

## EFFECTIVE DATE

Pub. L. 112-144, title VIII, §801(b), July 9, 2012, 126 Stat. 1079, provided that: “Section 505E of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355f], as added by subsection (a), applies only with respect to a drug that is first approved under section 505(c) of such Act (21 U.S.C. 355(c)) on or after the date of the enactment of this Act [July 9, 2012].”

**§ 356. Expedited approval of drugs for serious or life-threatening diseases or conditions**

**(a) Designation of a drug as a breakthrough therapy**

**(1) In general**

The Secretary shall, at the request of the sponsor of a drug, expedite the development and review of such drug if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. (In this section, such a drug is referred to as a “breakthrough therapy”.)

**(2) Request for designation**

The sponsor of a drug may request the Secretary to designate the drug as a breakthrough therapy. A request for the designation may be made concurrently with, or at any time after, the submission of an application for the investigation of the drug under section 355(i) of this title or section 262(a)(3) of title 42.

**(3) Designation**

**(A) In general**

Not later than 60 calendar days after the receipt of a request under paragraph (2), the Secretary shall determine whether the drug that is the subject of the request meets the criteria described in paragraph (1). If the Secretary finds that the drug meets the criteria, the Secretary shall designate the drug as a breakthrough therapy and shall take such actions as are appropriate to expedite the development and review of the application for approval of such drug.

**(B) Actions**

The actions to expedite the development and review of an application under subparagraph (A) may include, as appropriate—

- (i) holding meetings with the sponsor and the review team throughout the development of the drug;
- (ii) providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable;
- (iii) involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review;
- (iv) assigning a cross-disciplinary project lead for the Food and Drug Administration

review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and

(v) taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment.

**(b) Designation of drug as fast track product**

**(1) In general**

The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition, or if the Secretary designates the drug as a qualified infectious disease product under section 355f(d) of this title. (In this section, such a drug is referred to as a “fast track product”.)

**(2) Request for designation**

The sponsor of a new drug may request the Secretary to designate the drug as a fast track product. A request for the designation may be made concurrently with, or at any time after, submission of an application for the investigation of the drug under section 355(i) of this title or section 262(a)(3) of title 42.

**(3) Designation**

Within 60 calendar days after the receipt of a request under paragraph (2), the Secretary shall determine whether the drug that is the subject of the request meets the criteria described in paragraph (1). If the Secretary finds that the drug meets the criteria, the Secretary shall designate the drug as a fast track product and shall take such actions as are appropriate to expedite the development and review of the application for approval of such product.

**(c) Accelerated approval of a drug for a serious or life-threatening disease or condition, including a fast track product**

**(1) In general**

**(A) Accelerated approval**

The Secretary may approve an application for approval of a product for a serious or life-threatening disease or condition, including a fast track product, under section 355(c) of this title or section 262(a) of title 42 upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. The approval described in the preceding sentence is referred to in this section as “accelerated approval”.

**(B) Evidence**

The evidence to support that an endpoint is reasonably likely to predict clinical benefit under subparagraph (A) may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.

**(2) Limitation**

Approval of a product under this subsection may be subject to 1 or both of the following requirements:

(A) That the sponsor conduct appropriate postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit.

(B) That the sponsor submit copies of all promotional materials related to the product during the preapproval review period and, following approval and for such period thereafter as the Secretary determines to be appropriate, at least 30 days prior to dissemination of the materials.

**(3) Expedited withdrawal of approval**

The Secretary may withdraw approval of a product approved under accelerated approval using expedited procedures (as prescribed by the Secretary in regulations which shall include an opportunity for an informal hearing) if—

(A) the sponsor fails to conduct any required postapproval study of the drug with due diligence;

(B) a study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the product fails to verify and describe such effect or benefit;

(C) other evidence demonstrates that the product is not safe or effective under the conditions of use; or

(D) the sponsor disseminates false or misleading promotional materials with respect to the product.

**(d) Review of incomplete applications for approval of a fast track product****(1) In general**

If the Secretary determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the Secretary shall evaluate for filing, and may commence review of portions of, an application for the approval of the product before the sponsor submits a complete application. The Secretary shall commence such review only if the applicant—

(A) provides a schedule for submission of information necessary to make the application complete; and

(B) pays any fee that may be required under section 379h of this title.

**(2) Exception**

Any time period for review of human drug applications that has been agreed to by the Secretary and that has been set forth in goals identified in letters of the Secretary (relating to the use of fees collected under section 379h of this title to expedite the drug development

process and the review of human drug applications) shall not apply to an application submitted under paragraph (1) until the date on which the application is complete.

**(e) Construction****(1) Purpose**

The amendments made by the Food and Drug Administration Safety and Innovation Act to this section are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs.

**(2) Construction**

Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 355 of this title (including the substantial evidence standard in section 355(d) of this title) or under section 262(a) of title 42. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well-controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B).

**(f) Awareness efforts**

The Secretary shall—

(1) develop and disseminate to physicians, patient organizations, pharmaceutical and biotechnology companies, and other appropriate persons a description of the provisions of this section applicable to breakthrough therapies, accelerated approval, and and<sup>1</sup> fast track products; and

(2) establish a program to encourage the development of surrogate and clinical endpoints, including biomarkers, and other scientific methods and tools that can assist the Secretary in determining whether the evidence submitted in an application is reasonably likely to predict clinical benefit for serious or life-threatening conditions for which significant unmet medical needs exist.

(June 25, 1938, ch. 675, §506, as added Pub. L. 105-115, title I, §112(a), Nov. 21, 1997, 111 Stat. 2309; amended Pub. L. 112-144, title VIII, §803, title IX, §§901(b), 902(a), July 9, 2012, 126 Stat. 1079, 1083, 1086.)

## REFERENCES IN TEXT

The Food and Drug Administration Safety and Innovation Act, referred to in subsec. (e)(1), is Pub. L. 112-144. For the amendments made to this section by the Act, see 2012 Amendment notes below.

## PRIOR PROVISIONS

A prior section 356, act June 25, 1938, ch. 675, §506, as added Dec. 22, 1941, ch. 613, §3, 55 Stat. 851; amended Pub. L. 102-300, §6(b)(2), June 16, 1992, 106 Stat. 240; Pub. L. 103-80, §3(o), Aug. 13, 1993, 107 Stat. 777, related to certification of drugs containing insulin, prior to re-

<sup>1</sup> So in original.

peal by Pub. L. 105–115, title I, §125(a)(1), Nov. 21, 1997, 111 Stat. 2325.

#### AMENDMENTS

2012—Pub. L. 112–144, §901(b), amended section generally. Prior to amendment, section consisted of subsecs. (a) to (d) relating to designation of drugs as fast track products, approval of applications for fast track products, review of incomplete applications for approval of fast track products, and awareness efforts, respectively.

Subsec. (a). Pub. L. 112–144, §902(a)(3), added subsec. (a). Former subsec. (a) redesignated (b).

Subsec. (a)(1). Pub. L. 112–144, §803, amended subsec. (a)(1), as amended by Pub. L. 112–144, §901(b), by inserting “, or if the Secretary designates the drug as a qualified infectious disease product under section 355f(d) of this title” after “such a disease or condition”.

Subsecs. (b) to (d). Pub. L. 112–144, §902(a)(1), redesignated subsecs. (a) to (c) as (b) to (d), respectively. Former subsec. (d) relating to awareness efforts redesignated (f).

Subsec. (f). Pub. L. 112–144, §902(a)(2), which directed the redesignation of subsec. (d) as (f), was executed by redesignating the subsec. (d) relating to awareness efforts as (f), to reflect the probable intent of Congress.

Subsec. (f)(1). Pub. L. 112–144, §902(a)(4), substituted “applicable to breakthrough therapies, accelerated approval, and” for “applicable to accelerated approval”.

#### EFFECTIVE DATE

Section effective 90 days after Nov. 21, 1997, except as otherwise provided, see section 501 of Pub. L. 105–115, set out as an Effective Date of 1997 Amendment note under section 321 of this title.

#### FINDINGS AND SENSE OF CONGRESS ON ENHANCEMENT OF ACCELERATED PATIENT ACCESS TO NEW MEDICAL TREATMENTS

Pub. L. 112–144, title IX, §901(a), July 9, 2012, 126 Stat. 1082, provided that:

“(1) FINDINGS.—Congress finds as follows:

“(A) The Food and Drug Administration (referred to in this section as the ‘FDA’) serves a critical role in helping to assure that new medicines are safe and effective. Regulatory innovation is 1 element of the Nation’s strategy to address serious and life-threatening diseases or conditions by promoting investment in and development of innovative treatments for unmet medical needs.

“(B) During the 2 decades following the establishment of the accelerated approval mechanism, advances in medical sciences, including genomics, molecular biology, and bioinformatics, have provided an unprecedented understanding of the underlying biological mechanism and pathogenesis of disease. A new generation of modern, targeted medicines is under development to treat serious and life-threatening diseases, some applying drug development strategies based on biomarkers or pharmacogenomics, predictive toxicology, clinical trial enrichment techniques, and novel clinical trial designs, such as adaptive clinical trials.

“(C) As a result of these remarkable scientific and medical advances, the FDA should be encouraged to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate. This may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs.

“(D) Patients benefit from expedited access to safe and effective innovative therapies to treat unmet

medical needs for serious or life-threatening diseases or conditions.

“(E) For these reasons, the statutory authority in effect on the day before the date of enactment of this Act [July 9, 2012] governing expedited approval of drugs for serious or life-threatening diseases or conditions should be amended in order to enhance the authority of the FDA to consider appropriate scientific data, methods, and tools, and to expedite development and access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions.

“(2) SENSE OF CONGRESS.—It is the sense of Congress that the Food and Drug Administration should apply the accelerated approval and fast track provisions set forth in section 506 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356), as amended by this section, to help expedite the development and availability to patients of treatments for serious or life-threatening diseases or conditions while maintaining safety and effectiveness standards for such treatments.”

#### GUIDANCE; AMENDED REGULATIONS

Pub. L. 112–144, title IX, §901(c), July 9, 2012, 126 Stat. 1085, provided that:

“(1) DRAFT GUIDANCE.—Not later than 1 year after the date of enactment of this Act [July 9, 2012], the Secretary of Health and Human Services (referred to in this section as the ‘Secretary’) shall issue draft guidance to implement the amendments made by this section [amending this section]. In developing such guidance, the Secretary shall specifically consider issues arising under the accelerated approval and fast track processes under section 506 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 356], as amended by subsection (b), for drugs designated for a rare disease or condition under section 526 of such Act (21 U.S.C. 360bb) and shall also consider any unique issues associated with very rare diseases.

“(2) FINAL GUIDANCE.—Not later than 1 year after the issuance of draft guidance under paragraph (1), and after an opportunity for public comment, the Secretary shall—

“(A) issue final guidance; and

“(B) amend the regulations governing accelerated approval in parts 314 and 601 of title 21, Code of Federal Regulations, as necessary to conform such regulations with the amendment made by subsection (b).

“(3) CONSIDERATION.—In developing the guidance under paragraphs (1) and (2)(A) and the amendments under paragraph (2)(B), the Secretary shall consider how to incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence in such guidance, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical.

“(4) CONFORMING CHANGES.—The Secretary shall issue, as necessary, conforming amendments to the applicable regulations under title 21, Code of Federal Regulations, governing accelerated approval.

“(5) NO EFFECT OF INACTION ON REQUESTS.—The issuance (or nonissuance) of guidance or conforming regulations implementing the amendment made by subsection (b) shall not preclude the review of, or action on, a request for designation or an application for approval submitted pursuant to section 506 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 356], as amended by subsection (b).”

Pub. L. 112–144, title IX, §902(b), July 9, 2012, 126 Stat. 1087, provided that:

“(1) IN GENERAL.—

“(A) GUIDANCE.—Not later than 18 months after the date of enactment of this Act [July 9, 2012], the Secretary of Health and Human Services (referred to in this section as the ‘Secretary’) shall issue draft guidance on implementing the requirements with respect to breakthrough therapies, as set forth in section 506(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(a)), as amended by this section. The

Secretary shall issue final guidance not later than 1 year after the close of the comment period for the draft guidance.

“(B) AMENDED REGULATIONS.—

“(i) IN GENERAL.—If the Secretary determines that it is necessary to amend the regulations under title 21, Code of Federal Regulations in order to implement the amendments made by this section to section 506(a) of the Federal Food, Drug, and Cosmetic Act, the Secretary shall amend such regulations not later than 2 years after the date of enactment of this Act.

“(ii) PROCEDURE.—In amending regulations under clause (i), the Secretary shall—

“(I) issue a notice of proposed rulemaking that includes the proposed regulation;

“(II) provide a period of not less than 60 days for comments on the proposed regulation; and

“(III) publish the final regulation not less than 30 days before the effective date of the regulation.

“(iii) RESTRICTIONS.—Notwithstanding any other provision of law, the Secretary shall promulgate regulations implementing the amendments made by this section only as described in clause (ii).

“(2) REQUIREMENTS.—Guidance issued under this section shall—

“(A) specify the process and criteria by which the Secretary makes a designation under section 506(a)(3) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 356(a)(3)]; and

“(B) specify the actions the Secretary shall take to expedite the development and review of a breakthrough therapy pursuant to such designation under such section 506(a)(3), including updating good review management practices to reflect breakthrough therapies.”

Pub. L. 105-115, title I, §112(b), Nov. 21, 1997, 111 Stat. 2310, provided that: “Within 1 year after the date of enactment of this Act [Nov. 21, 1997], the Secretary of Health and Human Services shall issue guidance for fast track products (as defined in [former] section 506(a)(1) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 356(a)(1)]) that describes the policies and procedures that pertain to section 506 of such Act.”

### § 356-1. Accelerated approval of priority countermeasures

#### (a) In general

The Secretary of Health and Human Services may designate a priority countermeasure as a fast-track product pursuant to section 356 of this title or as a device granted review priority pursuant to section 360e(d)(5) of this title. Such a designation may be made prior to the submission of—

(1) a request for designation by the sponsor or applicant; or

(2) an application for the investigation of the drug under section 355(i) of this title or section 262(a)(3) of title 42.

Nothing in this subsection shall be construed to prohibit a sponsor or applicant from declining such a designation.

#### (b) Use of animal trials

A drug for which approval is sought under section 355(b) of this title or section 262 of title 42 on the basis of evidence of effectiveness that is derived from animal studies pursuant to section 123<sup>1</sup> may be designated as a fast track product for purposes of this section.

#### (c) Priority review of drugs and biological products

A priority countermeasure that is a drug or biological product shall be considered a priority

drug or biological product for purposes of performance goals for priority drugs or biological products agreed to by the Commissioner of Food and Drugs.

#### (d) Definitions

For purposes of this title:<sup>1</sup>

(1) The term “priority countermeasure” has the meaning given such term in section 247d-6(h)(4)<sup>1</sup> of title 42.

(2) The term “priority drugs or biological products” means a drug or biological product that is the subject of a drug or biologics application referred to in section 101(4) of the Food and Drug Administration Modernization Act of 1997.

(Pub. L. 107-188, title I, §122, June 12, 2002, 116 Stat. 613.)

#### REFERENCES IN TEXT

Section 123, referred to in subsec. (b), is section 123 of Pub. L. 107-188, title I, June 12, 2002, 116 Stat. 613, which is not classified to the Code.

This title, referred to in subsec. (d), is title I of Pub. L. 107-188, June 12, 2002, 116 Stat. 596, which enacted this section, section 669a of Title 29, Labor, and sections 244, 245, 247d-3a, 247d-3b, 247d-7a to 247d-7d, 300hh, 300hh-11 to 300hh-13, 1320b-5, and 7257d of Title 42, The Public Health and Welfare, amended sections 247d to 247d-6, 264, 266, 290hh-1, and 5196b of Title 42, and enacted provisions set out as notes preceding section 8101 of Title 38, Veterans' Benefits, and under sections 201, 244, 247d, 247d-6, 300hh, 300hh-12, and 1320b-5 of Title 42. For complete classification of this title to the Code, see Tables.

Section 247d-6(h)(4) of title 42, referred to in subsec. (d)(1), was redesignated section 247d-6(e)(4) by Pub. L. 109-417, title III, §304(3), Dec. 19, 2006, 120 Stat. 2861.

Section 101(4) of the Food and Drug Administration Modernization Act of 1997, referred to in subsec. (d)(2), is section 101(4) of Pub. L. 105-115, which is set out as a note under section 379g of this title.

#### CODIFICATION

Section was enacted as part of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, and not as part of the Federal Food, Drug, and Cosmetic Act which comprises this chapter.

### § 356a. Manufacturing changes

#### (a) In general

With respect to a drug for which there is in effect an approved application under section 355 or 360b of this title or a license under section 262 of title 42, a change from the manufacturing process approved pursuant to such application or license may be made, and the drug as made with the change may be distributed, if—

(1) the holder of the approved application or license (referred to in this section as a “holder”) has validated the effects of the change in accordance with subsection (b) of this section; and

(2)(A) in the case of a major manufacturing change, the holder has complied with the requirements of subsection (c) of this section; or

(B) in the case of a change that is not a major manufacturing change, the holder complies with the applicable requirements of subsection (d) of this section.

#### (b) Validation of effects of changes

For purposes of subsection (a)(1) of this section, a drug made with a manufacturing change

<sup>1</sup> See References in Text note below.