February 27, 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need; Public Hearing; Request for Comments, Docket No. FDA-2012-N-1248 (Jan. 15, 2013)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to the Food and Drug Administration’s (FDA) notice of public hearing and request for comments on a potential new drug approval pathway intended to expedite the development of new medicines for serious or life-threatening conditions that would address an unmet medical need, including medicines for serious or life-threatening infections caused by antibiotic-resistant bacteria. PhRMA is a voluntary, non-profit association that represents the country’s leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA members invested approximately $50 billion in 2011 in discovering and developing new medicines, representing the vast majority of private investment in new medicines in the United States. PhRMA member companies are committed to the development of innovative, life-saving and life-altering treatments and cures for serious and life-threatening conditions.

PhRMA is committed to helping ensure that patients have access to safe and effective new medicines, and we recognize the particular importance of developing and securing the approval of new antibiotic and anti-infective agents that can prevent the mortality and debilitating morbidity associated with emerging or resistant pathogens. PhRMA understands that for patients affected by such pathogens, timely access to new medicines can be a matter of life or death. We have, therefore, long supported FDA’s appropriate use of innovative approaches and regulatory flexibility when considering the type and quantity of data required to establish the safety and efficacy of these medicines—as well as other innovative medicines to address unmet medical needs.

Congress highlighted the need for use of broad flexibility conducive to promoting and incentivizing the development of medicines for unmet medical needs when it enacted the Food and Drug Administration Safety and Innovation Act (FDASIA) last year. Specifically, Congress included enhancements of FDA’s existing accelerated approval pathway and fast track designation procedures, and it created a new “breakthrough therapy” designation. PhRMA supports FDA’s use of these and other tools, such as priority review.

Although PhRMA believes that FDA’s existing regulatory armamentarium is strong, we also recognize that development of new antibiotics represents an urgent and unique challenge that requires special attention. For this reason, PhRMA stands ready to continue its work with FDA and other stakeholders toward establishment of an appropriate and targeted regulatory approach that will accelerate the development and availability of sorely needed novel antibiotic and anti-infective medicines. To accelerate the development of novel antibiotics and anti-infectives, PhRMA believes that FDA could initiate a new program using a combination of (i) existing regulatory flexibility granted under the Federal Food, Drug, and Cosmetic Act (FDCA) and (ii) voluntary stewardship programs managed by healthcare professionals to address possible resistance issues.

Among the first tasks FDA should address is one set out for FDA by Congress in 2012: issuance of science-based guidance related to clinical trials for antibiotics and the pathogen-focused development of antibiotics. Such guidance will address a significant need, and it should be pursued by the agency in an expedited manner. While the focus and desire for novel approaches to the development of antibiotics is important, PhRMA also strongly encourages the agency to employ its existing regulatory flexibility when considering the quantum and type of clinical data necessary for approval of all drugs and biologics intended to address unmet medical needs for patients with serious or life-threatening conditions. For example, whenever scientifically and medically appropriate, streamlined clinical trials should be used to support approvals and to bring innovative, life-saving, or life-altering medicines to patients in need. PhRMA supports the consideration of the patients’ perspective, including the perspectives of specific subpopulations of patients, of acceptable benefits and risks when evaluating the benefit-risk profile of new drugs and biologics.

As FDA continues to explore ways to enhance its use of regulatory flexibility to accelerate development of novel antibiotics and anti-infectives, it will also be important to consider ways to ensure that any new regulatory approach would not result in confusion of expectations or a diversion of resources from existing and proven pathways, as well as from pathways that remain to be implemented. Stakeholders and FDA should work together to avoid such an outcome, which could hamper access to important therapies for patients in need. Furthermore, any program implemented by FDA should seek to avoid unintended consequences that could harm patient care, such as the possibility of direct or indirect government restrictions on the practice of medicine.
I. Development of New Antibiotic and Anti-infective Products Is a Public Health Imperative

The dramatic increase in the emergence of antibiotic-resistance bacteria over the last decade is now a public health crisis. The Centers for Disease Control and Prevention (CDC) has identified antimicrobial resistance as a major public health issue and the World Health Organization (WHO) has identified antimicrobial resistance as a global health concern.2,3 According to the CDC, the emergence of drug-resistant bacteria has significant consequences on the health of patients and the costs of health care delivery. Individuals that are infected with drug-resistant organisms are more likely to have longer and more expensive hospital stays, suffer more when treated with less effective, more toxic, and more expensive second- or third-choice drugs, may require more complicated treatment, and may be more likely to die as a result of the infection.4

Even when antibiotics are used appropriately, antimicrobial resistance is an inevitable evolutionary consequence of antibiotic use. This biological fact underscores the importance of a constant supply of new antibiotic medicines to augment existing options. Appropriate use of antibiotic agents helps slow the emergence of antibiotic-resistant organisms, but a sustainable pipeline of safe and effective antibiotics is still urgently needed to successfully treat serious and life-threatening infections. PhRMA stands ready to work with the agency and other stakeholders to explore effective ways to facilitate antibiotic and anti-infective development and approval using its existing regulatory flexibility, and the strengthening of antibiotic and anti-infective stewardship programs designed and operated by health care providers and health care systems.

II. Continued and Proactive Use of FDA’s Existing Regulatory Flexibility Can Help Facilitate Development and Rapid Approval of New Antibiotics and Anti-infectives

A. Specific Regulatory Tools That May Be Used To Expedite the Development and Approval of Antibiotics and Anti-infectives

As outlined above, PhRMA shares the agency’s sense of urgency about the need for innovative antibiotics and anti-infectives that provide novel treatment options for patients with drug-resistant or difficult to treat infections. PhRMA believes that innovative use of the existing mechanisms listed below can help to expedite the availability of new treatments for patients.

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**Clinical trial design.** PhRMA believes that FDA can—and should—explore approaches to pre-clinical and clinical trial design and analysis that might foster antibiotic and anti-infective development and approval. This could include, as proposed in a recent article by John Rex *et al.* in the *Lancet Infectious Diseases*, acceptance of clinical trial designs that account for prior knowledge of effectiveness and respond to the inherent challenges in testing antibiotics. As described in the *Lancet* article, the agency could approve a new antibiotic in any of four scenarios: (A) pursuant to two phase 3 studies; (B) pursuant to one phase 3 study, plus small comparative and descriptive studies; (C) pursuant to small comparative and descriptive studies; or (D) pursuant to animal efficacy studies and adequate human safety studies. Implementation of the proposed framework in the *Lancet* article through the development of guidance and use of existing regulatory flexibility would permit and encourage the development of innovative antibiotics to address unmet medical needs.

PhRMA suggests that FDA consider the proposal in the *Lancet* article when preparing the guidance documents required under FDASIA relating to revision of clinical trial guidance and the approval of pathogen-specific antibiotics and anti-infectives. Section 804 of FDASIA requires FDA to review and, as appropriate, revise at least three clinical trials guidance documents per year. This must include guidance documents relating to the conduct of clinical trials with respect to antibacterial and antifungal drugs. The agency must also revise these guidance documents to reflect developments in scientific and medical information and technology and to ensure clarity regarding the procedures and requirements for approval of antibacterial and antifungal drugs. Section 806 of FDASIA requires FDA to publish a guidance on pathogen-focused antibacterial drugs that is intended to facilitate the development of antibacterial drugs for serious or life-threatening bacterial infections. Implementation and use of such tools, clarification of FDA’s expectations in guidance, and regulatory flexibility can accelerate the development of antibiotic products.

**Labeling.** We agree with the authors of the *Lancet* article that the current regulatory framework and current FDA authority is adequate and sufficiently flexible to permit FDA to grant either disease-based or pathogen-based indications, with labeling that clearly communicates the data upon which new indications rely. FDA can and does limit the scope of its approval to the populations for which the benefit-risk balance is positive.

FDA can tailor approved labeling to what is currently known about the benefit-risk balance of a new antibiotic, in view of the preclinical and clinical testing

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5 See generally John H. Rex, *et al.*, A comprehensive regulatory framework to address the unmet need for new antibacterial treatments, THE LANCET (Jan. 15, 2013). The authors propose a 4-tiered regulatory framework under which differing quantities of clinical evidence may be required. They also argue that antibacterial drugs are well suited to orthogonal datasets and a totality-of-the-evidence approach and that by providing both dose justification and proof of mechanism (the antibiotic acts through its pharmacological effect on bacteria), the well understood pharmacokinetic-pharmacodynamic relations between drug exposure, isolate susceptibility, and outcome meet the demanding standard of causal confirmation proposed by Peck and colleagues and allow extrapolation of likely efficacy to future patients. *Id.* at 1* (internal citations omitted).

6 FDASIA § 804.
that has been done and the tools that have been used to expedite its approval. Where the agency determines that a particular product’s benefit-risk profile compels narrow labeling, it may limit the scope of the approval through narrow indications statements, specific contraindications, and warnings. This authority has been applied to new antibiotic drugs. For example, on December 28, 2012, FDA granted accelerated approval to the orphan product-designated antibiotic Sirturo (bedaquiline) with a recommended usage statement in the Indications and Usage section.7

The agency also has adopted specific regulations that govern the labeling of systemic antibacterial drug products.8 For example, the “Indications and Usage” section of an antibiotic product label must include the following statement:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of (insert name of antibacterial drug product) and other antibacterial drugs, (insert name of antibacterial drug product) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and

7 Sirturo’s “Indications and Usage” section provides:

SIRTURO is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO for use when an effective treatment regimen cannot otherwise be provided. SIRTURO should be administered by directly observed therapy (DOT).

This indication is based on analysis of time to sputum culture conversion from two controlled Phase 2 trials in patients with pulmonary MDR-TB.

Limitations of Use:

The safety and efficacy of SIRTURO for the treatment of latent infection due to Mycobacterium tuberculosis has not been established. The safety and efficacy of SIRTURO for the treatment of drug-sensitive TB has not been established. In addition, there are no data on the treatment with SIRTURO of extra-pulmonary TB (e.g., central nervous system). Therefore, use of SIRTURO in these settings is not recommended.

8 21 C.F.R. § 201.24.
susceptibility patterns may contribute to the empiric selection of therapy.\textsuperscript{9}

Thus, the agency can narrowly tailor an indication for an antibiotic to a specific subpopulation and provide information about what is known about use of the antibiotic and the limitations of the data.

B. General Tools That Can Be Used to Expedite the Development and Approval of Antibiotics and Anti-infectives

Taking into account the new FDASIA authorities, there are a number of tools available to FDA that may expedite the development and review of new antibiotics and anti-infectives. Use of the regulatory flexibility inherent in the existing statutory framework is critical to address the antibiotic public health crisis. The tools described below can also be used to facilitate development and approval of non-anitibiotic treatments that address unmet needs or serious diseases or conditions. We urge FDA to use the tools whenever possible.

- **Accelerated Approval:** Approval can be granted on the basis of studies establishing that the drug or biologic “has an effect on a surrogate endpoint that is reasonably likely to predict a 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.”\textsuperscript{10}

- **Breakthrough Therapy Designation:** A drug can be designated a “breakthrough therapy” in order to facilitate the expedited development and review of such a drug when preliminary clinical evidence indicates the drug may demonstrate a substantial improvement over existing therapies.

- **“Totality of the evidence” approach:** A “totality-of-the-evidence” approach integrates various types of information about a product’s safety and efficacy to reach an overall assessment of the product’s benefit-risk profile for a defined patient population.

- **Allowing a Single Adequate and Well-controlled Trial, When Scientifically Appropriate:** Congress in 1997 amended section 505 of the FDCA to clarify that, based on relevant science, data from a single adequate and well-controlled clinical investigation with confirmatory evidence (obtained prior to or after such investigation) are sufficient to

\textsuperscript{9} 21 C.F.R. § 201.24.

\textsuperscript{10} FDCA § 506(b)(1)(A).
establish effectiveness.\footnote{FDAMA § 115(a), amending FDCA § 505(d)(7).} FDA’s resulting guidance offers numerous examples of “substantial evidence” grounded in a single adequate and well-controlled trial and independent substantiation.

- **Adaptive Trial Design:** An adaptive design clinical trial is one that includes a prospectively planned opportunity for modification of one or more specified aspects of study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.\footnote{FDA, Draft Guidance, Adaptive Design Clinical Trials for Drugs and Biologics (Feb. 2010), at 6.} Adaptive trial designs can lead to shorter and smaller trials, and consequently more efficient clinical development programs, compared to traditional non-adaptive trial designs.

- **Fast Track:** The fast track process is designed to expedite the review of drugs to treat serious conditions that also address an unmet medical need, so they can reach patients earlier.

- **Priority Review:** Priority review significantly shortens FDA’s goal for its application review period (from 10 months to six months) and can therefore expedite the approval of certain therapies.

- **Animal Rule:** The Animal Rule permits approval of drugs and biologics that may not otherwise be approvable due to the lack of clinical (human) efficacy data.

In brief, the statutory and regulatory tools and flexibility discussed above (and in more detail in the Appendix) — particularly a “totality of the evidence” approach — should be applied to important new antibiotic and anti-infective therapies whenever scientifically and medically appropriate.\footnote{For example, the agency has the option to designate an antibiotic or anti-infective as a fast track product or a breakthrough therapy. It can use the accelerated approval pathway and apply priority review to expedite its review timeline. An antibiotic or anti-infective may be approved on the basis of a single clinical trial with confirmatory evidence, on the basis of innovative trial designs (e.g., adaptive trials), or on the basis of animal data using a totality-of-the evidence approach.} We also urge FDA to implement the related FDASIA requirements intended to facilitate and expedite drug development and approval. This includes implementing a structured benefit-risk assessment framework in the new drug approval process, which would help reduce regulatory uncertainty and expedite drug development. It also includes issuing required guidance documents relating to breakthrough therapies, fast track and accelerated approval, and feasible development programs for antibiotics in a timely manner.
III. FDA Should Consider Implementation of a Special Program to Focus on Accelerated Development and Approval of Antibiotics and Anti-infectives

PhRMA agrees with FDA that it is vitally important to encourage and facilitate the development and speed the approval of novel antibiotics and anti-infectives. PhRMA stands ready to work with stakeholders to help achieve this important public health goal. PhRMA supports focused attention by FDA on clarifying and expediting the regulatory framework governing antibiotic and anti-infective approval in order to help facilitate an increase in the number of innovative antibiotics and anti-infectives available to combat antimicrobial resistance. Appropriate use of antibiotics slows development of antimicrobial resistance. PhRMA recognizes the important role that healthcare provider-led stewardship programs for antibiotics and anti-infectives play in slowing the development and spread of resistance, although stewardship will not eliminate or solve the public health crisis. Addressing and resolving the issues below could be a significant step in determining whether a new program that is applicable to new antibiotics and anti-infectives is needed, and how such a program, if required, should operate in practice.

First, FDA and other stakeholders should assess the impact of a potential new proposal on the practice of medicine. PhRMA supports providing health care providers with accurate information about the benefits and risks of approved drugs, including information about the nature of the evidence supporting approval and limitations of the data that may be relevant to future use. But prescribing restrictions and healthcare provider monitoring (which some might envision to accompany the proposed new formal designation and labeling) could interfere with the ability of health care providers to provide empiric treatment to patients in need. The protection of the physician-patient relationship and the ability of health care providers to act on their professional judgment to provide timely, individualized care to patients are of paramount concern. With respect to any proposal that is adopted, clear boundaries must be established to ensure that FDA does not inadvertently encroach on the practice of medicine.

Second, new efforts beyond current authorities to limit the use of a new drug or biologic by healthcare professionals to a specific category of patients would likely require increased resources to monitor and enforce. Indeed, a significant increase in the number of products subject to REMS would also require increased resources to monitor and enforce.

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14 The Supreme Court has noted that off-label use is an “accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine.” Buckman Co. v. Plaintiffs’ Legal Comm., 531 U.S. 341, 350 (2001). Further, “FDA-approved indications were not intended to limit or interfere with the practice of medicine nor to preclude physicians from using their best judgment in the interest of the patient.” Weaver v. Reagen, 886 F.2d 194, 198-99 (8th Cir.1989) (internal quotation marks omitted).

15 The FDCA does not provide FDA with authority to regulate the practice of medicine, and the agency itself has acknowledged that “Congress did not intend the Food and Drug Administration to regulate or interfere with the practice of medicine . . . .” 37 Fed. Reg. 16503 (Aug. 15, 1972).
Finally, FDA and its stakeholders should consider whether a potential new program and associated designation would have other collateral consequences such as creating regulatory confusion and uncertainty, influencing reimbursement issues, or raising liability concerns for health care providers that prescribe the products. Immediate access to and empirically-guided treatment with antibiotics are essential to the appropriate and timely treatment of patients with potentially serious or life-threatening infections. Studies show that mortality increases significantly each hour that a patient goes without antibiotic treatment. Additional restrictions on health care provider and patient access to necessary therapies to treat serious and life-threatening diseases, beyond the existing safeguards in current law and regulations, might restrict, unnecessarily and inappropriately, patient access to novel therapies. Given the existing statutory and regulatory flexibility that it possesses to approve new medicines, collateral consequences should be considered before any new pathway is considered.

IV. Conclusion

PhRMA looks forward to a continued dialogue with FDA and other stakeholders on the important issues raised in FDA’s notice and discussed in this comment. We hope the agency continues to solicit public, transparent stakeholder input as it considers how to facilitate the approval of antibiotics, as well as all new drugs and biologics intended to treat unmet medical needs.

If you have any questions, please do not hesitate to contact us.

Respectfully submitted,

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16 See, e.g., A. Kumar, et al., Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival benefit in human septic shock, CRITICAL CARE MED., 2006 34(6): 1589-96 (Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hours was associated with an average decrease in survival of 7.6 %).
APPENDIX: Summary of FDA’s Tools Under Existing Authority to Expedite Development and Approval of Therapies for Unmet Medical Needs

Statutory pathways governing new drug and biological product approvals are drafted broadly.

FDA’s governing statutes are broadly worded and are intended to give FDA considerable flexibility. While the FDCA requires “substantial evidence” of effectiveness,\(^\text{17}\) consisting of “adequate and well-controlled clinical investigations,”\(^\text{18}\) it was amended in 1997 to make clear that data from one such investigation are sufficient, provided there is “confirmatory evidence (obtained prior to or after the investigation)” of effectiveness.\(^\text{19}\) FDA has appropriately interpreted the substantial evidence requirement flexibly. Similarly, while FDA takes the view that the PHSA also requires “substantial evidence” of effectiveness, it also interprets the phrase flexibly in the context of biologics.\(^\text{20}\) FDA has thus approved biological products on the basis of a single, multicenter study with “statistically very persuasive” results.\(^\text{21}\)

Statutory and regulatory tools that can be used to expedite the development and approval of new drug and biologics that address unmet medical needs

1. Accelerated Approval

In 1988, in response to the AIDS epidemic and as a precursor to the accelerated approval pathway, FDA promulgated the Investigational New Drug (IND) Subpart E regulation for drugs intended to treat life-threatening and severely-debilitating illnesses to help expedite drug development and provide patients with

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17 Substantial evidence is defined by the FDCA 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.” FDCA § 505(d).

18 21 C.F.R. § 314.126.

19 FDAMA § 115(a), FDCA § 505(d)(7).

20 FDA reviews biological license applications (BLA) to ensure that biological products licensed for marketing have been demonstrated to be “safe, pure, and potent.” PHSA § 351(a)(2)(B). Potency has long been interpreted to include effectiveness, and proof of effectiveness for biological products similarly consists of adequate, well-controlled clinical trials, unless waived because they are not applicable for the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness. 21 C.F.R. § 600.3(s); 21 C.F.R. § 601.25(d)(2). One such alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists. FDA, Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (May 1998), at 4.

earlier access to promising therapies, if appropriate.\textsuperscript{22} The purpose of the regulation was to “establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists.”\textsuperscript{23}

The subsequent promulgation of accelerated approval regulations was FDA’s response to the continued AIDS crisis and the need to expedite the development and approval of drugs that address a life-threatening disease. In 1992, FDA’s NDA Subpart H and BLA Subpart E regulations established procedures for an accelerated approval pathway.\textsuperscript{24} Under the 1992 regulations, approval could be granted on the basis of studies establishing that the drug or biologic “has an effect on a surrogate endpoint that is reasonably likely . . . to predict a clinical benefit.” Approval would be conditioned upon subsequent (post-approval) trials to verify and describe the clinical benefit, at which point traditional approval would be granted. Congress then in 1997 gave FDA explicit authority to approve drugs and biologics on an accelerated basis and to condition that approval on completion of postmarketing studies.\textsuperscript{25} Since accelerated approval was established in 1992, more than 80 new products have been approved through this pathway.\textsuperscript{26}

Last year, Congress amended section 506 to make clear the breadth of circumstances under which the agency might use the accelerated approval pathway, and it revised the language describing the endpoints on which accelerated approval could be based.\textsuperscript{27} Congress also specified the type of evidence that can be used to support an endpoint that is reasonably likely to predict clinical benefit (or an effect on irreversible morbidity or mortality) for purposes of accelerated approval — epidemiological, pathophysiological, therapeutic, and pharmacologic evidence, as well as evidence developed using biomarkers or other scientific methods or tools.\textsuperscript{28}

\begin{itemize}
\item \textsuperscript{22} 21 C.F.R. § 312.80.
\item \textsuperscript{23} 21 C.F.R. § 312.80.
\item \textsuperscript{24} 21 C.F.R. part 314, subpart H, and 21 C.F.R. part 601, subpart E.
\item \textsuperscript{25} FDAMA § 112, enacting FDCA § 506.
\item \textsuperscript{26} FDA, FY 2012 Innovative Drug Approvals: Bringing Life-Saving Drugs to Patients Quickly and Efficiently (Dec. 2012), available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm).
\item \textsuperscript{27} The amended section 506 provides that “[t]he Secretary may approve the application of a product for a serious or life-threatening disease or condition, including a fast track product . . . 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 italicized language, which is new, clarifies the breadth of clinical endpoints that may be used, and expressly requires FDA to consider the condition the drug will treat as well as the unmet medical need. FDASIA § 901(b) (amending FDCA § 506).
\item \textsuperscript{28} Id.
\end{itemize}
2. **Breakthrough Therapies**

Last year, Congress created another tool to expedite the development of certain drugs that, alone or in combination, treat a serious or life-threatening disease or condition. Section 902 of FDASIA amended section 506 of the FDCA by creating the “breakthrough therapy” designation in order to facilitate the expedited development and review of such a drug when preliminary clinical evidence indicates the drug may demonstrate a substantial improvement over existing therapies. This new pathway has the potential to significantly expedite the development, review, and approval of new therapies.29 The agency is required to issue guidance on breakthrough therapies within 18 months of enactment (January 9, 2014),30 but has already designated a product as a breakthrough therapy and has stated that additional designations will follow.31

3. **Totality of the Evidence**

A “totality-of-the-evidence” approach integrates various types of information about a product’s safety and efficacy to reach an overall assessment of the product’s benefit-risk profile for a defined patient population. It can take many forms and is particularly common in the approval of orphan drugs. Indeed, the agency has not only approved orphan drugs on the basis of a single well-controlled clinical trial, but also approved orphan drugs in the absence of any “well-controlled” studies at all because of a “totality of the evidence” approach.32 From 1983, when the orphan drug provisions were added to the FDCA, to June 30, 2010, CDER approved 135 new chemical entities for non-cancer indications as orphan drugs. Two thirds of these approvals required some exercise of regulatory flexibility by FDA — i.e., the quantum of efficacy evidence did not meet the conventional or traditional standards. The agency has thus approved orphan drugs on the basis of a retrospective unblinded case

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29 Under the statute, FDA may engage in a variety of different activities to help expedite the approval of breakthrough therapies. These activities may include: (1) holding meetings with the sponsor and the review team throughout the development of the drug; (2) 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; (3) involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review; (4) assigning a cross-disciplinary project lead for the FDA 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 (5) 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. FDASIA § 902 (amending FDCA § 506).

30 FDASIA § 902(b)(1)(A).


32 The requirements for the approval of orphan drugs are identical to the standard for other drugs — i.e., there must be ‘substantial evidence’ that demonstrates the effectiveness of the drug for its intended uses — but FDA acknowledges that CDER and other regulators “typically exercise considerable flexibility in dealing with orphan drug development programs.” J. Woodcock, The Future of Orphan Drug Development, 92 Clinical Pharmacology & Therapeutics 146 (August 2012).
series and comparison to a historical control;\textsuperscript{13} historically controlled, unblinded studies;\textsuperscript{34} published literature and a single double-blind placebo-controlled trial that failed;\textsuperscript{35} a single, non-inferiority trial on an unvalidated surrogate primary endpoint;\textsuperscript{36} a federal government database;\textsuperscript{37} a single open-label historically-controlled trial;\textsuperscript{38} a post-hoc analysis of trials in which the primary endpoints and pre-specified analysis failed to yield statistically significant results;\textsuperscript{39} and a post-hoc pooling of five small clinical trials (four open-label and one double-blind placebo-controlled).\textsuperscript{40}

4. A Single Adequate and Well-controlled Trial, When Scientifically Appropriate

The PHSA has never required two trials for approval, and the agency has in fact licensed biological products on the basis of a single clinical study.\textsuperscript{41} Congress in 1997 amended section 505 of the FDCA to clarify that, based on relevant science, data from a single adequate and well-controlled clinical investigation with confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness.\textsuperscript{42} FDA’s resulting guidance offers numerous examples of “substantial evidence” grounded in a single adequate and well-controlled trial and independent substantiation.\textsuperscript{43} The guidance notes that independent substantiation does not necessarily require replication of the clinical finding. Instead, “[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.”\textsuperscript{44} The 1998 guidance also suggests that this additional flexibility may play a special role with respect to drugs intended for narrow disease states and populations.\textsuperscript{45}

\textsuperscript{13} E.g., FDA Briefing Document for Carbaglu (N-carbamylglutamate) 9-10, attached to Memorandum to the Advisory Committee from Dr. Donna Griebel (FDA) (December 16, 2009) (cited in F. Sasinowski, Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs: Cataloguing FDA’s Flexibility in Regulating Therapies for Persons with Rare Disorders, 46 Drug Information J. 238, 241 (2012)).
\textsuperscript{34} Agrylin (anagrelide HCl), F. Sasinowski, Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs: Cataloguing FDA’s Flexibility in Regulating Therapies for Persons with Rare Disorders, at 248 (2012).
\textsuperscript{35} Cystadane (betaine HCl), Sasinowski, supra note 35, at 249.
\textsuperscript{36} Exjade (deferasirox), Sasinowski, supra note 35, at 252.
\textsuperscript{37} DTPA (diethylenetriamine pentaacetic acid), Sasinowski, supra note 35, at 252.
\textsuperscript{38} Myozyme (aglucosidase ALFA), Sasinowski, supra note 35, at 258.
\textsuperscript{39} Rilutek (riluzole) Label at 2 (cited in Sasinowski, supra note 35, at 259).
\textsuperscript{40} Increlex (mecasermin recombinant), Sasinowski, supra note 35, at 256.
\textsuperscript{41} See FDA, Guidance for Industry, Providing Clinical Evidence of Effectiveness (May 1998), at 4.
\textsuperscript{42} FDAMA § 115(a), amending FDCA § 505(d)(7).
\textsuperscript{43} See generally FDA, Guidance for Industry, Providing Clinical Evidence of Effectiveness (May 1998).
\textsuperscript{44} Id., at 5.
\textsuperscript{45} Id., at 2 (“As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus, for example, on a more specific disease stage or clinically distinct subpopulation.”).
5. Adaptive Trial Design

An adaptive design clinical trial is one that includes a prospectively planned opportunity for modification of one or more specified aspects of study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. Adaptive trial designs can lead to shorter and smaller trials, and consequently more efficient clinical development programs, compared to traditional non-adaptive trial designs. They may also be more likely to detect an effect if one exists in subpopulations of patients. FDA has noted “two obvious benefits” of adaptive trial design: (1) “the resulting better optimization of the drug’s use from the more extensive data may lead to an improved balance of benefit and risk”; and (2) minimizing the risk that “a successful drug development program … might have failed because of inadequate optimization.”

6. Fast Track

Once a drug is designated for the fast track process, FDA provides input to the sponsor early in the development process and will meet frequently with the sponsor to discuss the development plan and data collection strategies. This input is intended to facilitate the swift resolution of issues that may arise. In particular, through early and frequent discussions, sponsors may receive critical feedback regarding clinical study design or other issues that could prevent delays later in the process. FDA’s December 2012 report on innovative drug approvals noted that of the 12 drugs that received fast track designation in FY2012, 75 percent were approved in the first review cycle. In addition, sponsors have the option to submit NDAs and BLAs with fast track designations on a rolling basis (i.e., a section at a time, as they are ready) instead of submitting the full application when complete. This too may decrease the time until a fast track product becomes available to patients. For most years from 1998 to 2006, the median approval time for fast track products was significantly lower than that of standard NDAs and BLAs.

7. Priority Review

Priority review is available for drugs and biologics that offer major advances in treatment or provide a treatment where no adequate therapy exists, and applies to serious illnesses. FDA has approved priority review drugs in compressed

46 FDA, Draft Guidance, Adaptive Design Clinical Trials for Drugs and Biologics (Feb. 2010), at 6.
47 Id., at 233.
50 FDCA § 506(c)(1).
51 Susan Thaul, CRS Report for Congress: FDA Fast Track and Priority Review Programs (Feb. 21, 2008), at 5.
52 In 1992, the Prescription Drug User Act (PDUFA) authorized FDA to collect fees from companies that produce certain human drug and biological products. FDA then agreed to specific goals for
time frames, such as 3 to 4 months. For example, FDA approved Kalydeco (ivacaftor) for patients with cystic fibrosis and a specific genetic defect in just over 3 months; it approved Gleevec (imatinib mesylate) for chronic myeloid leukemia in 4 months; Kaletra (lopinavir and ritonavir) for treatment of HIV/AIDS in 3.5 months; and Pegasys (peginterferon alfa-2a) for the treatment of Hepatitis C in 4 months.53

8. Animal Rule

The Animal Rule permits approval of drugs and biologics that may not otherwise be approvable due to a lack of clinical (human) efficacy data at the time of approval. FDA regulations allow the submission of data from animal studies of efficacy, accompanied by adequate human safety data, as evidence to support applications of certain new products “when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible.”54 In December 2012, FDA approved raxibacumab via the Animal Rule to treat inhalational anthrax.55