COMMENTS

SIMPLIFYING FDASIA: THE "FAST TRACK" TO EXPEDITED DRUG APPROVAL EFFICIENCY

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INTRODUCTION

Housed under the umbrella of the Department of Health and Human Services (HHS), the United States Food and Drug Administration (FDA) is underfunded given the amount of commerce it regulates.[1] The FDA regulates approximately twenty cents of each consumer dollar spent in the United States,[2] which translated to over $2.28 trillion in 2013 alone.[3] The FDA has faced additional cutbacks to its budget recently,[4] but this should be nothing new to an agency that routinely regulates very much with comparatively little.[5] If past trends are any indication, the FDA will also almost certainly be left to function and protect the public health with a very limited budget in future years.[6]

Prior to the most recent budget cuts, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012,[7] creating a new designation in the FDA regime of expedited new

1. *See* OFFICE OF MGMT. & BUDGET, EXEC. OFFICE OF THE PRESIDENT, BUDGET OF THE UNITED STATES GOVERNMENT, FISCAL YEAR 2014, 93–101 (2013) (granting the United States Food and Drug Administration (FDA) $4.7 billion in total programing resources while admitting the need for outside user fee programs to support implementation of "key elements" of prior laws).

2. U.S. FOOD & DRUG ADMIN., ABOUT FDA: 2014 FDA CONGRESSIONAL BUDGET JUSTIFICATION, 1–3 FDA.GOV, http://www.fda.gov/downloads/AboutFDA/Reports ManualsForms/Reports/BudgetReports/ucms47422.pdf (last visited Jan. 31, 2014).

3. *See* U.S. DEP'T OF COMMERCE, BUREAU OF ECON. ANALYSIS, NAT'L INCOME AND PROD. ACCOUNTS TABLES, BEA.GOV, http://www.bea.gov/iTable/iTable.cfm?reqid=9& step=1&acrdn=2#reqid=9&step=3&isuri=1&903=58 (last visited Jan. 31, 2014). This illustrates in Table 2.1, Line 29 that Americans will likely spend over $11 trillion on personal consumer expenditures in 2013, as estimated by the first two quarters of the year. When multiplied by the FDA's figure estimating that it regulates twenty cents of every consumer dollar spent, the $2.28 trillion figure is reached.

4. *See* OFFICE OF MGMT. & BUDGET, REPORT TO THE CONGRESS ON THE JOINT COMMITTEE SEQUESTRATION FOR FISCAL YEAR 2013, 24 (Mar. 1, 2013) (citing a $209 million cutback to the FDA for fiscal year 2013).

5. *Compare* OFFICE OF MGMT. & BUDGET, *supra* note 1, at 93–101 (2013) (granting the FDA $4.7 billion in total programing resources), *with* text accompanying note 3 (finding that the FDA will regulate an estimated $2.28 trillion in consumer spending with its 2013 budget).

6. This prediction is based upon budgetary information gathered over the last three fiscal years under the Obama Administration and the estimate that the FDA regulates twenty cents of each consumer dollar spent. Under the 2013 budget, the FDA received $4.5 billion to regulate $2.2 trillion in consumer spending; in 2012, it received $4.4 billion to regulate $2.1 trillion; and in 2011, it received $4.0 billion to regulate $2.0 trillion. OFFICE OF MGMT. & BUDGET, FISCAL YEAR 2013 BUDGET OF THE U.S. GOV'T, 110 (2012); OFFICE OF MGMT. & BUDGET, FISCAL YEAR 2012 BUDGET OF THE U.S. GOV'T, 82 (2011); OFFICE OF MGMT. & BUDGET, FISCAL YEAR 2011 BUDGET OF THE U.S. GOV'T, 76 (2010); *Nat'l Income and Prod. Accounts Tables*, *supra* note 3.

7. Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), Pub.

drug review, "Breakthrough Therapies."[8] Though the FDA already had in place a fast track designation, priority review status, and an accelerated approval method,[9] the agency added the breakthrough therapy designation with the hope that patients with serious or life-threatening conditions could have another chance to quickly receive the drugs they need.[10] While this goal is laudable, the creation of this additional designation is unwise because of its similarity to an existing expedited method, the fast track designation.[11] This repetition is a mistake given the FDA's constant budget constraints because it entails extra evaluation, making an adjustment to the expedited drug review regime necessary.[12] Because a final guidance document on breakthrough therapies is due by July 2014,[13] the FDA should consider that this repetition lends itself to a merger between the fast track and breakthrough therapies designations rather than a mere explanation of breakthrough therapies alone.

The only major differences between the fast track designation and the breakthrough therapy designation are whether a therapy for a serious illness or life-threatening condition already exists, and what preliminary evidence is necessary to support the request for each expedited designation.[14] Though the designations both convey the same basic benefits, drug sponsors applying for breakthrough therapy status must file a separate request from those seeking fast track status because each program

L. No. 112-144, 126 Stat. 993 (codified as amended in scattered sections of 21 U.S.C.).

8. *Id.* § 902.

9. 21 U.S.C. §§ 356, 356–61 (2012).

10. *See* 158 CONG. REC. S4610 (daily ed. June 26, 2012) (stating that FDASIA streamlines the drug approval process and spurs innovation to develop drugs for life-threatening conditions).

11. *See* U.S. FOOD & DRUG ADMIN., REGULATORY INFORMATION FREQUENTLY ASKED QUESTIONS: BREAKTHROUGH THERAPIES, FDA.GOV, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm341027.htm (last visited Jan. 31, 2014) (explaining that the difference between the fast track and breakthrough therapies designations is whether there is an existing therapy for a life-threatening condition and what supporting evidence is needed for the designation).

12. *See id.* (stating that the breakthrough therapy and fast track designations are maintained as separate programs despite repetitions such as overlapping benefits); *cf.* 158 CONG. REC. S4617–19 (June 26, 2012); Elie Dolgin, *First 'Breakthrough' Drugs Designated, but Dilution Worries Linger*, 19 NATURE MED. 116–17 (2013) (praising benefits of the breakthrough therapy designation with regard to patient access to new drugs and ignoring any budgetary issues caused by the new designation).

13. FDASIA § 902(b); U.S. FOOD & DRUG ADMIN., FDASIA-TRACK, FDA.GOV, http://www.fda.gov/AboutFDA/Transparency/track/ucm328907.htm (last visited Jan. 31, 2014).

14. *Frequently Asked Questions*, *supra* note 11.

is separate.[15] Additionally, no automatic review takes place for one designation if the other fails,[16] which leads to greater delay—the very demon that expedited access seeks to fight.

This Comment recommends simplifying the expedited new drug review regime, thereby making it more efficient. To support this recommendation, the Comment first discusses the expedited new drug review regime as it stood prior to the enactment of FDASIA, explaining each of the existing expedited designations. Part II addresses the creation of breakthrough therapies, what the term means, and how the designation fits into the existing regime. Part III compares and contrasts the breakthrough therapies designation with the fast track designation. Finally, Part IV concludes by recommending that rather than maintaining the breakthrough therapies designation as an independent status for expediting drug review, it should be merged with the fast track designation. This merger would add efficiency because both designations carry the same benefits, and maintaining their reviews as separate programs can only be an unnecessary expense.

I. THE PRE-FOOD AND DRUG ADMINISTRATION SAFETY AND INNOVATION (FDASIA) EXPEDITED DRUG REVIEW REGIME

The process of approving new drugs for the American public is one of the FDA's most important and well-recognized duties. Because the approval and placement of new drugs on the market is inherently linked to public safety, the FDA maintains rigorous standards for determining the safety and effectiveness of new drugs.[17] A new drug cannot be sold without FDA approval.[18] While these standards and the new drug approval process have been critiqued and pushed to transform throughout the existence of the FDA,[19] prior to the enactment of FDASIA, the regime was not so

15. *Id.*

16. *Id.*

17. *See generally* 21 U.S.C. § 355 (2012); SUSAN THAUL, CONG. RESEARCH SERV., R41983, HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 5–6 (2012) (detailing the new drug application process and procedures).

18. *See generally* 21 U.S.C. § 355 (2012); PETER BARTON HUTT, ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS 576–77 (3d ed. 2007).

19. *E.g.,* Melissa Marie Bean, Comment, *Fatal Flaws in the Food and Drug Administration's Drug-Approval Formula*, 2003 UTAH L. REV. 881 (2003) (arguing that politics, corporate pressures, money, and morality have corrupted the drug approval process). For an example of how new drug approval has radically changed, compare Federal Food and Drugs Act of 1906, Pub. L. No. 59-381, 34 Stat. 768 (codified as amended in scattered sections of 21 U.S.C.) (containing no provision for premarket approval of drugs), with 21 U.S.C. § 355(b) (1958) (current version at 21 U.S.C. § 355 (2012)) (containing a provision for premarket approval based on safety only), and 21 U.S.C. § 355(b) (1964) (codifying the 1962 Kefauver

repetitive as to cause budgetary concern.

A. Current Standard for New Drug Approval

When a new chemical entity is discovered, it must go through the FDA approval process to reach the public. This highly expensive process can take well over a decade due to the rigorous standards a new drug must meet.[20] Additionally, approval for any compound costs over a billion dollars,[21] with the drug's sponsor bearing about 62% of that cost through the Prescription Drug User Fee Act (PDUFA).[22] Currently, a drug following the standard drug approval pathway must prove that it is safe, effective, and properly labeled via multiple rounds of clinical (human) and nonclinical (animal) trials.[23]

Prior to any FDA involvement, a drug sponsor must first synthesize and purify an active pharmaceutical ingredient (API) for testing; computer technology has simplified this process in recent years.[24] Once an API is isolated, nonclinical trials can begin to determine the compound's potential for effectiveness, reliable reproduction, and safety.[25] Though the FDA does not directly regulate nonclinical testing, it utilizes results from this phase to determine whether subsequent clinical trials may go forward. After nonclinical trials, a drug sponsor submits an investigational new drug (IND) application to the FDA, and the FDA decides if the sponsor may conduct clinical trials.[26] Thirty days after the FDA receives a satisfactory IND with adequate information to determine the safety of the drug, clinical trials may begin.[27] This information must include the investigation's design, reports allowing an assessment of its safety, chemistry and manufacturing

Harris Amendment requiring premarket approval based on both safety *and* effectiveness).

20. HUTT ET. AL., *supra* note 18, at 577.

21. *Id.*

22. U.S. FOOD & DRUG ADMIN., TOTAL COSTS OF THE PROCESS FOR THE REVIEW OF HUMAN DRUG APPLICATIONS, FDA.GOV, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/PDUFA/UCM363593.pdf (last visited Jan. 31, 2014); *see* FDASIA, Pub. L. No. 112-144, §§ 102–03 126 Stat. 993 (codified as amended in scattered sections of 21 U.S.C.) (reauthorizing the Prescription Drug User Fee Act (PDUFA) scheme first implemented in 1992 to increase efficiency in the new drug approval process). PDUFA requires drug sponsors to pay user fees for review of their product to supplement the FDA's baseline appropriations in exchange for improved FDA performance in the review process. See HUTT, ET AL., *supra* note 18, at 679–83 for a more complete history of the PDUFA program.

23. HUTT, ET AL., *supra* note 18, at 577, 620–24.

24. *Id.* at 620–21.

25. *Id.*

26. *Id.* at 620.

27. 21 U.S.C. § 355(i)(2) (2012).

information on the drug, available controls for the drug, and primary data from prior studies.[28] Barring the issuance of a clinical hold by the FDA, clinical trials for the new drug may go forward, beginning at Phase I.[29] Even attaining this step in the approval process is extremely difficult; estimates suggest that for every five thousand APIs screened, only five will proceed to clinical testing, and only one will eventually be approved by the FDA.[30]

Clinical testing for a new drug is broken into three parts, Phases I through III, with each Phase becoming larger and more difficult than the last to successfully pass.[31] In Phase I, the drug is given to a small number of healthy human subjects in low doses "to determine dosing, document how a drug is metabolized and excreted, and identify acute side effects."[32] Phase I results are used to design well-controlled and scientifically valid Phase II studies, which seek to gain preliminary data on effectiveness in patients that have the disease for which the new drug is indicated.[33] If the new drug produces satisfactory results in Phase II clinical trials, it will move on to Phase III trials, which are larger and both controlled and uncontrolled.[34] In this final phase of clinical testing, additional information about safety and effectiveness is gathered so that an overall risk-benefit analysis of the new drug may be completed and evaluated in a new drug application (NDA) to the FDA.[35]

Each phase of nonclinical and clinical trials can take many years.[36] If, after all of the phases of trials, a new drug has shown compelling results, the drug sponsor will submit a NDA to the FDA providing the drug's trial results, ingredients, manufacturing process, indications, labeling, and samples.[37] The FDA has 180 days to answer the NDA, during which it

28. *Id.*

29. *Id.* § 355(i)(3).

30. HUTT, ET AL., *supra* note 18, at 624.

31. *See id.* (explaining that a decreasing number of new drugs pass each phase of clinical trials until only about twenty percent of those operating under an investigational new drug (IND) will reach FDA approval).

32. THAUL, *supra* note 17, at 4 (quoting information from the FDA website); HUTT, ET AL., *supra* note 18, at 630.

33. HUTT, ET AL., *supra* note 18, at 630–31.

34. *Id.* at 631. In a controlled trial, a group of patients receives the new drug while a second "control" group does not. The results from both groups are then compared to determine the safety, effectiveness, and beneficial qualities of the new drug. This is an example of an ideal controlled trial, but in some studies, the control group receives a lower dose of the drug than the uncontrolled group due to ethical considerations.

35. *Id.*

36. *Id.* at 624.

37. 21 U.S.C. § 355(b)(1) (2012); *see generally* THAUL, *supra* note 17 (describing the FDA's process for drug approval and regulation).

evaluates the safety and effectiveness of the new drug based on a standard of "substantial evidence."[38] After 180 days, the FDA must either approve or deny the NDA.[39] If a NDA is denied, the applicant must be given the reason or reasons for denial and an opportunity for a hearing.[40] Even after the lengthy standard drug approval process, the FDA retains post-market controls over approved drugs, including the ability to revoke approval upon new evidence of risks, to request changes in labeling, and to issue a risk evaluation and mitigation strategy, all in the interest of consumer safety.[41]

B. Pressures that Led to Expedited Review for New Drugs

Though the current form of the FDA's new drug approval process has been in force for decades, it is not immune to adjustment and adaptation, as is sometimes required in the interest of public health. In the 1980s, the FDA found itself in the midst of the AIDS epidemic, which proved to be the impetus to pursue more expedited new drug development and review.[42] Starting with a regulation in 1988, the FDA recognized that different procedures and risk-benefit analyses may be appropriate for new drugs that address life-threatening or serious conditions because patients with those conditions will view their available treatments in a wholly different light than those evaluating a new drug impartially.[43] The FDA's 1988 regulation focused heavily on early consultation between drug sponsors and the FDA to speed drug development while also introducing the possibility of marketing a drug that had only reached Phase II trials.[44] This regulation has been criticized,[45] but it became a highly influential starting point for the

38. §§ 355(c)(1), (d). According to 21 C.F.R. § 314.126 (2013), the standard of "substantial evidence" is met by adequate and well-controlled studies, which are usually Phase III trials.

39. § 355(c)(1)(A).

40. § 355(c)(1), (d).

41. § 355(e), (o).

42. *See* Bean, *supra* note 19, at 886 (crediting the AIDS epidemic for transforming the slow drug approval process that was once characterized as "swimming through Jell-O"). *See generally* Ellen C. Cooper, *Changes in Normal Drug Approval Process in Response to the AIDS Crisis*, 45 FOOD DRUG COSM. L.J. 329 (1990) (detailing how the FDA responded to the AIDS crisis, beginning a shift away from traditional drug approval that has continued today, as illustrated by FDASIA).

43. *See* 21 C.F.R. § 312.80, Subpart E (2013) (defining what conditions may be included, allowing for extra meetings in drug development, and evaluating additional information in risk-benefit analysis for the drug).

44. *Id.* §§ 312.82, 312.84.

45. *See* Bean, *supra* note 19, at 888 (crediting the 1988 regulation and its progeny with eroding the safety of the FDA drug approval process by allowing the manipulation of the process and the premature approval of unsafe drugs).

expedited drug review regime—early and frequent communications with the FDA as well as marketing based on earlier clinical results motivate many drug sponsors to request the current expedited review designations.[46]

Further leaps in expedited new drug access were made in 1992,[47] 1996,[48] and 1997,[49] when accelerated approval, priority review, and fast track status were promulgated.[50] These designations will be discussed in further detail below. Despite the advances in recent decades toward increased and faster patient access to new drugs, patients with life-threatening conditions will continue to pressure the FDA, which must fight to balance its interests in public health and in the integrity of ongoing drug studies.[51] While the AIDS epidemic has subsided in the United States, AIDS and diseases like cancer continue to threaten the American public and push the FDA to go further and faster.

C. Expedited Review Designations Prior to FDASIA

In its fight to find an ideal balance between protecting the public health and the integrity of clinical drug trials, prior to FDASIA, the FDA

46. *See* Center for Drug Education and Research, DEP'T OF HEALTH & HUMAN SERVS., Docket No. FDA-2013-D-0575, GUIDANCE FOR INDUSTRY EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS–DRUGS AND BIOLOGICS 9–12 (2013) (draft proposed June 26, 2013) (explaining the benefits available to the fast track and breakthrough therapy designations, including increased communications and meetings with the FDA based upon nonclinical and early clinical evidence respectively).

47. *See* 21 C.F.R. § 314.510–.520 (allowing approval of a drug product based on effect on a surrogate endpoint predicting a clinical benefit rather than upon a clinical endpoint); *see infra* notes 56–57 and accompanying text (explaining the distinction between surrogate and clinical endpoints).

48. *See* U.S. FOOD & DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, MANUAL OF POLICIES AND PROCEDURES (2013), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/ucm082000.pdf (shortening application review time from ten to six months for new drugs treating serious or life-threatening conditions).

49. *See* Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.) (allowing benefits like increased contact with the FDA and rolling review of a new drug application (NDA) for new drugs treating serious or life-threatening conditions where there is an unmet medical need).

50. SUSAN THAUL, CONG. RESEARCH SERV., RS22814, FDA FAST TRACK AND PRIORITY REVIEW PROGRAMS 3 (2008); HUTT, ET AL., *supra* note 18, at 708–13.

51. *See* Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 700 (D.C. Cir. 2007) (upholding the FDA's decision not to further expedite terminally ill patients' access to experimental drugs and thereby protecting the FDA's interests in ensuring the safety of new drugs and in maintaining the system of clinical drug trials).

established three different designations for new drugs that expedited review in cases of life-threatening or serious conditions, each with different requirements and benefits. These designations are accelerated approval, priority review, and fast track status.[52] This Section will describe the first two designations, but it will focus primarily on the third. While discussion of accelerated approval and priority review provides essential information for understanding breakthrough therapies and their comparison with the fast track designation,[53] accelerated approval and priority review differ significantly from breakthrough therapies and deserve to be maintained independently from the new program.[54]

The FDA promulgated the first method of expedited drug review, called accelerated approval, in 1992 to allow accelerated approval of a NDA in two forms to address an unmet medical need.[55] In trials, "endpoints" determine the effectiveness of a new drug, and clinical endpoints are the highest standard in evaluation because they measure tangible, visible results, such as mortality.[56] Surrogate endpoints are physiological assessments that are indicators of clinical benefit, and they provide an alternative when measuring clinical endpoints is not practical, usually due to time constraints.[57] For example, because the clinical endpoint of reducing bone fractures for osteoporosis patients is difficult to measure, studies use the more easily assessed surrogate endpoint of bone density.[58] The two allowable forms of accelerated approval are: (1) approval based on evidence showing that the new drug affected a surrogate endpoint reasonably suggesting a clinical benefit, or evidence showing that the new drug affected a clinical endpoint other than survival; and (2) approval of a new drug that can only be safe when its distribution or use is modified or

52. U.S. FOOD & DRUG ADMIN., FOR CONSUMERS: FAST TRACK, BREAKTHROUGH THERAPY, ACCELERATED APPROVAL AND PRIORITY REVIEW, FDA.GOV, http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm (last visited Jan. 31, 2014) [hereinafter *For Consumers*].

53. *See infra* notes 56–57, 74 and accompanying text (discussing the difference between surrogate and clinical endpoints in clinical trials and the use of priority review in combination with the fast track designation respectively).

54. *See* DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 7–8 (providing direct comparisons between the current expedited drug access regime programs). Accelerated approval and priority review differ from the breakthrough therapy designation in nearly every category listed.

55. 21 C.F.R. §§ 314.510–.520 (2013).

56. HUTT, ET AL., *supra* note 18, at 639–40.

57. *Id.* at 640. The authors delicately avoid stating that clinical endpoints are not always feasible to measure because it would essentially require waiting for a subject to die, which can take decades beyond the time frame of a clinical trial.

58. *Id.* at 640–41.

restricted.[59] Because the FDA's accelerated approval of a new drug is often based on a surrogate endpoint, the studies determining the drug's effect on that endpoint must be adequate and well-controlled like other clinical trials.[60] No formal process exists for granting this approval pathway, but an obligation to conduct later confirmatory studies accompanies approval due to the dependence on surrogate endpoints.[61]

The second designation for expediting the drug approval process in existence prior to the enactment of FDASIA is priority review. A new policy clarified priority review in 1996, but it existed for decades prior.[62] Any drug can be designated a candidate for priority review if the drug would provide a significant improvement over currently available therapies in safety or effectiveness, or would address unmet medical needs.[63] While the clinical trial stages of drug development remain the same, under priority review, the FDA's review of the submitted NDA is shortened to six months from the usual ten months.[64] Applicants can expressly request the priority review designation upon submission of their NDAs, but the FDA will independently decide upon applying the designation to every NDA submitted within sixty days.[65]

The final designation for expedited new drug approval promulgated before FDASIA is the fast track designation, codified in the Food and Drug Administration Modernization Act of 1997 (FDAMA).[66] FDAMA provided a great number of advances for the FDA,[67] but perhaps the most important was the creation of this new designation to further speed up the review of new drugs for life-threatening or serious conditions when the new drug has the potential to address an unmet medical need.[68] The drug's sponsor is responsible for requesting the fast track designation either simultaneously with or at any time after the submission of an IND application, and the

59. 21 C.F.R. §§ 314.510–.520.

60. *For Consumers*, *supra* note 52.

61. *Id.*; 21 C.F.R. § 314.540.

62. *See* HUTT, ET AL., *supra* note 18, at 708–09 (explaining a complex priority system dating back to 1974); CDER MANUAL OF POLICIES AND PROCEDURES REVIEW DESIGNATION POLICY, *supra* note 48 (simplifying the priority review designation).

63. *For Consumers*, *supra* note 52.

64. *Id.*; THAUL, *supra* note 50, at 3.

65. *For Consumers*, *supra* note 52.

66. Food and Drug Administration Modernization Act (FDAMA) of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.).

67. *Id.* FDAMA reauthorized the PDUFA, modified the regulation of nutrient content claims in foods, and amended laws regarding the dissemination of treatment information for drugs.

68. 21 U.S.C. § 356(a)(1) (2012).

FDA must respond to the request within sixty days.[69] A fast tracked drug's sponsor receives more frequent meetings and correspondence with the FDA during the clinical trial process, which can be helpful in preventing delays in approval based on miscommunications.[70] However, the receipt of rolling review of submitted sections of a NDA in fast tracking is even more important in expediting the approval process.[71] Rolling review means that a drug sponsor may submit portions of its NDA as they become ready rather than submitting a complete NDA all at once.[72] This helps to expedite the review process because the FDA has been following the drug trials and development all along, in more easily digestible pieces. While fast track designation may improve review time, this designation does not expressly shorten the review like a priority review designation.[73] However, drug sponsors who apply for fast track may also apply for priority review if they meet the relevant criteria so that the two designations may work in tandem, effectively shortening fast track review to six months.[74]

II. FDASIA'S BREAKTHROUGH THERAPIES DESIGNATION

In July 2012, not only were each of the above expedited review designations modified or shifted within the Federal Food, Drug, and Cosmetic Act,[75] but FDASIA also added the new designation of "Breakthrough Therapies."[76] The breakthrough therapies proposal was a late entrant to the mixture of ideas that became FDASIA,[77] but it had already been introduced individually in the Senate in March 2012.[78] The breakthrough therapies portion of FDASIA found support on both sides of

69. *Id.* § 356(a)(2)–(3).

70. *For Consumers*, *supra* note 52; THAUL, *supra* note 50, at 2.

71. 21 U.S.C. § 356(c)(1).

72. *For Consumers*, *supra* note 52.

73. *Id.*

74. *Id.*

75. *See* FDASIA, Pub. L. No. 112-144, §§ 802–803, 126 Stat. 993, 1079 (codified as amended in scattered sections of 21 U.S.C.) (applying priority review and fast tracking to qualified infectious disease products); § 901(b) (indicating a broadening of surrogate endpoints to be considered in accelerated approval); § 901(c)(1) (allowing review of a fast track product's NDA before completion); § 902(a) (shifting all existing portions of 21 U.S.C. § 356 to come after the new breakthrough therapy section).

76. *Id.* § 902 (to be codified at 21 U.S.C. § 356(a)).

77. *See* Michael McCaughan, *RPM Report—"Breakthrough Therapy": New Pathway in FDASIA May Point the Way to Future Reforms*, FOCR.ORG, Aug. 20, 2012, http://www.focr.org/news/rpm-report-breakthrough-therapy-new-pathway-fdasia-may-point-way-future-reforms (detailing how the breakthrough therapies proposal made its way to Capitol Hill from the likes of the FDA and the oncology community).

78. Advancing Breakthrough Therapies for Patients Act of 2012, S. 2236, 112th Cong. (2012).

the aisle and within the FDA, as Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER), aided in developing the designation.[79] Indeed, given this show of support, FDASIA passed quietly and without incident.[80]

A. What are Breakthrough Therapies?

According to § 902 of FDASIA, the breakthrough therapy designation may be applied to a new drug that is "intended . . . to treat a serious or life-threatening disease or condition."[81] The new drug's preliminary clinical evidence must also indicate that it may demonstrate "substantial improvement over existing therapies on . . . clinically significant endpoints."[82] FDASIA's definition means that the breakthrough therapy designation encompasses new drugs indicated to treat the same kinds of conditions as the other expedited review methods. However, this designation is specifically for serious conditions that have some existing indicated treatment, and a new drug seeking breakthrough therapy status must present at least preliminary clinical evidence of its effects.[83] To receive the breakthrough therapy designation, the new drug's sponsor must request it either simultaneously with or at any time after submission of an IND to the FDA, and, as with the fast track designation request, the FDA must respond within sixty days.[84] Because the basis for granting the designation is a new drug's preliminary demonstration of improvement over an existing therapy, the data is not highly quantitative.[85] Determining whether the breakthrough therapy designation is proper can largely be "a matter of judgment."[86] Officially, both the magnitude of the treatment effect and the importance of the observed clinical outcome must show that the new drug maintains a clear advantage over the existing treatment.[87] But the measure of a quality, like importance, is subjective.

If the FDA grants a new drug the breakthrough therapy designation, the drug sponsor is entitled to a number of benefits, including: meetings with

79. *See* McCaughan, *supra* note 77 (explaining that Senator Michael Bennet (D-CO) along with Senators Orrin Hatch (R-UT) and Richard Burr (R-NC) took up the breakthrough therapies cause).

80. *Id.*

81. FDASIA, Pub. L. No. 112-144, § 902(a)(1), 126 Stat. 993, 1086 (codified as amended in scattered sections of 21 U.S.C.).

82. *Id.*

83. *Id.*

84. *Id.* § 902(a)(2)–(3).

85. *See For Consumers*, *supra* note 52 (explaining criteria for breakthrough designation).

86. *Id.*

87. *Id.*

the FDA throughout development; correspondence with and advice from the FDA on development; involvement of senior staff and cross-disciplinary personnel in review; and the possibility of more efficient clinical trials.[88] Despite this impressive list of benefits, they are not guaranteed to each breakthrough therapy drug, as these benefits are merely possibilities pursuant to the language of FDASIA.[89] Additionally, they are not very different from the benefits granted to new drugs under the fast track designation.[90] The FDA even expressly states that new drugs receiving the breakthrough therapy designation are eligible for all of the features of the fast track designation.[91] These similarities are specifically concerning when each designation is maintained as a separate program, a policy ripe for the future transformation that this Comment seeks to instigate.

B. The Future of Breakthrough Therapies

As soon as FDASIA was signed into law in July 2012, the breakthrough therapy designation took effect, allowing drug companies to immediately apply for it. Despite its legal existence, however, this designation is destined for additional administrative proceedings and possible growing pains.[92]

Following the definition of breakthrough therapies, FDASIA set a timeline for the Secretary of HHS to publish a guidance document on the topic of the new designation.[93] With the date of July 9, 2012 as a starting point, a draft guidance was due on or before January 9, 2014, and a final guidance is due on or before March 8, 2015 (one year plus sixty days comment time).[94] Rather than following this generous timeline, the FDA has set itself a much earlier target date for the publication of a final guidance document on breakthrough therapies—July 9, 2014[95]—

88. FDASIA, § 902(a)(3).

89. *See id.* (stating that actions to expedite development "may include" the benefits listed above).

90. *See infra* Part III-B (detailing the possibly similar benefits available to breakthrough therapies and fast track products).

91. *For Consumers*, *supra* note 52.

92. *See* FDASIA § 902(b)(1)(A) (requiring the issuance of a guidance document).

93. *See id.* (detailing that no later than eighteen months after the enactment of FDASIA, a draft guidance document is due regarding the implementation of breakthrough therapies, and no later than one year after the comment period closes on this draft guidance, a final guidance document is due).

94. These dates were calculated based on the timeline set in FDASIA § 902(b)(1)(A). January 9, 2014 is eighteen months after July 9, 2012, and March 8, 2015 is one year and sixty days after January 9, 2014.

95. FDASIA–TRACK, FDA.GOV, http://www.fda.gov/AboutFDA/Transparency/track/ucm328907.htm (last visited Jan.. 31, 2014).

decreasing the amount of time available to adjust FDASIA via the first guidance document issued. While ambitious, this hurried approach could actually prove to be counterproductive because it slashes the time during which the FDA can consider suggestions and any implications of its actions.

Nevertheless, in accordance with this hastened trend, CDER prepared and published a draft guidance document on expedited drug review, including breakthrough therapies, for comment on June 26, 2013.[96] Within this draft guidance, CDER has worked to delineate the differences between each of the expedited new drug review programs with tables and explanations,[97] but there remain an unsettling number of similarities between the breakthrough therapy and fast track designations.[98]

Other parties with an interest in the success of the breakthrough therapy designation have already cited a concern beyond its repetition of the fast track designation—they worry that overuse of the breakthrough therapy tag will dilute its effectiveness.[99] Because the major advantages of the designation are meant to be additional meetings with and attention from the FDA as well as advice from and involvement of senior FDA staff to expedite development and review,[100] it is easy to see how these benefits could be diluted and lost if there are too many new drugs vying for the same considerations. In addition to budgetary constraints, this is a very real concern that the FDA should be aware of when contemplating the future of breakthrough therapies.

III. A COMPARISON OF BREAKTHROUGH THERAPIES AND FAST TRACK DESIGNATION

Before worrying about the possible dilution of the breakthrough therapies designation in the expedited drug review regime, the FDA must address the issue of how closely this designation resembles that of fast tracking. Maintaining two separate but repetitive programs will waste valuable resources, which are all the more important when the FDA's constant budgetary constraints are considered.[101] To offer a well-informed solution to this issue, both designations must be analyzed side-by-side to determine where the most problematic repetitions lay within the statutes.

96. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 1.

97. *Id.* at 7–23.

98. *See infra* Part III (describing the similarities between the application processes and possible benefits for receipt of both the breakthrough therapy and fast track designations).

99. Dolgin, *supra* note 12, at 116–17; FDASIA, §902(a)(3).

100. FDASIA, § 902(a)(3)(a)(3)(B).

101. *See supra* notes 2–3 and accompanying text (outlining the FDA's limited budget with which it must regulate over $2.28 trillion of consumer spending).

A. Application Requirements

To qualify for the breakthrough therapy designation, a new drug must meet a number of requirements. First, the new drug must be intended to treat a life-threatening or serious condition.[102] A "serious condition" is defined as one which is "associated with morbidity that has a substantial impact on day-to-day functioning" as determined by factors like "survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."[103] Additionally, "intended to treat" is defined as intending to affect a serious aspect of a condition, such as "a direct effect on a serious manifestation or symptom."[104]

If a breakthrough therapy candidate meets these requirements, the FDA must then decide if the drug sponsor has submitted sufficient preliminary clinical evidence showing that the drug may demonstrate a substantial improvement over existing therapies on a clinically significant endpoint.[105] While substantial improvements and clinical endpoints were addressed previously in Part I-C,[106] what may constitute permissible and persuasive "preliminary clinical evidence" merits discussion. For breakthrough therapy designation, the drug sponsor must submit evidence acquired in the clinical trial stages of drug development. Clinical trials typically follow the FDA's acceptance of an IND application from a drug sponsor.[107] Yet, contrary to the established practice of drug sponsors conducting clinical trials following the FDA's acceptance of the IND, FDASIA allows a drug sponsor to request the breakthrough therapy designation concurrently with its IND application.[108] Logically, this would mean that drug sponsors have not conducted clinical trials because under the Federal Food, Drug, and Cosmetic Act it is illegal to conduct clinical trials without an accepted IND.[109] However, CDER specifically acknowledges this inconsistency

102. FDASIA § 902(a)(3)(a)(1) (quoting 21 C.F.R. §312.300(b)(1) (2013)).

103. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 2–3.

104. *See id.* at 3 (listing further examples of how a new drug may be intended to treat a certain condition).

105. § 902(a)(3)(a)(1).

106. *See supra* notes 57–59, 61, 83 and accompanying text (differentiating clinical from surrogate endpoints and discussing the subjective judgment used to determine "substantial improvement" respectively).

107. If a drug sponsor does not hear anything from the FDA within thirty days of submitting the IND, the application is considered accepted. *See supra* notes 26–28 and accompanying text (detailing the contents of an IND and its place in the drug approval process).

108. § 902(a)(3)(a)(2).

109. *See* 21 U.S.C. § 355(a), (i) (2012) (functioning together to create an exemption from legal action against a drug sponsor conducting clinical trials if an IND application is filed

between FDASIA and the existing law by suggesting that most drug sponsors will likely submit their preliminary clinical evidence as an amendment to the original IND because that evidence is instrumental to being granted the breakthrough therapy designation.[110] If a request for breakthrough therapy status satisfies all of these requirements, the FDA will consider its validity and respond within sixty days.[111]

The application process for receiving the fast track designation is similar to that of breakthrough therapies. Like a breakthrough therapy, a fast track product is also intended to treat a life-threatening or serious condition.[112] Unlike breakthrough therapies, however, fast track products are meant to address an unmet medical need rather than a condition with an existing treatment.[113] An unmet medical need can exist both where there is no available therapy and where there *is* an available therapy, but the new drug would influence an unaddressed outcome or offer an improvement in areas like efficacy, toxicity, or safety.[114] If this sounds confusingly similar to the requirement that a breakthrough therapy offer a substantial improvement over an existing therapy, it is.[115] An "available" or "existing" therapy is defined as an approved or licensed therapy that is intended to treat the same condition as the new drug and is relevant to the current United States standard of care for the indication.[116] With these most current definitions in hand, it is nearly impossible to tell which new drugs may qualify as a fast track product rather than a breakthrough therapy—either designation may be applied to a new drug improving upon an existing therapy. Even Percy Ivy, the Associate Chief of the Investigational Drug Branch at the U.S. National Cancer Institute's Cancer Therapy Evaluation Program, could not provide a concrete distinction when asked.[117] According to Ivy,

with and accepted by the FDA). An exception to this rule exists when clinical trials have commenced overseas, but concerns remain about the safety of clinical testing performed abroad.

110. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 27.

111. FDASIA § 902(a)(3)(a)(3)(A).

112. 21 U.S.C. § 356(a)(1).

113. *Compare id.* (referencing unmet medical needs), *with* FDASIA § 902(a)(3)(a)(1) (requiring a demonstration of "substantial improvement over existing therapies"). The term "unmet medical need" is defined as "a condition whose treatment or diagnosis is not addressed adequately by available therapy" in the recent CDER guidance. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 4.

114. *See* DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 4–6 (providing a more complete listing of all unmet medical needs that a fast track product may address).

115. *See supra* notes 82–83 and accompanying text (quoting FDASIA's definition of breakthrough therapies).

116. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 3.

117. Dolgin, *supra* note 12, at 116.

"You're just going to know [a breakthrough therapy] when you see it."[118]

Fortunately, the evidentiary requirements a drug sponsor needs to meet to receive the fast track designation appear clearer. A sponsor of a new drug vying for the fast track designation must show that the drug has an effect either on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit.[119] This differs from the breakthrough therapy requirement that the drug demonstrates a significant improvement on a clinically significant endpoint, but due to the FDA's preference for tangible, clinical endpoints in studies, the difference in language may be an illusory distinction between the designations. Aside from dictating the kind of endpoint used in trials, the FDA also requires the drug sponsor to submit proof from specific types of trials to receive the fast track designation.[120] Because the drug sponsor must submit a request for the fast track designation either simultaneously with an IND application or at any time after, the trial evidence a sponsor must provide can vary.[121] If the drug sponsor submits a request early on during drug development, the request may be supported by nonclinical trial findings, but if the drug sponsor submits the request later in development, the request should be accompanied by the latest promising clinical findings.[122] While this requirement for fast tracking differs from the requirements for breakthrough therapies in that nonclinical findings may support a grant of the fast track designation, if the drug sponsor submits the fast track request later in development, the distinction between the two designations will disappear because both will require clinical evidence. As with a breakthrough therapy designation request, the FDA must respond to a fast track request within sixty days of receipt.[123]

B. Benefits of Each Designation

Once a new drug sponsor successfully requests either the breakthrough therapy or fast track designation, the new drug may receive certain benefits and advantages over drugs that remain on the standard approval track in order to expedite development, review, and patient access.[124] When a new

118. *Id.*

119. 21 U.S.C. § 356(a)(1) (2012).

120. *See* DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 9 (detailing the nonclinical evidence that is allowable in requests for fast track status submitted early in drug development and the clinical evidence that is required in requests submitted later in development).

121. *Id.*; 21 U.S.C. § 356(a)(2).

122. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 9.

123. 21 U.S.C. § 356(a)(3).

124. *Id.*; FDASIA, Pub. L. No. 112-144, § 902(a)(3)(a)(3)(B), 126 Stat. 993, 1083–85

drug is granted the fast track designation, one of the important benefits that a drug sponsor may receive is increased communication with the FDA.[125] These communications include meetings with the FDA at multiple phases during development and additional correspondence with the FDA regarding trial design or any other issues that may emerge during trials.[126] A fast track product may also be eligible for the priority review designation if the proper clinical data is submitted with the NDA, shortening the review to a six month maximum.[127] Finally, and perhaps most importantly, the FDA will likely give a fast track product the advantage of what is called "rolling review."[128] Under FDAMA, the final review of the NDA usually did not occur until the entire application was complete.[129] The enactment of FDASIA eliminated this potential stumbling block by allowing NDA review to commence before a completed application is submitted.[130]

As with fast tracking, once a drug sponsor has successfully received the breakthrough therapy designation, a number of possible benefits may follow.[131] These benefits may include meetings with the FDA review team during drug development, increased communication with the FDA for added developmental efficiency, involvement of senior FDA staff, and utilizing a cross-disciplinary review team.[132] As with the application process, though the language differs between the advantages of fast tracking and those of the breakthrough therapy designation, the distinctions are not so clear. The advantages again focus on increased contact with the FDA throughout drug development. The FDA admits that the designations are quite similar when it states that all breakthrough therapies are entitled to the features of fast tracking because each breakthrough therapy would also meet the requirements of fast tracking.[133] However, the FDA attempts to

(amending 21 U.S.C. §356(c)(2)).

125. *For Consumers*, *supra* note 52.

126. *Id.*

127. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 9.

128. *See For Consumers*, *supra* note 52 and accompanying text; *see also supra* notes 71–72 and accompanying text (defining rolling review for fast track products).

129. *For Consumers*, *supra* note 52.

130. FDASIA, Pub. L. No. 112-144, § 901(b), 126 Stat. 993, 1086–87 (amending 21 U.S.C. § 356). Because a portion of application review can now occur immediately after a step is taken in development, any problems that may delay approval can be dealt with almost immediately rather than after more studies have been completed based on the results of faulty ones.

131. *See id.* § 902(a)(3)(B) (stating that actions to expedite development of breakthrough therapies "may include, as appropriate" methods of increasing communication and efficiency).

132. *Id.*

133. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 12.

differentiate the designations by permitting breakthrough therapies, but not fast track products, to receive intensive and early guidance on drug development and senior FDA staff involvement.[134]

These features sound impressive and may lead one to believe that the breakthrough therapy designation is a great leap forward from fast tracking. When analyzed closely though, there remain only small differences between the breakthrough therapies and fast track designations. First, the intensive early guidance the FDA grants breakthrough therapies throughout the drug development process is merely a slightly modified version of the fast track designation's increased meetings and communications. The interactions between the FDA and a drug sponsor are meant to foster a more efficient development process with the possibility of fewer patients being subjected to less effective trials.[135] While the FDA places greater emphasis on efficiency in the breakthrough therapies designation, these goals are parallel to those of fast tracking, which seeks to eliminate problems in development before they delay it and to streamline trial designs.[136]

The second additional advantage to the breakthrough therapy designation, involvement of senior and cross-disciplinary FDA staff in review, offers more differentiation between breakthrough therapies and fast tracking. The expressed primary goal of both designations is to expedite drug development, review, and patient access, but with this possible benefit, it seems that a new drug deemed a breakthrough therapy may have a better chance of achieving that goal. As this benefit is specifically codified in FDASIA, there is a more concrete plan in place with which the FDA can expedite a new drug's review time.[137] While the same senior involvement could occur when a new drug is fast tracked, it is not codified anywhere. Therefore, this feature provides a benefit to breakthrough therapies that fast track products may or may not receive.

Although the possible benefits of the breakthrough therapy designation seem like only a minor improvement over fast tracking, the new designation has its proponents among drug professionals and patients. Former FDA Commissioner Scott Gottlieb has touted the new designation as having "real significance,"[138] while oncology patients and professionals have

134. *Id.* at 13.

135. *Id.* at 12–13.

136. *For Consumers*, *supra* note 52.

137. *See* FDASIA, Pub. L. No. 112-144, 126 Stat. 993 (codified as amended in scattered sections of 21 U.S.C.); § 902(a)(3)(B)(iii)–(iv) (involving senior and cross-disciplinary FDA staff in drug review to foster collaboration and facilitate review).

138. Stephanie Fischer, *Risk-taking in the Search for New Therapies*, PHRMA.ORG, Apr. 19, 2013, http://phrma.org/world-orphan-drug-congress-explores-policies-impacting-development.

benefitted greatly from it—of twenty breakthrough therapy designations granted before June 4, 2013, eight were for oncology drugs.[139] The Friends of Cancer Research organization has also advocated for the breakthrough therapy designation, believing that it signals renewed cooperation from the FDA in advancing the development of promising new drugs.[140] Current statistics show that since its implementation on July 9, 2012, CDER has received one hundred nineteen requests for the breakthrough therapy designation, of which thirty-five were granted, fifty-eight were denied, and twenty-six remain pending.[141] The FDA has also succeeded in responding to requests within the required sixty-day window over 96% of the time.[142] The breakthrough therapy proponents' enthusiasm is understandable given the statistics on use of the designation. However, supporters overstate the benefits of breakthrough therapies because the same new drugs would likely have been approved as fast track products if the drug sponsors had used a different application form.[143]

C. How the Designations Differ

Since the inception of the breakthrough therapy designation, the FDA has maintained separate programs for it and the fast track designation, requiring separate requests to be considered for either.[144] This means that if a new drug is denied one designation, it will not be automatically reviewed for the other, and the drug sponsor must submit another request to the FDA.[145] This policy makes sense for two inherently different programs, and in some ways, the breakthrough therapy and the fast track designations are distinct from one another. First, the codified involvement of senior FDA staff and cross-disciplinary experts in review of a new breakthrough therapy differs from fast track review, which may involve such personnel.[146] Second, efficiency in the drug development process

139. Jennifer Wall, *Cooperation for Patient Health*, PHRMA.ORG, June 4, 2013, http://www.phrma.org/catalyst/cooperation-for-patient-health.

140. Dolgin, *supra* note 12, at 117.

141. *Frequently Asked Questions*, *supra* note 11. These statistics are the current sums of the breakthrough therapy requests received by CDER from fiscal years 2012, 2013, and 2014 and the disposition of those requests.

142. Id.

143. *See supra* notes 102–123 and accompanying text (detailing the similarities between the application processes for breakthrough therapies and fast tracking).

144. *Frequently Asked Questions*, *supra* note 11.

145. *Id.*

146. *Compare* FDASIA, Pub. L. No. 112-144, §§ 902(a)(3)(B)(iii)–(iv), 126 Stat. 993, 1086–87 (amending 21 U.S.C. § 356) (allowing for the involvement of senior and cross-disciplinary staff in drug review), *with* 21 U.S.C. § 356(a)(1) (2012) (including no reference to senior or cross-disciplinary staff in drug review in the possible benefits to fast tracked products).

seems to be more of a priority in the breakthrough therapy designation than it seems in fast tracking.[147] In addition to simply using the word "efficient" in the sections of FDASIA codifying breakthrough therapies,[148] patients and industry sponsors helped to establish the designation specifically with the goals of innovation and improvement over the existing expedited designations in mind.[149] Finally, if a request for the fast track designation is received early in drug development, it is possible that the FDA will grant the designation based upon nonclinical evidence, which differs from the requirements of a breakthrough therapy.[150]

However, despite these distinctions between breakthrough therapies and fast tracking, the similarities between the programs are overwhelming when they are analyzed side-by-side. Both designations apply to new drugs intended to treat life-threatening or serious conditions;[151] both can address a condition where an available therapy already exists;[152] the granting of both may be based upon preliminary clinical evidence;[153] and both may be given the fast track advantages of increased communication with the FDA during drug development and rolling review because breakthrough therapies receive all of the benefits of fast track products.[154]

IV. RECOMMENDATIONS FOR THE EXPEDITED NEW DRUG REVIEW REGIME

Because of the significant overlap between the breakthrough therapy and fast track designations, maintaining both designations as isolated programs requiring separate applications is not efficient. The FDA is an underfunded agency[155] which must choose its budgetary expenditures wisely, and the

147. *See* FDASIA, §§ 902(a)(3)(B)(ii), (a)(3)(B)(v) (expressly using the word "efficient" when discussing the actions the FDA may take upon granting the breakthrough therapy designation).

148. *Id.*

149. *See* McCaughan, *supra* note 77 (chronicling the reasons for the development of breakthrough therapies and the involvement of influential groups like Friends of Cancer Research).

150. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 9.

151. FDASIA, § 902(a)(3); 21 U.S.C. § 356 (a)(1).

152. FDASIA, § 902(a)(3); 21 U.S.C. § 356(a)(1); *see supra* note 114 and accompanying text (explaining that an "unmet medical need" can include conditions for which there is an available therapy).

153. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 9–10.

154. *Frequently Asked Questions*, *supra* note 11.

155. *See supra* text accompanying notes 1–3 (outlining the FDA's limited budget and the amount of industry it is expected to regulate); PEG MCGLINCH, HOLLOW GOVERNMENT: RESOURCE CONSTRAINTS AND WORKLOAD EXPANSION AT THE FDA (2001), *available at* http://nrs.harvard.edu/urn-3:HUL.InstRepos:8944673 (discussing how the expansion of

repetition of qualifications and benefits evident in the current expedited drug review regime runs counter to this idea. Though some have championed modifications to the drug approval regime, the proposals of students and politicians alike have included large and unrealistic overhauls of the drug approval system which point out more problems than solutions.[156] To address the issue of repetitive designations within the expedited approval regime, this Comment proposes a simpler and more focused solution: a merger between the currently separate designations for breakthrough therapies and fast track products. If implemented, this merger would clear the confusion between the two designations, saving time and resources that are important to the FDA, patients, and drug sponsors. Additionally, it would still allow for the innovation that the breakthrough therapy designation was meant to encourage.

Rather than promulgating a new designation in FDASIA, Congress, the drug industry, and CDER Director Janet Woodcock would have been wise to shape the law to focus on overhauling and updating the existing fast track designation.[157] This is, after all, what breakthrough therapies appear to do. Now that both designations exist, the FDA must work backwards and merge them into a single, updated "progressive"[158] designation that takes on the added benefits of the breakthrough therapy designation. First, the FDA must address the differences in the application process for each designation, which have been shown to be largely illusory.[159] The FDA can accomplish this task simply by revising what must be submitted to qualify

the FDA's workload is outpacing its resources, leading to a hollowing effect within the agency: resources are spread too thinly to perform any agency responsibility well, particularly in CDER).

156. *See, e.g.*, Bean, *supra* note 19, at 10–12 (arguing, for example, that to address multiple serious problems within the drug approval process, the FDA should be better funded rather than relying on user fees, the development and review process should be lengthened, the American public must be more involved and informed, and an independent safety review board should be founded); Maurice Hinchey, *The Fight to Safeguard American Drug Safety in the Twenty-First Century*, 35 HOFSTRA L. REV. 685, 687–89 (2006) (proposing a rerouting of user fees to the United States Treasury coupled with increased minimal funding for the FDA and a new Center for Drug Safety and Effectiveness to prevent a conflict within CDER between approval authority and post-market safety review duties).

157. *See supra* Part II-A (discussing the main players involved in the creation of breakthrough therapies).

158. This name is borrowed from the biotechnology industry, which advocated for a new approval method often referred to as "progressive approval." This progressive approval model became an important step on the path to today's breakthrough therapies. McCaughan, *supra* note 77.

159. *See supra* Part III-A (detailing how the fast track's "unmet medical need" can include conditions with existing treatments and how both designations may be supported by clinical evidence of effect on clinical endpoints).

for the new progressive designation. The new application should require that a new drug: (1) be intended to treat a life-threatening or serious condition; (2) show a substantial improvement over either an available therapy or the absence of a therapy; and (3) illustrate this improvement with preliminary clinical evidence of effect on a clinically significant endpoint. A drug sponsor should submit an application meeting these requirements after, but never simultaneously with, an IND to gather proper clinical data. While this progressive application is slightly more demanding than the current fast track request, it successfully integrates requirements of breakthrough therapies while not differing greatly from the old application. This is supported by the FDA's definition of "unmet medical need," which includes available therapies,[160] and the preference for tangible, clinical endpoints based on clinical data, which will provide stronger evidence than surrogate endpoints and earlier, nonclinical data.

To successfully complete the merger of the two designations, the FDA must also address the differences in advantages that are given to new drugs granted either fast track or breakthrough therapy status. This step of the transition should be even smoother than the application update given that the breakthrough therapy designation already includes all of the fast track features.[161] The additional advantages currently reserved only for breakthrough therapies, including the involvement of senior staff and cross-disciplinary experts in drug review and an increased focus on efficiency in development,[162] would also benefit fast track products. Therefore, these benefits should be open to any new drug that satisfies the requirements of the progressive designation.

Though the administrative process to complete this merger of designations would require additional work in the form of either eventually changing FDASIA itself or publishing a wholly amended guidance document, the overall reward for overcoming this obstacle would be worthwhile. The FDA's current position maintains separate programs and procedures for breakthrough therapies and fast track products,[163] but agency interpretations are not "carved in stone."[164] Multiple methods exist with which to modify the FDA policy laid out in CDER's draft guidance. First, the process of developing an initial guidance document invites public comment, which influences and shapes an agency's policy by allowing the

160. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 46, at 4.

161. *Id.* at 12.

162. FDASIA, Pub. L. No. 112-144, § 902(a)(3)(a)(3)(B), 126 Stat. 993, 1086–87 (2012) (amending 21 U.S.C. § 356).

163. *Frequently Asked Questions*, *supra* note 11.

164. Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837, 863 (1984).

public to make suggestions regarding the document's proposal.[165] Second, even after a guidance document is finalized and published, the FDA may amend it based on new information.[166] Therefore, CDER's draft guidance document remains subject to change via public comment or FDA initiative and could be revised to include an interpretation of FDASIA's breakthrough therapy designation that more squarely merges it with the fast track designation.

This Comment assumes that the FDA will issue a final guidance document that does not include a merger between the breakthrough therapies and fast track designations.[167] Consequently, modification of FDASIA after the promulgation of the final guidance will need to be carried out either by way of an amended guidance document or a new law. Because formally passing a new law is time consuming and easily frustrated by partisan politics in Congress, changing the expedited drug review regime would be better done by publishing an amended guidance document. Should CDER issue an amended guidance document that includes a merger between fast tracking and breakthrough therapies, opposition would be unlikely for two reasons. First, the statutes establishing both designations lack barriers to a merger.[168] Consolidating both designations would still serve the overall purpose of expediting drug review for serious and life-threatening conditions. Second, even if opposition to a merger existed and the FDA had to defend CDER's policy choice in court, deference to the

165. *See* U.S. FOOD & DRUG ADMIN., FACT SHEET: FDA GOOD GUIDANCE PRACTICES, FDA.GOV, http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm285282.htm (last visited Jan. 31, 2014) (discussing the consideration of comments in formulating final guidance documents); REGULATIONS.GOV, http://www.regulations.gov/#!docketBrowser;rpp=25;po=0;dct=PS;D=FDA-2013-D-0575 (last visited Jan. 31, 2014) (listing and providing access to the comments received regarding CDER's draft guidance document dated June 26, 2013). No comment suggests the sweeping merger recommended in this Comment, but the Leukemia & Lymphoma Society's comment addresses the strain on resources that will occur with too many breakthrough therapy designations.

166. *See, e.g.*, CTR. FOR BIOLOGICS EVALUATION AND RESEARCH, DEP'T OF HEALTH & HUMAN SERVS., Docket No. FDA-2012-D-0307, DRAFT GUIDANCE FOR INDUSTRY: AMENDMENT TO "GUIDANCE FOR INDUSTRY: REVISED PREVENTIVE MEASURES TO REDUCE THE POSSIBLE RISK OF TRANSMISSION OF CREUTZFELDT-JAKOB DISEASE AND VARIANT CREUTZFELDT-JAKOB DISEASE BY BLOOD AND BLOOD PRODUCTS" AVAILABILITY (June 11, 2012) (amending a guidance document issued in 2010 to reflect new knowledge regarding transmission of infection).

167. *See supra* note 165 (stating that no comment on the draft guidance suggested such a merger).

168. *See* 21 U.S.C. § 356 (2012) (containing language indicating an intent to expedite drug review without any indication of program exclusivity); FDASIA, Pub. L. No. 112-144, § 902, 126 Stat. 993, 1086–87 (amending 21 U.S.C. § 356) (same).

agency would be applied on review.[169] The FDA could also easily defend the reasonableness of a merger between the designations based upon the resources that it would save, the elimination of confusion for drug sponsors, and the increased efficiency in getting patients needed treatments.

If CDER is to be prompted to issue an amended guidance regarding expedited drug review, interested parties must exert pressure on the FDA.[170] To accomplish a merger of the fast track and breakthrough therapy designations, stakeholders, patients, and the general public should continue to submit comments to the FDA even after the consideration deadline established in the existing draft guidance passes. Any interested person has the legal right under the APA to petition an agency to issue, amend, or repeal a rule, and anyone can submit a comment on any guidance even after it has been implemented.[171] Upon receipt of such comments, the FDA reviews suggestions and revises the questioned guidance "if necessary."[172]

Though the FDA provides only the vaguely-stated goal of necessity to work toward, persuading the agency that a revision to the expedited drug review regime is essential is not so daunting when the benefits of a merger between fast tracking and breakthrough therapies are considered. This merger would benefit the FDA itself by allowing it to save resources. Because separate programs for breakthrough therapies and fast track products would no longer be necessary, money and manpower could be expended elsewhere, making a consistently constrained budget slightly more manageable. Merging the designations would also eliminate confusion for drug sponsors, allowing them to work more efficiently and productively without fear of filing the wrong request to the FDA and having to start anew. Finally, added efficiency throughout the expedited new drug approval process would benefit patients suffering from life-threatening or serious conditions by providing them with innovative treatments sooner, which is the overriding goal of the entire regime. While the administrative hurdles may be great, the rewards of merging the fast track and

169. *See* United States v. Mead Corp., 533 U.S. 218 (2001) (holding that while *Chevron* deference does not apply to informal policy determinations, some deference to an agency's interpretation in proportion to its persuasiveness is due based on the agency's experience).

170. For an example of the effect public pressure can have upon the FDA, *see, e.g.*, U.S. FOOD & DRUG ADMIN., BISPHENOL A (BPA): USE IN FOOD CONTACT APPLICATION, FDA.GOV, http://www.fda.gov/newsevents/publichealthfocus/ucm064437.htm (last visited Jan. 31, 2014) (citing recently expressed concerns over Bisphenol A (BPA) as the reason for newly initiated studies regarding its safety, stating that outside input may lead to the FDA updating its assessment of BPA, and supporting steps to reduce infant exposure to BPA).

171. 5 U.S.C. § 553(e) (2012); *Fact Sheet*, *supra* note 165.

172. *Fact Sheet*, *supra* note 165.

breakthrough therapy designations are greater, benefitting every involved party and making the submission of additional comments worthwhile.

CONCLUSION

In July 2012, FDASIA was signed into law, bringing with it some necessary advancements for the FDA[173] but also bringing problems within the expedited new drug review regime. Though the FDA is a chronically underfunded agency,[174] FDASIA instituted use of a new designation in the regime, breakthrough therapies,[175] that had much in common with the pre-existing fast track designation. The FDA currently maintains these two designations as separate programs, despite their repetitive qualities in both the benefits to the designations and the requirements to qualify for them.[176] This repetition is inefficient and especially concerning for the FDA, which routinely suffers under limited budgets that are disproportionate to its vast regulatory duties.[177]

The best way to address this problem within the expedited drug review regime is for interested parties, such as drug companies and patients, to act and pressure the FDA to merge the fast track and breakthrough therapy designations. This change can occur at any time if enough comments are received in favor of a merger because the FDA retains the power to amend guidance documents even after implementation. While unlikely, any challenge to consolidation would probably be unsuccessful because merging both designations is a reasonable interpretation of the statutes creating fast tracking and breakthrough therapies. This change should be the goal of not only drug companies and patients, but the FDA itself and the American people because it will lead to increased efficiency and more responsible spending of the FDA's limited budget.

173. *E.g.*, FDASIA, Pub. L. No. 112-144, §§ 103–07, 126 Stat. 993, 996–1002 (codified as amended in scattered sections of 21 U.S.C.) (amending and reauthorizing PDUFA for another five years).

174. *See supra* notes 2–3 and accompanying text (citing the FDA's limited budget with which it must regulate over $2.28 trillion of consumer spending and the phenomenon of agency hollowing caused by too few agency resources being spread over too many responsibilities).

175. FDASIA, § 902.

176. *Frequently Asked Questions*, *supra* note 11.

177. *See supra* note 5 (comparing the FDA's 2013 budget with the estimated amount of consumer spending it will be required to regulate).