

REPORT 2 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-18)  
FDA Expedited Review Programs and Processes  
Resolution 201-I-17  
(Reference Committee K)

## EXECUTIVE SUMMARY

**Objective.** To examine expedited FDA drug approval programs or processes in place in the United States, including so-called fast track, accelerated approval, designated breakthrough therapies, and “priority review” for drugs and biologics, and whether the operation of such programs needs to be re-examined or modified.

**Methods.** English-language reports were selected from a PubMed and Google Scholar search from 1992 to August 2018, using the MeSh terms “\*biomarkers,” “\*surrogate end points,” “drug approval/\*methods/\*statistical outcomes/\*legislation & jurisprudence, \*validation,” “United States Food and Drug Administration,” product surveillance/\*postmarketing” and “government regulation,” combined with the text terms “clinical trials,” “treatment outcome,” “accelerated approval,” “breakthrough therapy,” “priority review,” and “fast track.” Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the U.S. Food and Drug Administration (FDA).

**Results.** Different programs have been put in place over the last 25 years by the FDA and Congress to expedite the review of promising new therapies and to approve drugs for initial marketing based on lower evidentiary standards, including the use of surrogate markers. The use of surrogate endpoints has assumed increasing importance as approximately 40% of pivotal clinical trials for drug approvals or new indications rely on them. More than 60% of fast track approvals are now characterized as specialty drugs. Priority review processes have been successful in reducing the average application review time. One overarching theme is the strength of evidence relied on by the FDA to support marketing of new drugs. While various analyses have been conducted over different time frames examining the impact of expedited review programs on drug safety and efficacy, the most comprehensive review found that, for the most part, the use of surrogate endpoints has been successful, and the majority of sponsors have approached the conduct of confirmatory studies in a timely manner, although some failures do exist.

**Conclusion.** Over the years, the FDA has implemented various approaches to expedite the review and approval of new drug and biologic applications, as well as new indications for existing products. Accelerated approval, fast track, prior review, and breakthrough therapy designations have been developed, but these expedited programs differ and should not be lumped together from a scientific, public health, or policy point of view. Key variables include the requirement for post-approval studies for drugs marketed under accelerated approval, whether a surrogate endpoint that has not been validated is used to support approval, and the need to confirm clinical benefit and the risk-benefit profile for drugs approved based on limited evidence, regardless of their review designation. While it is important for the agency to retain regulatory flexibility, and many positive aspects of expedited programs are apparent, some changes should be made to improve implementation, establish the value of surrogate endpoints, and provide more transparency for clinicians and their patients.

## REPORT OF COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2-I-18

Subject: FDA Expedited Review Programs and Processes  
Resolution 201-I-17

Presented by: Robyn F. Chatman, MD, MPH, Chair

Referred to: Reference Committee K  
(Darlyne Menscer, MD, Chair)

---

### 1 INTRODUCTION

2 Resolution 201-I-17, “Improving FDA Expedited Approval Pathways,” introduced by the Resident  
3 and Fellow Section and referred by the House of Delegates asked:

4 That our American Medical Association work with U.S. Food and Drug Administration (FDA)  
5 and other interested stakeholders to design and implement via legislative action (including  
6 ensuring appropriate FDA staffing) a process by which drugs which obtain FDA approval via  
7 the Fast Track, Accelerated Approval, or Breakthrough Therapy pathways be granted FDA  
8 approval on a temporary basis not to exceed 5 years, pending further evidence of safety and  
9 efficacy that is at the level set for the standard drug approval process; and,

10 That our AMA work with the FDA and other interested stakeholders in improving the process  
11 by which drugs are selected for the expedited pathway to improve the prevalence of these  
12 drugs that are classified as “specialty drugs.”

13 This report examines expedited FDA drug approval processes in place in the United States,  
14 including so-called fast track, accelerated approval, designated breakthrough therapies, and  
15 “priority review” for drugs and biologics. Such programs are “intended to facilitate and expedite  
16 development and review of new drugs to address unmet medical needs in the treatment of serious  
17 or life-threatening conditions” (especially when no satisfactory alternative therapies exist), and “be  
18 available to patients as soon as it can be concluded that the therapies’ benefits justify the risks.”<sup>1-3</sup>  
19 Accordingly, under the current regulatory structure for approval of new chemical entities or new  
20 indications (efficacy supplements), the specific drug development program, including eligibility for  
21 expedited programs, is determined by the seriousness and prevalence of the disease, availability of  
22 existing treatments, and evidence that the drug can offer significant improvement compared with  
23 available therapies.

24 Two specific topics, one referred to in the resolution (specialty drugs) and the other which also  
25 impacts the FDA’s review of new drug applications (user fees) are not specifically evaluated in this  
26 report. The FDA does not define “specialty drugs” nor is it a term found in regulations or statute.  
27 The term specialty drug is generally used for complex, high-cost medications; they are often  
28 derived from a living source, characterizing them as biologics. Historically, they have been used to

© 2018 American Medical Association. All rights reserved.

Action of the AMA House of Delegates 2018 Interim Meeting: CSAPH Report 2  
Recommendation Adopted as Amended, and Remainder of Report Filed.

1 treat serious, chronic conditions such as rare diseases, cancer, rheumatoid arthritis, and multiple  
2 sclerosis. In recent years, specialty drugs have targeted more common conditions such as high  
3 cholesterol, asthma and hepatitis C, significantly increasing the potential pool of patients that  
4 receive them. Specialty drugs are not stocked at most pharmacies, are often injectable medications,  
5 and may have unique storage or shipment requirements, such as refrigeration. These medications  
6 usually require additional patient education and support beyond traditional dispensing and  
7 counseling activities to maintain adherence and ensure patient safety. The growth in specialty drugs  
8 has been exponential. In the past four years nearly 100 new specialty drugs were launched, and in  
9 the same time there were 80 supplemental approvals establishing new indications for existing  
10 products.<sup>4</sup> Based on the number and high degree of success in getting such drugs approved, special  
11 attention to these types of drugs, with respect to drug development, is not warranted. Concerns also  
12 have been expressed that the high cost of many specialty drugs is not justified when compared with  
13 their clinical benefits. Cost is a variable that is not under the purview of the FDA.  
14

15 The Prescription Drug User Fee Act (PDUFA), first enacted in 1992, established the current  
16 framework by which pharmaceutical manufacturers help fund the FDA by submitting a fee along  
17 with their application. Monies derived from so-called “user fees” have been used to expand FDA  
18 staffing dedicated to the review of new drug (NDA) and biological license applications (BLA) and  
19 efficacy supplements (sNDA); the latter are submitted when sponsors seek approval to add a new  
20 indication to prescription drug labeling. A comparable user fee process also is now in place for  
21 abbreviated new drug applications (ANDA) that govern generic drug approval. Because user fees  
22 support FDA drug reviews in general, and are not an expedited program or process *per se*, the  
23 impact of PDUFA review times on drug safety and patient benefits is not further evaluated in this  
24 report.  
25

## 26 METHODS

27

28 English-language reports were selected from a PubMed and Google Scholar search from 1992 to  
29 August 2018, using the MeSh terms “\*biomarkers,” “\*surrogate end points,” “drug  
30 approval/\*methods/\*statistical outcomes/\*legislation & jurisprudence, \*validation,” “United  
31 States Food and Drug Administration,” product surveillance/\*postmarketing” and “government  
32 regulation,” combined with the text terms “clinical trials,” “treatment outcome,” “accelerated  
33 approval,” “breakthrough therapy,” “priority review,” and “fast track.” Additional articles were  
34 identified by manual review of the references cited in these publications. Further information was  
35 obtained from the Internet site of the US Food and Drug Administration (FDA).  
36

## 37 CURRENT AMA POLICY

38

39 AMA Policy H-100.992, “FDA,” supports the concept that an FDA decision to approve a new  
40 drug, to withdraw a drug’s approval, or to change the indications for use of a drug must be based on  
41 sound scientific and medical evidence derived from controlled trials and/or postmarket incident  
42 reports *as provided by statute*. The statute regarding evidentiary standards for drug approval was  
43 modified in 1997 permitting FDA to approve a drug product “upon determination that the product  
44 has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict  
45 clinical benefit.” The evidence should be evaluated by the agency in consultation with its Advisory  
46 Committees and expert extramural advisory bodies, and any risk-benefit analysis or relative safety  
47 or efficacy judgments should not be grounds for limiting access to or indications for use of a drug  
48 unless the weight of the evidence from clinical trials and postmarket reports shows that the drug is  
49 unsafe and/or ineffective for its labeled indications.  
50

1 Policy D-100.978, “FDA Drug Safety Policies,” directs the AMA to monitor and respond, as  
2 appropriate, to implementation of the drug safety provisions of the FDA Amendments Act of 2007  
3 (FDAAA; P.L. 110-85). This directive was related primarily to the fact that FDA authorities around  
4 Risk Evaluation and Mitigation Strategies were strengthened by the 2007 law.

5 **DESCRIPTION OF EXPEDITED DRUG AND BIOLOGIC APPROVAL PROCESSES**

6

7 Regular approval was the only FDA approval pathway until 1992. Largely in response to the  
8 HIV/AIDS epidemic in the mid-late 1980s, the FDA institutionalized approaches by which certain  
9 drugs, including antiretroviral products at the time, could be initially approved based on less  
10 rigorous data, including the use of surrogate endpoints.

11

12 *Accelerated Approval*

13

14 Conceptualized in the 1980s, initially implemented in 1992 and further refined in 2012, the  
15 accelerated approval pathway for drugs and biologics is described in 21CFR parts 314 (subpart H)  
16 and 602 (subpart E) and contained in Section 506(c) of the Food Drug and Cosmetic (FD&C)  
17 Act.<sup>5-7</sup> It has been primarily used in settings where the course of the disease is long and an extended  
18 period would be required to measure the intended clinical benefit (e.g., decreased mortality from  
19 HIV infection, increased overall survival from cancer). Qualifying criteria are a drug that treats a  
20 serious condition, generally provides a meaningful advantage over available therapies and  
21 demonstrates an effect on a “surrogate endpoint that is reasonably likely to predict clinical benefit  
22 or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality.”  
23 Furthermore, the surrogate endpoint is *reasonably likely* to predict an effect on “some other clinical  
24 benefit (i.e., an intermediate clinical endpoint), considering the severity, rarity, or prevalence of the  
25 condition and the availability or lack of alternative treatments.” The accelerated approval  
26 designation requires post-approval testing to verify efficacy and confirm the anticipated risk-  
27 benefit profile. From 2000 to 2103, 37 new drugs were granted accelerated approval, or about 10%  
28 of new molecular entities (NMEs).<sup>8</sup>

29

30 A drug marketed under accelerated approval can be subject to expedited withdrawal if the surrogate  
31 endpoint(s) turns out to be faulty. The FDA maintains a list of drugs that have been withdrawn due  
32 to safety concerns or lack of efficacy.<sup>9</sup> Many of these products predate 1992. Since 1992 about 25  
33 drugs have been withdrawn from the market, most of which had gone through regular approval. A  
34 limited number of drugs marketed under accelerated approval have had their approval for specific  
35 indications withdrawn (see below).

36

37 **Surrogate Endpoints.** A surrogate is “a laboratory measurement or physical sign that is used in  
38 therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how  
39 a patient feels, functions, or survives and is expected to predict the effect of the therapy.”<sup>10</sup> Such  
40 measures are not intrinsically beneficial to patients, but are relied on to predict the benefits of  
41 treatment in the absence of data on patient-relevant final outcomes based on a “reasonably likely”  
42 standard. The use of surrogate endpoints allows for clinical trials with reduced sample size and  
43 shorter duration, thereby reducing expense and speeding patient access to new therapies. For most  
44 drugs marketed under accelerated approval, requiring the endpoint to be overall survival is not  
45 practical and may not be ethical.<sup>11</sup>

46

47 Approval of a drug based on a surrogate endpoint introduces uncertainty about the drug’s true  
48 clinical benefit and this degree of uncertainty must be considered acceptable in order for the new  
49 drug or indication to be approved. Different scenarios exist in which a treatment may significantly  
50 affect a surrogate marker, but not the clinically significant endpoint. The strength of evidence for  
51 validating a surrogate marker is based on: (1) the biological plausibility of the relationship between

1 the surrogate marker and patient outcomes; (2) epidemiologic evidence on the predictive value of  
2 the surrogate for the clinical outcome of interest; and (3) clinical trial level data confirming that the  
3 response of the surrogate marker to treatment corresponds to the effects of the treatment on the  
4 clinical outcome.<sup>12</sup> Optimally, the strength of the surrogate-survival correlation would already be  
5 established; however, many surrogate endpoints used during the drug approval process are not  
6 validated at the time. To validate all surrogate endpoints ahead of time would require several trials  
7 to be conducted on a specific research question, essentially defeating the purpose of the accelerated  
8 approval pathway.  
9

10 **The Use of Surrogate Endpoints for Drug Approval.** Surrogate endpoints have assumed increasing  
11 importance as approximately 40% of pivotal trials constituting the basis for approval of NMEs  
12 and/or new indications for existing drugs are based on surrogate endpoints, with a high percentage  
13 of these being for oncology drugs.<sup>12,13</sup>  
14

15 Several studies have been published examining the use of surrogate endpoints and accelerated  
16 approval of oncology drugs over the past 25 years.<sup>14-16</sup> Two snapshots covered the periods from  
17 1994-2004 and 2004-2011, with a few others covering different time periods.<sup>16,17</sup> A comprehensive  
18 review of oncology drugs approved as NMEs and for new indications via accelerated approval  
19 (n=93) was recently published covering the period from the inception of the program (1992)  
20 through May 2017 and is the focus of the following discussion.<sup>16</sup>  
21

22 Twenty-eight percent of accelerated approvals were supported by randomized controlled trials  
23 (RCTs), with single arm trials accounting for the remainder; the median patient population for  
24 determining efficacy was 143. Seven RCTs used time to progression as the end point and four used  
25 disease-free survival; the remainder of both RCTs and single arm trials (87%) used response rate  
26 (i.e., tumor burden) as the endpoint. Approximately 55% of the approvals have fulfilled their post-  
27 marketing requirements and verified benefit in a median 3.4 years after approval, based on  
28 measurement of progression-free survival or time to progression (i.e., disease control) (39%),  
29 overall survival (29%), response rate (26%) or disease-free recurrence or progression (6%). Most  
30 of the success stories had ongoing confirmatory trials planned and underway at the time of  
31 accelerated approval. Forty percent of accelerated approvals are still in the process of completing  
32 confirmatory trials and verifying clinical benefit; FDA approval was subsequently withdrawn for  
33 five new indications. Most of the unfulfilled commitments represent recent approvals (median time  
34 on the market = 18 months), although some outliers exist; eight of such products have been on the  
35 market for more than 5 years, mostly in rare patient populations. While one criticism of the  
36 accelerated approval pathway is the smaller sample size, review of documentation supporting  
37 accelerated approval indicates that the safety database is usually larger, about double the efficacy  
38 database.<sup>16</sup> The safety database includes patients “treated with the drug regardless of age,  
39 condition, or volunteer status.”<sup>16</sup> If the accelerated approval is for a new indication of an already-  
40 approved drug then more expansive safety information and postmarketing data are already  
41 available. Only one cancer drug approved under accelerated approval has been withdrawn from the  
42 market because of both efficacy and safety issues (gemtuzumab ozogamicin), and this drug was  
43 later reapproved for a narrower population.<sup>19</sup>  
44

45 Several trial-level analyses have “quantified the association between surrogate endpoints and  
46 overall survival, with one study finding that nearly 50% of meta-analyses reported correlation  
47 between surrogate outcomes and overall survival exceeding 0.7. On average surrogate endpoints  
48 are positively correlated with survival.”<sup>20</sup>  
49

50 *Fast Track Designation*  
51

1 The current fast track designation is defined in section 506(b) of the FD&C, as amended by the  
2 1997 Food and Drug Modernization Act (section 112) and 2012 Food and Drug Administration  
3 Safety and Innovation Act (FDASIA) (section 109). This designation was designed to facilitate the  
4 development, and expedite the review of drugs to *treat serious conditions and fill an unmet*  
5 *medical need*. Some critics maintain that the term “unmet medical need” has been overused and is  
6 too imprecise.<sup>21</sup> This pathway also is available for drugs that have been designated as a qualified  
7 infectious disease product. Fast track allows for approval based on preliminary evidence such as  
8 Phase 2 clinical studies (rarely Phase 1). A request for fast track designation can be filed with the  
9 investigational new drug application (IND) or after, but ideally before the pre-NDA or BLA  
10 meeting; the timeline for an FDA decision is within 60 calendar days of receipt of the request.

11  
12 Actions to expedite development and review include more frequent interactions with the review  
13 team to discuss, in part, study design, the extent of safety data required to support approval, dose-  
14 response concerns and use of biomarkers, and a “rolling review” where parts of the application can  
15 be acted on when they are ready, in sequence. Drugs with fast track designation also could be  
16 eligible for *priority review* (see below) if such a request is supported by sufficient data when the  
17 NDA, BLA, or efficacy supplement submission is submitted. Fast track designations can be  
18 rescinded if qualifying criteria are not met.

19  
20 From 2000 to 2013, the FDA approved 82 drugs under the fast track designation, or approximately  
21 22% of the NME’s approved during the same time period.<sup>8</sup> More than 60% of the fast track  
22 approvals were characterized as specialty drugs by the authors of this study.

23  
24 *Breakthrough Therapy*

25  
26 Described in Section 506(a) of the FD&C Act, the breakthrough therapy designation was created  
27 by the 2012 FDASIA to expedite the development and review of drugs which may demonstrate  
28 substantial improvement over available therapy. Qualifying criteria are that a drug is intended to  
29 treat a *serious condition* and *preliminary clinical evidence* indicates that the drug may demonstrate  
30 “substantial improvement on a clinically significant endpoint over available therapies.” The  
31 timeline for FDA response is the same as fast track and priority designations. In contrast to the fast  
32 track designation which could include theoretical or non-clinical data, a breakthrough designation  
33 requires clinical evidence which is sufficient to demonstrate substantial improvement in safety or  
34 effectiveness over available therapies, but additional evidence is still required for final approval.  
35 Determining if the “substantial improvement” criterion is met is a matter of judgement, and the  
36 evidence that is relied on for approval of drugs with this designation is heterogenous.<sup>22</sup> This  
37 designation triggers intensive guidance on the drug development program beginning as early as  
38 Phase 1, FDA commitment involving senior FDA managers, a rolling review of the application and  
39 eligibility for *priority review* designation.

40  
41 *Priority Review*

42  
43 This process was established by the 1992 PDUFA to improve the efficiency of NDA reviews for  
44 NMEs. A priority review designation can be assigned to applications for drugs “that treat *serious*  
45 *conditions* and provide *significant improvements* in the safety or effectiveness of the treatment,  
46 diagnosis, or prevention of serious conditions *compared to available therapies*.<sup>23</sup> A priority review  
47 designation is assigned at the time of the NDA, BLA or efficacy supplement filing. Priority review  
48 can be granted to applications for drugs with fast track or breakthrough therapy designation, or to  
49 applications submitted for review under accelerated approval. That decision is based on the  
50 information and data available at the time the application is submitted.”<sup>1</sup>

1 The timeline for FDA response is the same as fast track designations with a shorter timeframe for  
2 reviewing the application versus standard review cycles (6 months compared with the 10-month  
3 target for the latter). From FY 2007 through FY 2016, the (average) median time to application  
4 approval was 11.4 months for standard review compared with 7.9 months for priority review.<sup>23</sup>  
5 CLINICAL TRIAL EVIDENCE AND EXPEDITED REVIEW PROGRAMS  
6

7 *A Perspective on New Drug Safety-Related Issues.*

8  
9 One study conducted on postmarket safety outcomes for all NMEs (n=278) approved from 2002-  
10 2014 demonstrated that safety updates to the product labeling were the rule rather than the  
11 exception.<sup>24</sup> At least one safety update was added to 195 (70.1%) of the products, most commonly  
12 between the 2<sup>nd</sup> and 8<sup>th</sup> year after marketing. Safety information was added earlier after marketing  
13 for drugs approved with a fast-track designation or under an accelerated approval using a surrogate  
14 end point; safety issues also were more likely to arise for drugs with a fast track designation.  
15

16 *Evidentiary Standards*

17  
18 Another perspective on drugs approved via expedited reviews is to examine the strength of  
19 evidence accompanying market approvals, which clearly has important implications for patients,  
20 physicians, and payers. Concern has been expressed about the potential lack of systematic  
21 monitoring for confirmation of effectiveness for drugs that have been approved based on limited  
22 evidence, compared with standard approvals.<sup>25</sup>  
23

24 One recent review of cancer drugs approved from 2006-2016 found that when RCTs were lacking,  
25 approved indications were more likely to be based on accelerated approval, receive a breakthrough  
26 designation or have a companion diagnostic test. Indications not supported by RCTs had higher  
27 odds of post approval safety changes, but not major modifications in indications and dosage,  
28 warnings and precautions, boxed warnings, or contraindication sections of the labeling.<sup>26</sup>  
29

30 Analysis of all drugs approved by the FDA from 2005-2012 revealed that most indications were  
31 supported by at least 1 RCT, although more than one-third of indications were approved based on a  
32 single pivotal efficacy trial. Substantial variation existed in terms of the comparators and end  
33 points, trial duration, number of participants, and completion rates.<sup>12</sup> Surrogate endpoints served as  
34 the primary outcome for 91 of 206 (44%) of the approved indications.  
35

36 From 2005-2014, 295 supplemental NDAs for new indications were submitted. Thirty percent of  
37 these were supported by efficacy trials with an active comparator and 32% used a clinical endpoint.  
38 Among those expanding the patient population (almost all pediatric), only 11% used an active  
39 comparator, with 22% using a clinical endpoint.<sup>27</sup>  
40

41 **DISCUSSION**

42 Over the years, the FDA has implemented various approaches to expedite the review and approval  
43 of new drug and biologic applications, as well as new indications for existing products. Under the  
44 current regulatory structure, the specific drug development program, including eligibility for  
45 expedited programs, is determined by the seriousness and prevalence (or rarity) of the disease,  
46 availability of existing treatments, and evidence that the new drug can offer significant  
47 improvement compared with available therapies and/or otherwise address an unmet medical need.  
48 Accelerated approval, fast track, priority review, and breakthrough therapy designations have been  
49 developed to consider and address these variables. These expedited programs differ and should not  
50 be lumped together from a scientific, public health, or policy point of view. Key variables include  
51

1 the requirement for post-approval studies for drugs marketed under accelerated approval, whether a  
2 surrogate endpoint that has not been validated is used to support approval, and the need to confirm  
3 clinical benefit and the risk-benefit profile for drugs approved based on limited evidence,  
4 regardless of their review designation.

5 It has been argued that the process of approving medications based on more limited evidence,  
6 including fewer patients and patient years of exposure, makes the process of reducing healthcare  
7 disparities costlier.<sup>28</sup> Earlier drug approval reduces the power of studies to detect difference in risk  
8 and benefit in relevant subgroups and could direct the burden of medical uncertainty toward groups  
9 of people who are often disadvantaged. It may be advisable for the FDA to encourage that  
10 confirmatory trials enable appropriate sub-group analyses that were not possible during initial,  
11 lower-powered studies. Accelerating drug approval shifts the burdens of uncertainty away from  
12 clinical trial participants (who have undergone informed consent) to others who are exposed to the  
13 treatment under different conditions, socializing the costs of uncertainty while pharmaceutical  
14 companies profit from new drug development. The relevant question is “whether earlier access to  
15 drugs, driven by changes in regulatory policy or growing reliance on surrogate endpoints, benefits  
16 or harms patients.”<sup>29</sup>

17  
18 Confirmatory studies are needed for drugs approved based on limited evidence to avoid exposing  
19 patients to potentially unsafe or ineffective therapies. Even the use of uncertain surrogate endpoints  
20 is not problematic if confirmatory studies reliably demonstrate meaningful clinical endpoints. A  
21 report from the Government Accountability Office, in referring to the FDA’s activities in this area,  
22 concluded that “the agency needs to clarify the conditions under which it would use its authority to  
23 expedite the withdrawal of drugs granted accelerate approval,” when confirmatory studies are not  
24 conducted in a timely manner or fail to confirm predicted benefits.<sup>30</sup>

25  
26 Over the past 15 years, most accelerated approvals were for oncologic drugs, and that experience is  
27 instructive. The accelerated approval of bevacizumab for breast cancer has been held up as a prime  
28 example of harm, because it was approved based on the endpoint of progression-free survival, but  
29 eventually this drug was shown to not increase overall survival.<sup>19</sup> However, “clear and convincing  
30 evidence” has emerged from phase 2 (and some phase 1) trials leading to marketing approval of  
31 new chemical entities within 2-3 years accounting for “advances in treatment for molecular subsets  
32 of non-small cell lung cancer, melanoma, chronic leukemia, breast cancer, and acute myeloid  
33 leukemia,” among others.<sup>19</sup>

34  
35 Although critics have condemned a lack of “improved survival” as the optimal endpoint for clinical  
36 trials, there has been a “steady improvement in U.S. cancer mortality and survival over the past 2  
37 decades.”<sup>19</sup> in part because of new treatments, but also better screening and early detection.  
38 Nevertheless, more than half of oncologic drugs marketed under accelerated approvals relied on a  
39 surrogate endpoint that was chosen in the absence of any formal analysis of the strength of the  
40 surrogate-survival connection.<sup>31</sup> This observation reinforces the need for timely determination of  
41 the predicted clinical benefit and confirmation of the risk-benefit profile.

42  
43 Comprehensive evaluation of oncologic drugs marketed under accelerated approval confirms that  
44 satisfactory progress has been made on confirmatory trials. By balancing risk, accounting for  
45 uncertainty, and operating under a paradigm of regulatory flexibility, existing FDA expedited  
46 pathways can ensure early access to, and appropriate use of new drugs and biologics, including  
47 specialty drugs. The Institute of Medicine recommended that the FDA should “implement a benefit  
48 and risk assessment and management plan that would summarize the FDA’s evaluation of drug’s  
49 risk-benefit profile in a single document and that would be continuously updated” during the life-  
50 cycle of the drug on the market.<sup>32,33</sup> While it is important for the agency to retain regulatory  
51 flexibility, and mostly positive aspects of expedited programs are apparent, some changes should

- 1    be made to improve implementation, establish the value of surrogate endpoints, and provide more
- 2    transparency for physicians and their patients on the level of evidence used for marketing approval.

1     RECOMMENDATION  
2

3     The Council on Science and Public Health recommends that Policy H-100.992 be amended by  
4     addition and deletion to read as follows in lieu of Res-201-I-17, and the remainder of the report be  
5     filed:

6         (1) Our AMA ~~reaffirms its~~ supports for the principles that:

7             (a) an FDA decision to approve a new drug, to withdraw a drug's approval, or to change the  
8             indications for use of a drug must be based on sound scientific and medical evidence derived from  
9             controlled trials and/or postmarket incident reports as provided by statute;  
10             (b) ~~this~~ evidence for drug approval should be evaluated by the FDA, in consultation with its  
11             Advisory Committees and expert extramural advisory bodies, as appropriate;  
12             (c) expedited programs for drug approval serve the public interest as long as sponsors for drugs that  
13             are approved based on surrogate endpoints or limited evidence conduct confirmatory trials in a  
14             timely fashion to establish the expected clinical benefit and predicted risk-benefit profile;  
15             (d) confirmatory trials for drugs approved under accelerated approval should be planned at the time  
16             of expedited approval;  
17             (e) the FDA should pursue having in place a systematic process to ensure that sponsors adhere to  
18             their obligations for conducting confirmatory trials;  
19             (f) any risk-benefit analysis or relative safety or efficacy judgments should not be grounds for  
20             limiting access to or indications for use of a drug unless the weight of the evidence from clinical  
21             trials and postmarket reports shows that the drug is unsafe and/or ineffective for its labeled  
22             indications; and,  
23             (g) FDA should make the annual summary of drugs approved under expedited programs more  
24             readily available and consider adding information on confirmatory clinical trials for such drugs to  
25             the drugs trials snapshot.

26         (2) The AMA believes that social and economic concerns and disputes per se should not be  
27     permitted to play a significant part in the FDA's decision-making process in the course of FDA  
28     devising either general or product specific drug regulation.

29         (3) It is the position of our AMA that the Food and Drug Administration should not permit political  
30     considerations or conflicts of interest to overrule scientific evidence in making policy decisions;  
31     and our AMA urges the current administration and all future administrations to consider our best  
32     and brightest scientists for positions on advisory committees and councils regardless of their  
33     political affiliation and voting history.

Fiscal Note: Less than \$500

1 REFERENCES  
2

3 1. U.S. Food and Drug Administration. Guidance for Industry. Expedited Programs for Serious  
4 Conditions — Drugs and Biologics.  
5

6 2. 21 CFR 312.300(b)(1).  
7

8 3. Manual of Policies and Procedures. Center for Drug Evaluation and Research. Office of New  
9 Drugs. Review Designation Policy: Priority (P) and Standard (S) [h](#).  
10

11 4. What's special about specialty? <https://cvshealth.com/thought-leadership/whats-special-about-specialty>.  
12

13 5. Code of Federal Regulations. §314.510. [https://www.ecfr.gov/cgi-bin/text-idx?SID=7e3afa31ba9326a86c1c08ca7cb22f4c&mc=true&node=se21.5.314\\_1510&rgn=div8](https://www.ecfr.gov/cgi-bin/text-idx?SID=7e3afa31ba9326a86c1c08ca7cb22f4c&mc=true&node=se21.5.314_1510&rgn=div8).  
14 December 11, 1992. Accessed August 13, 2018.  
15

16 6. Code of Federal Regulations. §601.41. [https://www.ecfr.gov/cgi-bin/text-idx?SID=c03234aa22abbed0380923a4cc6ab001&mc=true&node=se21.7.601\\_141&rgn=div8](https://www.ecfr.gov/cgi-bin/text-idx?SID=c03234aa22abbed0380923a4cc6ab001&mc=true&node=se21.7.601_141&rgn=div8).  
17 December 11, 1992. Accessed August 13, 2018.  
18

19 7. Food and Drug Administration Safety and Innovation Act, 21 USC §301.  
20 <https://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf>. July 9, 2012. Accessed August 13, 2018.  
21

22 8. Kesselheim AS, Yongtian TT, Darrow JJ, Avorn J. Existing FDA pathways have potential to  
23 ensure early access to, and appropriate use of, specialty drugs. *Health Affairs*. 2014;10:1770-  
24 78.  
25

26 9. 21 CFR. §216.24. Drug products withdrawn or removed from the market for reasons of safety  
27 or effectiveness.  
28

29 10. Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs. *JAMA*.  
30 1999. 282;790-95.  
31

32 11. Califf RM. Balancing the need for access with the imperative for empirical evidence of benefit  
33 and risk. *JAMA*. 2017;318(7):614-616.  
34

35 12. Ciani O, Buyse M, Drummond M, et al. Time to review the role of surrogate end points in  
36 health policy: state of the art and the way forward. *Value Health*. 2017;20:487-95.  
37

38 13. Downing NS, Aminawung JA, Shah ND ,et al. Clinical trial evidence supporting FDA  
39 approval of novel therapeutic agents,2005–2012. *JAMA*. 2014;311:368–77.  
40

41 14. Dagher R, Johnson J, Williams G, Keegan P, Pazdur R. Accelerated approval of oncology  
42 products: a decade of experience. *J Natl Cancer Inst*. 2004;96(20):1500-1509.  
43

44 15. Johnson JR, Ning YM, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of  
45 oncology products: the Food and Drug Administration experience. *J Natl Cancer Inst*.  
46 2011;103(8):636-644.  
47

48

49

1 16. Beaver JA, Howie LJ, Pelosof L, et al. A 25-year experience of US Food and Drug  
2 Administration Accelerated Approvals of Malignant Hematology and Oncology Drugs and  
3 Biologics. *JAMA Oncology*. 2018;84956.

4

5 17. Shea M, Roberts SA, Walrath JC, Allen JD, Sigal EV. Use of multiple endpoints and approval  
6 paths depicts a decade of FDA oncology drug approvals. *Clin Cancer Res*. 2013;19:3722-31.

7

8 18. Richey E, Lyons A, Nebeker JR, et al. Accelerated approval of cancer drugs: Improved access  
9 to therapeutic breakthroughs or early release of unsafe and ineffective drugs. *J Clin Oncology*.  
10 2009;27:4398-4405

11

12 19. Chabner BA. Regarding “Oncology drug approvals: Evaluating endpoints and evidence in an  
13 era of breakthrough therapies. *Oncologist*. 2017 Jul;22(7): 757–758.

14

15 20. Prasad V, Kim C, Burotto M, Vandross A. The strength of association between surrogate  
16 endpoints and survival in oncology: a systematic review of trial level meta-analyses. *JAMA  
17 Intern Med*. 2015;175:1389-98.

18

19 21. Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory  
20 and clinical decisions, and are they currently overused. *BMC Medicine*. 2017. 15:134.

21

22 22. U.S Food and Drug Administration. FY 2017. Performance Report to Congress for the  
23 Prescription Drug User Fee Act.

24

25 23. Herink MC, Irwin AN, Zumach GM. FDA breakthrough therapy designation: Evaluating the  
26 quality of the evidence behind the drug approvals. *Pharmacotherapy*. 2018; Jul 24. doi:  
27 10.1002/phar.2167.

28

29 24. Pinnow E, Amr S, Bentzen SM et al. Postmarket safety outcomes for new molecular entity  
30 (NME) drugs approved by the food and drug administration between 2002 and 2014. *Clin  
31 Pharmacol Ther*. 2018;104;390-400.

32

33 25. Hatswell AJ, Baio G, Berlin JA, Irs A, Freemantle N. Regulatory approval of pharmaceuticals  
34 without a randomized controlled study: analysis of EMA and FDA approvals 1999-2014. *BMJ  
35 Open*. 2016;6:e011666. doi:10.1136/bmjopen-2016-011666.

36

37 26. Shepshelovich D, Tibau A, Goldvaser H, et al. Postmarketing modifications of drug labels for  
38 cancer drugs approved by the US Food and Drug Administration between 2006 and 2016 with  
39 and without supporting randomized controlled trials. *J Clin Oncology*. 2018;36:1798-1804.

40

41 27. Wang B, Kesselheim AS. Characteristics of efficacy evidence supporting approval of  
42 supplemental indications for prescription drugs in United States, 2005-14: systematic review.  
43 *Brit Med J*. 2015;351:h4679. doi: 10.1136/bmj.h4679.

44

45 28. London AJ. Accelerated drug approval and health inequality. *JAMA Int Med*. 2016;176:883-4.

46

47 29. Jena AB, Zhang Jie, Lakdawalia DN. The trade-off between speed and safety in drug  
48 approvals. *JAMA Oncology*. 2017;3:1465-66.

1 30. Government Accountability Office. GAO-09-866. New Drug Approval. FDA Needs to  
2 Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints. September  
3 2009. <https://www.gao.gov/new.items/d09866.pdf>. Accessed August 25, 2018.  
4

5 31. Kim C, Prasad V. Strength of validation for surrogate end points used in the U.S. Food and  
6 Drug Administration's approval of oncology drugs. *Mayo Clin Proc.* 2016 May 10. pii: S0025-  
7 6196(16)00125-7. doi: 10.1016/j.mayocp.2016.02.012.  
8

9 32. Institute of Medicine. Ethical and Scientific Issues in Studying the Safety of Approved Drugs.  
10 Washington, DC. National Academy Press. 2012.  
11

12 33. Psaty BM, Medlin EM, Breckenridge A. A lifecycle approach to the evaluation of FDA  
13 approval methods and regulatory actions: opportunities, provided by a new IOM report. *JAMA*.  
14 2012;307:2491-92.