).” FDA, Guidance for Industry: Streptococcal Pharyngitis and Tonsillitis—Developing Antimicrobial Drugs for Treatment 2-3 (Draft, July 1998), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071182.pdf>. FDA’s Anti-Infective Drugs Advisory Committee has also stated that sponsors of such drugs should be required to conduct only one trial if they use penicillin as the

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<sup>8</sup> FDA has also issued guidance on when data from a single clinical trial may support supplemental approvals for cancer drugs. See FDA, Guidance for Industry: FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products 4-6 (Dec. 1998), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071657.pdf>



comparator agent. See Strep Pharyngitis Drugs Should Be Compared to Penicillin—FDA Cmte., THE PINK SHEET, Aug. 10, 1998, at 23.

### III. REVIEW OF PRODUCTS APPROVED BY FDA FROM 1998 TO 2011

To evaluate FDA's actual practice of approving new drugs based on effectiveness data from one clinical trial, we reviewed the summary basis of approval (SBA) documents for all new drugs approved by FDA from 1998 to 2011.<sup>9</sup> Of 394 products approved via NDAs and biologics license applications (BLAs), we identified 30 that were approved pursuant to FDCA section 505(b)(1) or section 351 of the Public Health Services Act, 42 U.S.C. § 262(a), based on effectiveness data from only one trial.<sup>10</sup> The attached chart provides additional details regarding these 30 "one-trial" products.

We identified these one-trial products by first reviewing the FDA-approved labeling for all NDAs for new molecular entities (NMEs) and all BLAs approved during the specified period, with the exception of blood processing products, diagnostic products, and vaccines.<sup>11</sup> For any products that included a description of only one clinical trial in the Clinical Studies section of the approved labeling, we then reviewed the SBA documents to confirm whether FDA's rationale for approval included consideration of additional trials. Two products approved during this period were not reviewed because the originally-approved labeling and SBA documents are not available on FDA's website.<sup>12</sup>

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<sup>9</sup> The summary basis of approval (SBA) documents for Pulmozyme (dornase alfa) and Retrovir (zidovudine) have not been reviewed because they fall outside the period covered by this analysis. Contemporaneous reports indicate that Retrovir was approved based on the preliminary results of a single, phase II clinical trial that was stopped after demonstrating a dramatic reduction in deaths due to AIDS-related *pneumocystis carinii* pneumonia: 16 deaths in the placebo group compared to 1 in the treatment group. See Burroughs Wellcome's AZT to Be Standard Test Drug for AIDS Patients Who Have Had Pneumocystis Carinni Pneumonia, THE PINK SHEET, Sept. 22, 1986, at 3; Burroughs Wellcome's AZT Marketing Plans Include Review Committee to Evaluate Appropriateness of the Drug Therapy for Individual Patients, THE PINK SHEET, Jan. 19, 1987, at 11; Burroughs Wellcome Retrovir Approval, THE PINK SHEET, Mar. 23, 1987, at 3.

<sup>10</sup> We could not readily identify from the relevant SBA documents whether 4 of the products in the chart were approved under FDCA section 505(b)(1) or 505(b)(2). The products were Xeloda (capecitabine), Priftin (rifapentine), Temodar (temozolomide), and Cancidas (caspofungin acetate). The products were included, however, because none of the SBA documents referred to data derived from studies that were not conducted by or for the applicants and for which the applicants had not obtained rights of reference or use. See 21 U.S.C. § 355(b)(2).

<sup>11</sup> Other analyses have identified one-trial products, but they were not designed to comprehensively identify drugs approved on the basis of a single study. See, e.g., Tufts Ctr. for the Study of Drug Dev., Impact Report: Study Measures Single Controlled Trial Use in New Drug Development (2001); Christopher-Paul Milne, The Single Controlled Trial: Industry Survey Indicates that Implementation is Still a Work in Progress, 36 DRUG INF. J. 291 (2002); David M. Cocchetto, Regulatory Decision-Making in the United States Based on a Single Pivotal Clinical Study: Principles and Precedents, 21 CLINICAL RES. & REG. AFF. 101 (2004); David Coutant, et al., Substantial Evidence: When Is a Single Trial Sufficient for Approval and Promotion, 45 DRUG INF. J. 253 (2011); see also FRANK J. SASINOWSKI, QUANTUM OF EFFECTIVENESS EVIDENCE IN FDA'S APPROVAL OF ORPHAN DRUGS (2011) (identifying orphan drug products approved on the basis of evidence that does not meet the "usual, conventional, traditional showing of effectiveness . . . commonly referred to as 'the two adequate and well-controlled studies' standard").

<sup>12</sup> The 2 products are Gamunex (immune globulin intravenous (human)) and Flebogamma (immune

The 30 products described in the chart were the only products reviewed that appear to have been approved on the basis of effectiveness data from one clinical trial. Products were not included in the chart if FDA primarily relied on one trial, but described additional trials as “supportive” or “confirmatory” of effectiveness.<sup>13</sup> Though the chart includes two products for which there are results from two trials, the second trial for each product was an extension study that evaluated the same subjects who participated in the original clinical trial.

The SBA documents for the 30 products generally do not mention either FDA’s statutory authority to approve drugs on the basis of one clinical trial plus “confirmatory evidence” or its guidance on the circumstances in which approval may be based on one clinical trial. See 21 U.S.C. § 355(d); Clinical Evidence of Effectiveness Guidance, supra. Two exceptions are: (1) the clinical review for Xeloda (capecitabine), which referred to the then-draft version of the guidance; and (2) the clinical review and a division director memorandum for Tyzeka (telbivudine), which stated that effectiveness was demonstrated in a large trial designed to be consistent with FDAMA and the final guidance.

The following summarizes the results of the review:

- Total number of products approved: 394
- Total number of “one study” products identified: 30
- Over half of the 30 products were approved for either cancer or a hereditary deficiency or metabolic disorder:
  - Cancer: 12 products (40%)
  - Hereditary deficiencies/metabolic disorders: 6 products (20%)
- 3 products were approved on the basis of extremely large trials (13,000 to 18,000 patients each) that demonstrated reduced risk for cardiovascular events such as cardiovascular death, MI, stroke, and embolism
- 3 products were approved to treat various infectious diseases (pulmonary tuberculosis, invasive aspergillosis, chronic hepatitis B) and 1 more for sepsis; there were several common themes among the trials for these 4 products:
  - Large trials (500 to 1,300 patients each) for 3 of the products
  - Active- or historically-controlled trials demonstrating an improvement over existing therapies for the 3 infectious diseases, and a “powerful”

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globulin intravenous (human)).

<sup>13</sup> Several products were identified during the review that had approved labeling which described only one clinical trial, but SBA documentation referring to additional trials that “supported” their effectiveness. These products included Eloxatin (oxaliplatin) for carcinoma of the colon or rectum, Iressa (gefitinib) for non-small cell lung cancer, Revlimid (lenalidomide) for transfusion dependent anemia, and Tykerb (lapatinib ditosylate) for breast cancer.

demonstration of mortality benefit for sepsis

- FDA emphasis on the importance of new treatment options for each of the 3 diseases
- The remaining 5 products were approved for various diseases and conditions, and all on the basis of trials with statistically strong results
  - 3 of the products were approved on the basis of strong results in active-controlled trials:
    - Thymoglobulin for renal transplant rejection
    - Crosseal for control of surgical bleeding
    - Asclera for varicose veins
  - The final 2 products were both for orphan indications; the approvals were based on smaller trials with p-values < 0.001:
    - Arcalyst is for an autoimmune disease (cryopyrin-associated periodic syndromes, or CAPS); the SBA notes that the sponsor worked with FDA to design a trial that would support approval; the trial had about 50 patients, and demonstrated improvement over placebo with a p-value < 0.0001
    - Banzel is for a severe form of epilepsy (Lennox-Gastaut Syndrome, or LGS); the SBA notes that the results were “clearly and overwhelmingly positive, robust to numerous analyses”; the trial had about 130 patients, and demonstrated improvement over placebo for multiple endpoints, with p-values ranging from < 0.0001 to 0.0041

#### **IV. CONCLUSION**

For a new drug to be approved under section 505(b)(1), FDA must find “substantial evidence” of effectiveness. 21 U.S.C. § 355(d). Section 505(d) defines substantial evidence as evidence consisting of “adequate and well-controlled investigations,” which FDA has interpreted since 1963 “ordinarily” to require data from two or more clinical trials. Section 115(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA) amended section 505(d) to provide that FDA “may” find a new drug effective based on data from one clinical trial plus “confirmatory evidence.” 21 U.S.C. § 355(d).

The agency has issued guidance stating that a single trial may be sufficient if it has “one or more” of the following characteristics: large size; multicenter design; consistency across key patient subsets; multiple “studies” of drug effectiveness within the single trial; use of multiple endpoints each representing a beneficial but different effect; and statistically very persuasive findings. FDA has also stated that reliance on a single trial will generally be limited to drugs with an effect on mortality, irreversible morbidity, or disease with potentially serious

outcomes, so that confirmation of the results in an additional trial would be practically or ethically impossible. FDA has further asserted that approval based on a single trial would generally not be appropriate for a drug that provides only symptomatic benefit.

FDA approved 30 new drugs and biological products on the basis of effectiveness data from only one trial from 1998 to 2011, out of a total of 364 products.

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**ATTACHMENT**

**New Drugs and Biological Products Approved by FDA from 1998 to 2011 Based on Effectiveness Data from One Clinical Trial**

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Xeloda (capecitabine)	Apr. 30, 1998	505(b)	Priority Accelerated (surrogate endpoint)	Treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline- containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated	Open Label Single Arm Multicenter (21) 135 Subjects	Response Rate (RR)	18.5% RR in all subjects with measurable disease (95% CI: 12.4–26.1) 25.6% RR in subjects resistant to both paclitaxel and an anthracycline (95% CI: 13.5–41.2)	<p><u>Discussion at EOP1 Meeting:</u></p> <p>“[A] single trial is generally not sufficient to support an indication, although it is recognized that the proposed 150 patients will narrow the confidence intervals around the response rate over the typical Phase II study . . . a multi-center study where sites showed replication of results might be acceptable, depending on the magnitude of effect.”</p> <p><u>Medical Review:</u></p> <p>March 1997 draft clinical evidence of effectiveness guidance cited. (2-3)</p> <p>“The demonstration of efficacy for NDA #20-896 is based on data from a single, uncontrolled trial . . . .” (34)</p> <p>“Although the response rate is derived from a single trial, it is a multicenter trial. A single center, [redacted] accrued 37 patients (35 with measurable disease), serving as a nested Phase 2 trial and perhaps serving to confirm the overall results or provide a measure of consistency of results.” (34)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “open-label single arm trial.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Priftin (rifapentine)	June 22, 1998	505(b)	Priority Accelerated (surrogate endpoint) Orphan	Treatment of pulmonary tuberculosis	Open Label Randomized: Active Control (rifampin) Multicenter 549 Subjects	Negative Sputum Culture at End of Treatment  Negative Sputum Culture 6 Months Post- Treatment	End of treatment: 88% conversion rate; +5% difference compared to rifampin  6 months post- treatment: 11% relapse rate; +6% difference compared to rifampin (95% CI: 2–10)  Relative Risk 2.15 (95% CI: 1.0–4.25)	<p><u>Medical Review:</u></p> <p>“In support of the indication for treatment of newly diagnosed uncomplicated pulmonary tuberculosis, the applicant has submitted a single pivotal study . . . .” (8)</p> <p>“Since a single pivotal trial has been accepted by the FDA for submission, it is of interest to comment that the CDC is currently conducting a trial designed to study the use of rifapentine/INH (once weekly) versus rifampin/INH (twice weekly) during the continuation phase of therapy (month 3 through 6) for patients with acute pulmonary tuberculosis. . . . This study will lend additional information regarding the most effective regimen for rifapentine upon its completion and analysis.” (8)</p> <p>A single study might have been acceptable to FDA because Priftin required less frequent dosing than other products and there was a need for such products:</p> <p>“With the increasing need for directly observed therapy (DOT) to assure patient compliance, a therapeutic regimen which requires less frequent dosing is desirable.” (6)</p> <p>“There is a need for new anti-tuberculosis medications, and for medications which will potentially increase the adherence to dosing thereby decreasing the potential for the development of resistant organisms.” (8)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “open label, prospective, randomized, parallel group, active controlled trial.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Thymoglobulin (anti-thymocyte globulin (rabbit))	Dec. 30, 1998	351(a)	Standard	Treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression	Double Blind Randomized Noninferiority Trial Comparing to Atgam (anti-lymphocyte globulin (horse)) Multicenter (29) 163 Subjects	Weighted Estimate of Treatment Difference	11.1% compared to Atgam (lower one-sided 95% confidence bound 0.7%) (p = 0.061)	<p><u>Summary Basis of Approval:</u></p> <p>“SangStat Medical Corporation conducted one adequate, well-controlled, double-blind, clinical trial (Study SANG-93-3-K-THY-R) to evaluate the efficacy and safety of Thymoglobulin compared with Atgam® [Anti-lymphocyte Globulin, (Horse), Pharmacia &amp; Upjohn, MI] for the treatment of acute cellular rejection following renal transplantation under IND 5621.” (13)</p> <p>Additional uncontrolled trials were also described, but the relevance of these studies was not explicitly addressed in the SBA:</p> <p>“Clinical trials (non-IND) conducted outside of the United States studied the use of Thymoglobulin for the prevention or treatment of allograft rejection following kidney, heart, liver, and pancreas transplantation. Reported rates of reversal for acute rejection ranged from 78% to 100% for all types of rejection and from 74% to 94% for steroid-resistant renal rejection.”</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “controlled, double-blind, multicenter, randomized clinical trial comparing Thymoglobulin and Atgam.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Temodar (temozolomide)	Aug. 11, 1999	505(b)	Priority Accelerated (surrogate endpoint) Orphan	Treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine	Open Label Single Arm Multicenter (32) 162 Subjects (54 with disease progression on prior therapy)	Response Rate (RR) Duration of Response (Progression Free Survival and Overall Survival data also in label)	22% RR Median duration 50 weeks (95% CI: 16–114) for all responders and 64 weeks (95% CI: 52–114) for complete responders	<p><u>Medical Officer Review:</u></p> <p>“The applicant is requesting accelerated approval based on an objective tumor response rate in patients for whom there is no satisfactory available therapy . . . . There were 54 such patients in the sponsor’s C/I94123 trial.”</p> <p>*NOTE: Data from additional trials were reviewed for glioblastoma multiforme, metastatic malignant melanoma, and nonrefractory anaplastic astrocytoma; these data were not referenced in the medical officer’s conclusions regarding anaplastic astrocytoma.</p> <p>A single study might have been acceptable to FDA because there was an “urgent need” for effective chemotherapy in this indication:</p> <p>“In recurrent disease, no standard of care for . . . AA histology exists.” (13)</p> <p>“[T]here is an urgent need for new and effective therapies in recurrent glioma.” (14)</p> <p>“The search for effective chemotherapy for individuals with recurrent high-grade malignant glioma is one of the priorities in oncology. It is important to find an agent that is not only effective, but has an acceptable safety profile, does not adversely impact patients’ quality of life, and is easy to administer.” (14)</p> <p><u>Acting Director Comments:</u></p> <p>“The effectiveness of temozolamide in this indication is supported by Study C/I94123 . . . .”</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “single arm, multicenter study.”</p>



Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Cancidas (caspofungin acetate)	Jan. 26, 2001	505(b)	Priority	Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies	Open label Single Arm with Historical Control (standard antifungal therapy) Multicenter 63 Subjects	Clinical Response	41.3% (per independent expert panel) compared to 17.0% in historical control (no formal statistical comparison appropriate)	<p><u>Medical Review:</u></p> <p>“The aggregate of information supporting the efficacy of Cancidas® in invasive aspergillosis includes the efficacy of caspofungin demonstrated in the open label study (Study 019), the <i>in vitro</i> studies and efficacy in animal models of aspergillosis, the reported antifungal activity in supportive studies, a comparison of this information to the known efficacy of other antifungals from the clinical reviews of NDAs submitted to the Agency, and the reported efficacy of alternative antifungal agents in the literature.” (8)</p> <p>A single study might have been acceptable to FDA because this drug had potential to address an unmet medical need for a serious condition:</p> <p>“[G]ranted fast track designation by the Division due to the evidence presented supporting both its potential to address an unmet medical need and to treat a serious or life threatening condition.” (11)</p> <p>“Patients with aspergillosis refractory and/or intolerant to standard antifungal therapy have few therapeutic alternatives and a high mortality rate.” (Division Director Memorandum)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “open-label, noncomparative study.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Xigris (drotrecogin alfa)	Nov. 21, 2001	351(a)	Standard	Reduction of mortality in adult patients with severe sepsis . . . who have a high risk of death	Double Blind Randomized: Placebo Control Multicenter (164) 1,690 Subjects	28 Day All- Cause Mortality	-6% mortality rate difference (p=0.0054); relative risk 0.81 (95% CI: 0.70–0.93)	<p><u>Clinical Review:</u></p> <p>Includes review of “efficacy” data from both a P2 study and a P3 study, but states that the objective of the P2 study was to “identify the effective dose range and dose duration.” The P2 study involved 131 subjects at 40 centers and the results demonstrated a -5% mortality difference (p=0.55).</p> <p>The SBA does not expressly state that the P3 study was the only study supporting approval, but does suggest that a single study might have been acceptable because of its size, statistical significance, and demonstration of mortality benefit:</p> <p>“The PROWESS trial had 1690 patients and a p value of 0.005 on the prospectively defined primary endpoint. This places it among the most powerful demonstrations of mortality benefit in the history of clinical trials. (Indeed, more powerful demonstrations are improbable as data monitoring committees tend to stop trials for ethical reasons when strong mortality differences occur as happened in this case.” (143)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “international, multi-center, randomized, double-blind, placebo-controlled trial (PROWESS).”</p> <p><u>FDA Press Release:</u></p> <p>Refers to one, “placebo-controlled, multi-center, randomized clinical trial.” See Press Release, FDA, FDA Approves First Biologic Treatment for Sepsis (Nov. 21, 2001), <u>available at <a href="http://www.fda.gov/bbs/topics/NEWS/2001/NEW00780.html">http://www.fda.gov/bbs/topics/NEWS/2001/NEW00780.html</a></u>.</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Orfadin (nitisinone)	Jan. 18, 2002	505(b)(1)	Priority Orphan	Adjunctive therapy to dietary restrictions of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1	Open Label Single Arm with Historical Control (diet alone) Multicenter (87) 207 Subjects	2- and 4-Year Survival Survival without Need for Liver Transplantation Death or Transplantation Due to Liver Failure Development of Hepatocellular Carcinoma (HCC) Development of Porphyric Crisis	88% and 88% survival (95% CI: 65–100; 52–100) for subjects presenting with HT-1 under 2 months of age, compared to 29% and 29% 94% and 94% (95% CI: 85–100; 80–100) for subjects presenting with HT-1 under 6 months of age, compared to 74% and 60% Positive results for other endpoints also observed	<u>Medical Review:</u> “A Phase II-III nonrandomized, open label, noncomparative multicenter clinical study in 25 different countries, including the US, was performed to study the safety and efficacy of Orfadin™ . . . . For ethical reasons the study was open label and comparisons were made to historical controls treated with diet alone.” (8) A single study might have been acceptable to FDA because this drug is used for corrective treatment of a serious metabolic disorder and the NDA provided data on most of the patients in the world who had the condition: “This disorder can be characterized by liver failure, increased risk of hepatocellular carcinoma, coagulopathy, painful neurologic crises and renal tubular dysfunction resulting in rickets.” (7) “Including safety update reports, the NDA contains efficacy and safety information on approximately 300 patients treated in 25 different countries through 1999, for a total exposure of approximately 1000 patient-years. The population studied constitutes the majority of the patients identified with this condition worldwide.” (Division Director Memorandum) <u>Approved Labeling:</u> Refers to one, “open-label study.”
Aralast (alpha <sub>1</sub> -proteinase inhibitor (human))	Dec. 23, 2002	351(a)	Standard	Chronic augmentation therapy in patients having congenital deficiency of alpha <sub>1</sub> -proteinase inhibitor (α <sub>1</sub> -PI) with clinically evident emphysema	Double Blind Randomized Noninferiority Trial Comparing to Prolastin (alpha <sub>1</sub> -proteinase inhibitor (human)) Multicenter 28 Subjects	Mean Serum α <sub>1</sub> -PI Trough Level Mean Serum anti-Neutrophil Elastase Capacity Trough Level Mean Change in Serum anti-NE Capacity	Mean serum α <sub>1</sub> -PI trough level 90.5% compared to Prolastin for weeks 8-11 of treatment (95% lower confidence limit 81.7%) (p = 0.026); regression slope of mean serum trough levels in weeks 12-24 -0.003 μmol/L/week (90% CI: -0.04–0.04) Positive results for other endpoints also observed	<u>Detailed Clinical Summary:</u> “Alpha Therapeutics submitted one clinical trial in support of licensure.” (1) A single study might have been acceptable to FDA because this drug is used as replacement therapy for a serious hereditary deficiency: “Patients with [α <sub>1</sub> -PI deficiency] have a high risk for the development of emphysema in the third to fifth decades. Some patients also develop liver disease, which is not thought to be ameliorated by augmentation therapy with α <sub>1</sub> -PI.” (1) <u>Product Information Sheet:</u> Refers to one clinical study.

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Crosseal (fibrin sealant (human))	Mar. 21, 2003	351(a)	Standard	Adjunct to hemostasis in patients undergoing liver surgery, when control of bleeding by conventional surgical techniques, including suture, ligature, and cautery is ineffective or impractical	Single Blind Randomized; Active Control (FDA-approved topical hemostatic agents) Multicenter (15) 121 Subjects	Time to Reach Hemostasis	5.3 minutes compared to 7.7 minutes (p=0.011)	<u>Summary Basis of Approval:</u> “Crosseal™ was evaluated in a pivotal Phase III . . . study.” (9) The SBA does not suggest why a single study was acceptable to FDA, but it does address the possible criticism that data from one site was disproportionately responsible for the favorable effect seen:  “Center effects are to be expected in multicenter studies, particularly in surgical indications. Data from one center, which used a specific control agent, made a major contribution to this result. However, of the sixteen surgeons who treated more than one patient in this study, ten found the time to hemostasis to be equivalent to, or shorter than that achieved with some of the control agents.” (9)
Fabrazyme (agalsidase beta)	Apr. 24, 2003	351(a)	Priority Accelerated (surrogate endpoint) Orphan	Treatment of patients with Fabry disease to reduce globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types	<u>Controlled Trial</u> Double Blind Randomized: Placebo Control Multicenter 58 Subjects  <u>Extension Study</u> Open Label Single Arm Multicenter 58 Subjects	GL-3 inclusions in renal interstitial capillary endothelial cells (graded from 0 (normal or near normal) to 3 (severe inclusions))  GL-3 inclusions in interstitial capillary endothelium of heart and skin	<u>Controlled Trial</u> GL-3 inclusion score of 0 in 69% of treated subjects, compared to 0% of placebo subjects (p<0.001)  Similar results in heart and skin also observed  <u>Extension Study</u> Similar results	<u>Medical Officer’s Review:</u> The review included data from a controlled trial (AGAL-1-002-98) and an open label extension study (AGAL-005-99) where the active patients from the controlled trial continued treatment and the placebo patients began treatment. The interim results of the extension study (6 months of 18 planned) were analyzed in the review. “The results of AGAL-005-99 support the conclusion from AGAL-1-002-98 that [Fabrazyme] causes a reduction in capillary endothelium of the kidney, heart, and skin.” (71) A single study might have been acceptable to FDA because this drug is used as replacement therapy for a serious hereditary deficiency, which might lead to growth retardation, delay of puberty, lymphedema, skeletal deformities, renal disease, and neurological syndromes. “The median age of death for hemizygous males is 50 years.” (4) <u>Division of Clinical Trial Design and Analysis Memorandum:</u> “The study submitted by Genzyme is an adequate and well-controlled clinical trial which demonstrated an effect of agalsidase beta on substrate accumulation within certain cell types.” (2) <u>Approved Labeling:</u> Refers to results from both the “randomized, double-blind, placebo controlled, multinational, multicenter study of 58 Fabry patients” and the “open-label extension study.”

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Aldurazyme (Iaronidase)	Apr. 30, 2003	351(a)	Priority Orphan	Treatment for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms	<p><u>Controlled Trial</u> Double Blind Randomized: Placebo Control 45 Subjects</p> <p><u>Extension Study</u> Open Label Single Arm 45 Subjects</p>	<p>Change in Percent of Predicted Normal Forced Vital Capacity (FVC)</p> <p>Change in Distance Walked (m) in 6 Minutes ("six minute walk test"/6MWT)</p> <p>Change in Liver Size</p> <p>Urinary GAG Levels</p>	<p><u>Controlled Trial</u> FVC: mean change 4%, median 2% (95% CI: 0.4-7) (p=0.02) 6MWT: mean change 38 m, median 39 m (95% CI: -2-79) (p=0.07) Positive results in other endpoints also observed</p> <p><u>Extension Study</u> Improvements in FVC and 6MWT also observed</p>	<p><u>Clinical Review:</u> The review included data from a randomized trial and an open label extension study where the active patients from the randomized trial continued treatment and the placebo patients began treatment. The interim results of the extension study (24 weeks for all endpoints, 36 weeks for FVC and 6MW) were analyzed in the review, which states: "No conclusion can be drawn from these uncontrolled and unblinded data with a small clinical effect." (110). A single study might have been acceptable to FDA because this drug is used as replacement therapy for a rare, serious hereditary deficiency and there was a lack of alternative treatments: "Given the lack of alternative treatments in a rare disease with severe or fatal consequences, this reviewer recommends approval of Iaronidase, supported by the evidence of efficacy in the co-primary endpoints [FVC and 6MWT] and favorable trends in subsets of MPS I in secondary endpoints." (113)</p> <p><u>Approved Labeling:</u> Refers to one, "randomized, placebo-controlled clinical trial" and states that "[a]ll 45 patients received open-label ALDURAZYME for 36 weeks following the double-blind period."</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Alimta (pemetrexed disodium)	Feb. 4, 2004	505(b)(1)	Priority Orphan	Treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery	Single Blind Randomized: Active Control (cisplatin) & Combination  Multicenter (88) 448 Subjects	Overall Survival	12.1 months (95% CI: 10.0–14.4) compared to 9.3 months (95% CI: 7.8–10.7) (p=0.020)	<p><u>Clinical Review:</u></p> <p>“One single-blind, randomized, controlled trial, demonstrating the efficacy and safety of Alimta in combination with cisplatin . . . has been submitted and reviewed.” (311)</p> <p>A single study might have been acceptable to FDA because there was a lack of alternative treatments, as well as the study’s size and multicenter design:</p> <p>“The combination of Alimta plus cisplatin is the first chemotherapeutic regimen to demonstrate a survival benefit in malignant pleural mesothelioma in comparison to a control regimen.” (311)</p> <p>“Although a single randomized trial supports this NDA, this trial was multi-institutional with over 88 study centers enrolling over 574 patients and is the largest randomized study ever conducted in this disease.” (Division Director Memorandum, 7)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “multi-center, randomized, single-blind study.”</p>
Iplex (mecasermin rinfabate recombinant)	Dec. 12, 2005	505(b)(1)	Priority Orphan	Treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to growth hormone	Open Label Single Arm with Two Non-Randomized Cohorts  Multicenter 29 Subjects (25 evaluable)	Change in Height Velocity (HV)  Change in Height Standard Deviation Score (SDS)	<p>Cohort 1 (“low dose” regimen): 3.0 ± 1.3 cm/yr change in HV (95% C.I.: 2.3–3.7) (p&lt;0.0018); 0.5 ± 0.4 change in SDS (p&lt;0.002)</p> <p>Cohort 2 (“high dose” regimen): 6.6 ± 2.6 cm/yr change in HV (95% CI: 4.6–8.6) (p&lt;0.0001); 0.4 ± 0.3 change in SDS (p&lt;0.001)</p>	<p><u>Medical Officer Review:</u></p> <p>“Mecasermin rinfabate has been studied in one clinical trial . . . .” (7)</p> <p>A single study might have been acceptable to FDA because this drug is used as replacement therapy for a rare hereditary deficiency:</p> <p>“It is important to recognize that GHIS is an extremely rare disease. It has been estimated that the prevalence of Laron Syndrome worldwide is approximately 200-350. . . . The 29 patients studied in the mecasermin rinfabate clinical program represent approximately 10% of the Laron syndrome patient population.” (87)</p> <p>*NOTE: effectiveness of a similar replacement therapy product had also been shown previously. Recombinant human insulin-like growth factor-I (rhIGF-1) was approved 8/30/05 (Increlex) and this product was rhIGF-1 complexed non-covalently with rhIGF binding protein-3 (IGFBP-3). (6 &amp; n.7)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “prospective, open-label multicenter study.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Vectibix (panitumumab)	Sept. 27, 2006	351(a)	Priority Accelerated (surrogate endpoint)	Treatment of EGFR- expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan containing chemotherapy regimens	Open Label Randomized: Active Control (best supportive care (BSC)) & Combination  Multicenter (81) 463 Subjects	Progression Free Survival	Mean: 96 days (SD, Min, Max: 5.3, 0, 357), compared to 60 days for BSC alone (SD, Min, Max: 3.8, 0, 337) (p<0.0001)  Median: 56 days (95% CI: 55–59), compared to 51 for BSC alone (95% CI: 50–54)	<p><u>Pre-BLA Meeting:</u></p> <p>“FDA agreed that Study 20020408, with a primary endpoint of progression-free survival (PFS) . . . was adequate in design to support accelerated approval based on an improvement in PFS . . . .” (2)</p> <p><u>Clinical Review:</u></p> <p>“The integrated review of efficacy . . . is based on a single, multinational, randomized controlled trail [sic] . . . .” (34)</p> <p>Additional uncontrolled monotherapy trials were submitted, but they either did not “meet the criteria detailed in 21 CFR 314.126 . . . as adequate and well-controlled studies” or were not “designed to provide a reasonable assessment of benefit in the population for which licensure was sought.” (50-51)</p> <p>A single study might have been acceptable to FDA because there were limited treatment options for and a poor prognosis for patients with this type of cancer, as well as the statistical power of the result:</p> <p>“[P]atients who have progressed following irinotecan- and oxaliplatin-based chemotherapy have very limited treatment options and a uniformly poor prognosis.” (9)</p> <p>“Despite recent advances there are no FDA-approved drugs with full approval for patients with metastatic CRC who have failed prior (standard) chemotherapy treatments (eg fluorouracil, irinotecan, and oxaliplatin). These patients have only palliative or experimental treatment options available to them.” (22)</p> <p>“There was a highly statistically significant difference in PFS favoring the panitumumab plus BSC arm.” (60)</p> <p><u>Division Director Recommendation for Approval Action:</u></p> <p>“The effectiveness of Vectibix was established in a single, randomized, open-label trial . . . .” (5)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “open-label, multinational, randomized, controlled trial.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Tyzeka (telbivudine)	Oct. 25, 2006	505(b)(1)	Standard	Treatment of chronic hepatitis B (CHB) in patients with evidence of viral replication and active liver inflammation	Double Blind Randomized; Active Control (lamivudine (LAM)) Multicenter 1,367 Subjects	Therapeutic Response	HBeAg-Positive Subjects: 75.3% in intent to treat (ITT) group and 77.0% in efficacy evaluable (EE) group, compared to 67.0% and 67.1% (ITT p=0.0047; EE p=0.0007).  HBeAg-Negative Subjects: 75.2% in ITT group and 76.3% of the EE group, compared to 77.2% and 80.8% (ITT p=0.6187; EE p=0.2461).	<p><u>Clinical Review</u></p> <p>“Given the large number of planned subjects (n=1200) for the LdT Phase 3 trial and the separate analyses planned from HBeAg-positive and HBeAg-negative subjects, the Division agreed to a single, large, Phase 3 study. Essentially, NV-02B-007 was designed to have a target study population and size equivalent to the study population and size usually associated with two registrational HBV treatment trials. . . . Specific analysis and other considerations were also necessary for the Division to accept a single Phase 3 registrational study.” (19)</p> <p>“The primary source of clinical safety and efficacy data was derived from Study NV-02B-007 . . . . Additionally, data generated during the Phase 2b dose-finding study, NV-02B-003, and its follow-on study, NV-02B-010, were also reviewed, primarily for safety.” (25)</p> <p>“The pivotal Phase 3 study, NV-02B-007, was designed to meet the Food and Drug Administration Modernization Act (FDAMA) of 1997 criteria for one adequate and well-controlled clinical trial (plus confirmatory evidence) using appropriate endpoints and efficacy analysis.” (42)</p> <p><u>Medical Team Leader Memorandum:</u></p> <p>“The efficacy of LdT has been demonstrated in a single large pivotal trial . . . with supportive evidence derived from a number of phase 2 studies including NV-02B-001 and NV-02B-003.” (2)</p> <p><u>Division Director Memorandum:</u></p> <p>“The efficacy of telbivudine was demonstrated in a large phase 3 trial . . . . Although the Globe study was a single study, it was designed so that each patient group would be analyzed separately and is consistent with regulatory guidance regarding the use of a single study for registration. Specifically the study was multicenter, incorporated a type-one error of &lt;0.001, studied a range of chronic hepatitis B baseline characteristics, and evaluated multiple endpoints (virologic, serologic, histologic, and changes in transaminases), which were all concordant.” (2)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “international active-controlled, clinical study.”</p>



Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Torisel (temsirolimus)	May 30, 2007	505(b)(1)	Priority	Treatment of advanced renal cell carcinoma	Open Label Randomized (Three Arms): Active Control (IFN- $\alpha$ ) & Combination  Multicenter (148) 626 Subjects	Overall Survival (OS) Progression Free Survival (PFS)  Response Rate (RR)	Median OS 10.9 months for temsirolimus (95% CI: 8.6–12.7) compared to 7.3 months for IFN- $\alpha$ (95% CI: 6.1–8.8) (p=0.0078)  Positive results for PFS also observed, but not for RR	<p><u>Clinical Review:</u></p> <p>“The clinical reviewers recommend . . . regular approval . . . based upon demonstration of a clinically meaningful and statistically robust improvement in overall and progression-free survival in a randomized, active-controlled, three-arm trial . . . providing substantial evidence of safety and effectiveness in advanced RCC.” (5)</p> <p>“The results of the randomized, controlled trial provide substantial evidence of efficacy . . .” (10)</p> <p>Data from an additional P2 trial “was used to support the safety of temsirolimus, but not efficacy because it was a dose-finding study, and not a controlled trial.” (27)</p> <p>A single study might have been acceptable to FDA because there were limited treatment options for patients with this type of cancer:</p> <p>“Even with multimodality therapy, the median survival of patients with metastatic disease remains low at 10-12 months with long-term survival occurring in only 2% of these patients.” (16)</p> <p>“This drug is the first drug to demonstrate an improvement in overall survival and is accompanied by an improvement in PFS.” (Office Director Memorandum)</p> <p><u>Clinical Team Leader’s Review:</u></p> <p>“An interim analysis of a single prospectively randomized trial (3066K1-304-WW) provides the basis of efficacy and safety for this NDA . . . . The design of this study underwent a special protocol assessment (SPA) and was acceptable to the Agency.” (2)</p> <p><u>Division Director Summary Review:</u></p> <p>“The safety and efficacy of TORISEL is based on a single study . . . .” (1)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “phase 3, multi-center, three-arm, randomized, open-label study.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Tasigna (nilotinib hydrochloride monohydrate)	Oct. 29, 2007	505(b)(1)	Standard Accelerated (surrogate endpoint) Orphan	Treatment for chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included Gleevec (imatinib)	Open Label Single Arm Multicenter (41) 337 Subjects	Response Rate: unconfirmed major cytogenetic response (MCyR)for CML-CP; confirmed hematologic response (HR) for CML-AP  Duration of Response	39.7% MCyR in CML- CP (95% CI: 33.3– 46.3), 59% of responses ≥ 6 months  26% HR in CML-AP (95% CI: 18–35), 63% of responses ≥ 6 months	<p><u>Clinical Review:</u></p> <p>“Evidence of nilotinib efficacy is based on the results of a single Phase 2 study with two populations studied, CML-CP and CML-AP.” (85)</p> <p>A single study might have been acceptable to FDA because there were limited treatment options for patients with this type of cancer:</p> <p>“Patients with CML that is resistant to imatinib or who can not tolerate imatinib have limited therapeutic options, although dasatinib has also received accelerated approval for these indications.” (8)</p> <p><u>Summary Basis for Regulatory Action:</u></p> <p>“The efficacy and safety data come from a single, large, open label, multi-center, single-arm study in patients with imatinib-resistant or intolerant CML.” (2)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one, “single open label multicenter study.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Arcalyst (rilonacept)	Feb. 27, 2008	351(a)	Priority Orphan	Treatment for cryopyrin-assicated periodic syndromes (CAPS)	Double-blind Randomized: placebo controlled (all subjects received Arcalyst with a randomized withdrawal to placebo)	Reduction in mean disease activity at 6 wks (composite score based on sub-scores of 5 key symptoms on a 21 point scale)  Increase in mean disease activity over the withdrawal period	-2.6 +/- 1.9 versus - 0.3 +/- -0.7 on the placebo (p<0.0001)  Mean scores of placebo increased 0.9 (p<0.0001)	<p>A single study might have been acceptable to FDA because of the rare nature of the disease and because the single study was designed with input from FDA to provide internal replication of efficacy results:</p> <p><u>Summary Review:</u></p> <p>“Due to the rarity of the disease, the applicant requested that they be required to perform only one adequate and well-controlled study of Arcalyst. Working with the Agency, Regeneron designed a two-phase study that allowed replication of the results to provide more compelling support of the effectiveness of the product in a single trial. The Agency approved the use of this trial as the sole support for efficacy in the application.” (2)</p> <p>“As noted above, the applicant was only required to perform one adequate and well-controlled clinical trial, but worked with the Agency to design a trial that would provide some degree of internal replication of the efficacy results.” (6)</p> <p><u>Officer Director Memo:</u></p> <p>“The limited number of patients with CAPS disease made a designing a clinical program to demonstrate efficacy challenging. In close collaboration with the Division, the sponsors designed a single pivotal trial that was felt might provide convicting evidence of efficacy. The pivotal trial had two parts including two separate randomizations.” (3)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one “randomized, double-blind, placebo-controlled study with two parts.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Banzel Oral Tabs (rufinamide)	Nov. 14, 2008	505(b)(1)	Standard Orphan	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children older than 4 and adults	Double-Blind Randomized: placebo controlled Multicenter 138 Subjects	% change in seizure frequency % change in tonic-atonic seizure frequency Seizure severity (7 point scale)	Median % change was -32.7 versus -11.7 on the control (p=0.0015) Median % change was -42.5 versus 1.4 on the placebo (p<0.0001) Improvement in Seizure Severity Rating was 53.4 versus 30.6 on the control (p=0.0041)	A single study might have been acceptable to FDA because there were limited treatment options for patients with this rare disease: <u>Summary Review:</u> “With regard to Lennox-Gastaut Syndrome, however, I believe, upon further reflection, that the sponsor has presented substantial evidence of effectiveness for this indication. Although we had originally concluded that the evidence was not adequate to support such a claim...I think that the sponsor has provided substantial evidence of effectiveness, as provided by a single adequate and well-controlled trial and confirmatory evidence. ...First, the study is clearly and overwhelmingly positive, robust to numerous analyses. This is an unequivocal conclusion (even in the face of the previously mentioned baseline imbalance in seizure frequency)...Lennox-Gastaut Syndrome is a devastating seizure syndrome, and although other drugs carry this indication, as noted by Dr. Hershkowitz, these drugs are not without significant toxicities, and additional therapies are clearly needed for this condition..” (7-8) <u>Approved Labeling:</u> Refers to a “single multicenter, double-blind, placebo-controlled, randomized, parallel-group study.”
Firmagon (degarelix)	Dec. 24, 2008	505(b)(1)	Standard	Treatment of patients with advanced prostate cancer	Open-Label Randomized: active control (leuprolide) Three-arm Multicenter 620 patients	Probability of testosterone = 0.5 ng/ml from day 28 to 364 in each of three arms	98.3% (95% CI: 94.8%-99.4%), 97.2% (93.5%- 98.8%) and 96.4% (92.5%-98.2%) in the three arms respectively	<u>Medical Review:</u> “Based on the key findings as discussed below and with the fact that efficacious biochemical castration suppression of testosterone has been recognized and accepted as an established surrogate endpoint for evaluating agents intended to treat prostate cancer through suppressing testosterone, the reviewers recommend regular approval of degarelix...” (10 of 82) <u>Approved Labeling:</u> Refers to one “open-label, multi-center, randomized, parallel group study.”

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Afinitor (everolimus)	Mar. 30, 2009	505(b)(1)	Priority	Treatment of advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib	Double-blind Randomize: placebo- controlled Multicenter 416 Subjects	Progression- free survival (PFS)	4.9 months of survival versus 1.9 months on the control (95% CI: 4.0-5.5, 1.8-1.9) 0.33 HR (95% CI: 0.25 - 0.43) (p<0.0001)	<p><u>Summary Review:</u> “A single randomized trial was submitted in support of the application.” (5)</p> <p><u>Medical Review:</u> “The risk benefit analysis to support this recommendation was based on the efficacy and safety results of one randomized, placebo-controlled, double-blind study.” (8 of 84)</p> <p>The SBA documents do not indicate why FDA might have accepted a single study to support efficacy, but it might have been acceptable because there were limited treatment options for patients with this type of cancer and because of the statistical significance of the results.</p> <p><u>Approved Labeling:</u> Refers to one “international, multicenter, randomized, double-blind trial.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Effient (prasugrel)	July 10, 2009	505(b)(1)	Priority	<p>Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI including:</p> <ul style="list-style-type: none"> <li>• Patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI)</li> <li>• Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed</li> </ul>	<p>Double-blind Randomized: active control (clopidogrel) Parallel group Multicenter 13,608 Subjects</p>	<p>Composite of cardiovascular death, nonfatal MI, or nonfatal stroke in UA/STEMI and STEMI populations</p>	<p>UA/STEMI: 9.3% of patients experienced events versus 11.2% on the control (p=0.002) Relative Risk Reduction 18% (95% CI: 7.3-24.1) STEMI: 9.8% of patients experienced events versus 12.2% on the control (p=0.019) Relative Risk Reduction 20.7% (95% CI: 3.2-35.1)</p>	<p><u>Medical Review:</u> “The sponsor submitted one trial...for the efficacy claim.” (15) The SBA documents do not suggest why a single study was acceptable to FDA, but it might have been acceptable because of the extremely large size of the trial and the success demonstrated in multiple patient populations.</p> <p><u>Approved Labeling:</u> “The clinical evidence for the effectiveness of Effient is derived from the TRITON-TIMI 38 (TRial to Assess Improvement in 365 Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) study, a 13,608-patient, multicenter, international, 366 randomized, double-blind, parallel-group study comparing Effient to a regimen of clopidogrel, each added to aspirin and other 367 standard therapy, in patients with ACS (UA, NSTEMI, or STEMI) who were to be managed with PCI.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Folotyn (Pralatrexate injection)	Sept. 24, 2009	505(b)(1)	Priority Orphan Accelerated	Treatment of patients with relapsed or refractory peripheral T-cell lymphoma	Open-Label Single-arm Multicenter 115 Subjects	Overall Response Rate (ORR)	29 patients responded to treatment (27%) (95% CI: 19-36)	<p>Efficacy was based on a single study designed with input from FDA under a special protocol assessment.</p> <p><u>Summary Review:</u></p> <p>“The application is based on a single study which was conducted under a special protocol assessment agreement. Because of the rarity of PTCL and the absence of effective therapies for patients with relapsed or refractory PCTCL it was a greed that depending on the magnitude of the response rate, the duration of response, and the risk benefit ratio, a single study in at least 100 patients may be sufficient to support approval.” (2)</p> <p>A single study might have been acceptable to FDA because there were limited treatment options for patients with this type of cancer:</p> <p>“There are no approved agents for treatment of relapsed or refractory PTCL, thus there is an unmet medical need for new agents. The response rate reported by the sponsor was 27% (95% CI: 19-36%). However, due to the major concerns elaborated in Section 3.1.5, the duration of response cannot be accurately estimated by Kaplan-Meier method. Instead, the FDA proposed a response rate for those responses being confirmed to last at least 14 weeks, and such durable response rate was 12% (95% CI: 17-20%). An ODAC meeting was held on Sep 2, 2009 to discuss whether or not the results of this single arm trial demonstrate a favorable benefit-risk profile for pralatrexate in the treatment of patients with refractory or relapsed PTCL. The ODAC voted in favor of the approval of pralatrexate (10 vs 4) as there is an unmet need in this population. and believed that pralatrexate may produce durable response in a small subpopulation of PTCL patients.” (8)</p> <p><u>Officer Director Memo:</u></p> <p>“Although the trial supporting this application was a single arm non-randomize trial, the magnitude of pralatrexate treatment...was considered likely to predict clinical benefit in patients with PTCL, a rare disease without currently available therapies.” (8)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one “open-label, single-arm, multicenter, international trial.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Carbaglu (carglumic acid)	Mar. 18, 2010	505(b)(1)	Priority Orphan	Pediatric and adult patients as an adjunctive therapy for the treatment of acute hyperammonemia due to NAGS deficiency, and as maintenance therapy for chronic hyperammonemia due to NAGS deficiency	Retrospective , unblinded and uncontrolled review of patient records  23 Subjects	Short-term efficacy evaluated using mean and median change in plasma ammonia levels from baseline to days 1 to 3.  Long-term efficacy evaluated using long-term mean and median change in plasma ammonia level	The overall mean baseline plasma ammonia level was 271 µmol/L.  Day 3, normal plasma ammonia levels attained in all patients for whom data were available.  Long-term efficacy measured using the last reported plasma ammonia level for each of the 13 patients analyzed (median length of treatment was 6 years; range 1 to 16 years). The mean and median ammonia levels were 23 µmol/L and 24 µmol/L, respectively, after a mean treatment duration of 8 years.	<p><u>Officer Director Memo:</u></p> <p>“The efficacy of carglumic acid was assessed using clinical information from 23 patients that was collected retrospectively from chart reviews. Clinical information from three additional patients treated on an ongoing, phase 2 study conducted by Mendel Tuchman at the Children’s National Medical Center, Washington, DC, was considered supportive.” (2)</p> <p>A single retroactive analysis might have been acceptable to FDA because the drug treats an extremely rare hereditary disease:</p> <p><u>Summary Review:</u></p> <p>“Although the retrospective case series data submitted in this NDA are not derived from traditionally defined adequate and well controlled investigations, the plasma ammonia level data submitted for review do stand as evidence on the basis of which it could fairly and responsibly be concluded by experts that the drug will have the effect it purports or is represented to have.” (1)</p> <p><u>Medical Review:</u></p> <p>“The Applicant did not provide any data from prospective, controlled trials to support the efficacy and safety of carglumic acid, and stated that prospective trials were not feasible due to the rarity of NAGS deficiency.” (35 of 191)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one retrospective review of the clinical course of 23 NAGS deficiency patients who received Carbaglu for a median of 7.9 years.</p>



Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Asclera (polidocanol)	Mar. 30, 2010	505(b)(1)	Standard	Uncomplicated spider veins (varicose veins <= 1mm in diameter) and uncomplicated reticular veins (varicose veins 1 to 3 mm in diameter) in the lower extremity	Double-Blind Randomized: placebo & comparator controlled  Multicenter (19) 338 Subjects	Improvement of treated veins on a 5-grade scale on standardized digital photographic images at 12 (±2) weeks after injection	Polidocanol: 4.52 ± 0.65 (154)  Sotradecol: 4.47 ± 0.74 (104)  Placebo: 2.19 ± 0.68 (53)  (p< 0.0001)	<p><u>Officer Director Memo:</u></p> <p>“The principle support for effectiveness comes from the EASI Trial...” (3)</p> <p><u>Medical Review:</u></p> <p>“Efficacy data for the primary endpoint is derived from a single pivotal, placebo and comparator controlled, double-blind, multicenter, EASI trail...” (46 of 198)</p> <p>“The OHIO trial, a randomized, double-blind, active-controlled trial with valid data for efficacy evaluation in the earlier submission to FDA, did not have a placebo group. The results of the OHIO trial do not contribute to the regulatory decision to recommend approval which is based solely on the efficacy findings of the EASI trial. The OHIO trial does provide information that the efficacy (and safety) profile of polidocanol and Sotradecol® in patients in the United States appeared to be generally comparable with that observed in patients in Europe (the EASI trial).” (47 of 198)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one “multicenter, randomized, double-blind, placebo- and comparator-controlled trial (EASI-study).”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Jevtana (cabazitaxel)	June 17, 2010	505(b)(1)	Priority	Hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen	Open-Label Randomized: active control (mitoxantrone ) Multicenter 755 Subjects	Overall Survival (OS)	234 deaths versus 279 on control  Median OS 15.1 months versus 12.7 on control (95% CI: 14.1-16.3, 11.6-13.7) (p<0.0001)  0.70 HR (95% CI: 0.59-0.83)	<p><u>Officer Director Memo:</u> “This application is primarily supported by a single randomized, open label, multi-center, international study (EFC6193 (TROPIC))...” (2)</p> <p><u>Medical Review:</u> “This application is based on the primary endpoint of overall survival in a single, randomized, open-label study comparing cabazitaxel with prednisone to mitoxantrone with prednisone in 755 patients.” (33) A single study might have been acceptable to FDA because there were limited treatment options for and a poor prognosis for patients with this type of cancer, as well as the statistical power of the result: “The proposed patient population currently has no treatment options which offer a survival benefit, and the robust results in overall survival demonstrated by cabazitaxel would provide a new treatment option for these patients.” (3)</p> <p><u>Approved Labeling:</u> Refers to one “randomized, open-label, international, multi-center study.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Pradaxa (dabigatran etexilate mesylate Capsules)	Oct. 19, 2010	505(b)(1)	Priority	To reduce risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation	Open-Label Randomized: active control (warfarin) Multicenter (951) 18,113 Subjects Non-inferiority	Occurrence of the composite endpoint, stroke and systemic embolism	134 (2.2%) patients had a stroke on 150 mg of Pradaxa and 183 (3%) on 110 mg of Pradaxa versus 202 (3.4%) on control HR versus Control: 0.65 (95% CI: 0.52- 0.81) for 150 mg 0.90 (95% CI: 0.74- 1.10) for 110 mg	<p><u>Medical Review:</u></p> <p>“In support of the proposed indication, the sponsor conducted a single phase 3 trial titled ‘Randomized Evaluation of Long term anticoagulant therapy’ comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-center, parallel-group, non-inferiority trial (RE-LY).” (41 of 302)</p> <p>The SBA documents do not suggest why a single study was acceptable to FDA, but it does address possible criticisms related to the open-label nature of the study:</p> <p><u>Summary Review:</u></p> <p>“The review team and the Advisory Committee paid much attention to the ‘hybrid’ study design, in particular that fact that randomization to warfarin or dabigatran was open-label....However, because RE-LY incorporated a randomized double-blind comparison of the lower and higher doses of dabigatran, we can have greater confidence in the results. Although the comparison of dabigatran 150 mg bid to 110 mg bid was a post-hoc analysis, the results show a statistically compelling difference on the 1° endpoint of stroke or systemic emboli.” (12-13)</p> <p><u>Approved Labeling:</u></p> <p>Refers to one “multi-center, multi-national, randomized parallel group trial.”</p>

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Zytiga (abiraterone acetate)	Apr. 28, 2011	505(b)(1)	Priority	Combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel	Double-blind Randomized: placebo controlled Multicenter (147) 1129 Subjects	Overall Survival (OS) Primary analysis conducted after 552 deaths Updated analysis conducted after 775 deaths	Primary Analysis 42% died versus 55% for placebo Median OS was 14.8 months versus 10.9 months for placebo (95% CI: 14.1-15.4, 10.2-12) (p<0.0001) 0.646 HR (95% CI: 0.543-0.768) Updated Analysis 63% died versus 69% for placebo Median OS was 15.8 months versus 11.2 months for placebo (95% CI: 14.8-17, 10.4-13.1) 0.740 HR (95% CI: 0.638-0.859)	<u>Officer Director Memo:</u> "This application is supported by the results of a randomized, placebo-controlled multicenter trial..." (2) <u>Medical Review:</u> "No clinical studies were submitted as supplemental evidence during the review." (23) A single study might have been acceptable to FDA because there were limited treatment options for and a poor prognosis for patients with this type of cancer, as well as the large size and statistical power of the result: <u>Summary Review:</u> "Because of the improvement in overall survival described below, this application is being given an expedited review. This review will summarize the design and results of the randomized trial and the recommendations of each review discipline." (2) <u>Approved Labeling:</u> Referencing "a randomized, placebo-controlled, multicenter phase 3 clinical trial."
Brilinta (ticagrelor)	July 20, 2011	505(b)(1)	Standard	Reduction in thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction)	Double-blind Randomized: active control (clopidogrel) Multicenter 18,624 Subjects	Composite of first occurrence of cardiovascular death, non-fatal MI, or non-fatal stroke (components individually assessed as secondary endpoints)	Composite was 864 (9.3%) occurrences versus 1014 (10.9%) with clopidogrel (p = 0.0003) 0.84 HR (95% CI: 0.77-0.92)	There was substantial controversy over whether to approve Brilinta on the basis of the one clinical trial due to a significant regional discrepancy in results from the U.S. and Europe. The clinical analysis focused on this issue rather than on why one trial was sufficient as opposed to two, but the extremely large size of the trial might have been factor. <u>Officer Director Memo:</u> Referring to "the large outcome trial intended to support approval" (2) <u>Approved Labeling:</u> "The clinical evidence for the effectiveness of brilinta is derived from PLATO a randomized double-blind study comparing brilinta to clopidogrel."

Drug	Date	Type	Review	Indication	Trial Design	Endpoint(s)	Results	Notes
Erwinaze (asparaginase erwinia chrysanthemi)	Nov. 18, 2011	351(a)	Orphan	Component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to e.coli-derived asparaginases	Open-Label Single Arm Multicenter 58 Subjects	Proportion of patients achieving a serum trough asparaginase level $\geq$ 0.1 International Unites/mL	At 48 hours, 100% achieved the endpoint (95% CI: 90-100)	<p>The available approval documents do not suggest why a single study was acceptable to FDA, but it might have been acceptable because the drug is a replacement therapy in a rare form of cancer.</p> <p><u>FDA News Release:</u> (<a href="http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280525.htm">http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280525.htm</a>)</p> <p>“The safety and effectiveness of erwinaze was evaluated in one clinical trial of 58 patients. Additional safety data was collected from the Erwinaze Master Treatment Protocol (EMTP), an expanded access program that enrolled 843 patients.”</p> <p><u>Approved Labeling:</u></p> <p>Refers to one “single-arm, multi-center, open-label, safety and clinical pharmacology trial” and additional data obtained in an expanded access program.</p>