

# Optimizing the Use of Accelerated Approval

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The Accelerated Approval (AA) Program has been an important regulatory mechanism for FDA to allow for earlier approval of drugs that treat serious and life-threatening illnesses than would occur through the traditional approval program. Created in 1992, the AA program was conceived as a direct response to patient therapy during the HIV/AIDS epidemic and in recognition of the urgency of access to new therapy needs faced by patients with life-threatening illnesses. As opposed to traditional approval, which is based upon a direct measure of clinical benefit (Glossary) or a validated surrogate, AA is intended to allow for the initial approval of a drug based on a demonstration of effect on a surrogate endpoint—or an intermediate clinical endpoint—that is reasonably likely to predict a clinical benefit.<sup>1-3</sup> Under FDA regulations, sponsors should conduct post-marketing studies that verify and describe the expected clinical benefit of the drug with a clinical trial design as agreed upon with FDA at the time of AA.<sup>3</sup> The AA statute also establishes provisions for withdrawal of an AA drug where confirmatory trials fail to verify clinical benefit or safety concerns arise.

In 2012, the AA program (Subpart H – drugs and Subpart E – biologics) was amended by the FDA Safety and Innovation Act (FDASIA)<sup>4</sup>:

*“The [Secretary](#) may approve an application for approval of a product for a serious or life-threatening disease or condition, including a fast track product, under [section 355\(c\) of this title](#) or section 351(a) of the [Public Health Service Act \[42 U.S.C. 262\(a\)\]](#) upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.”*

FDASIA maintained the reliance of an AA on an intermediate endpoint (either surrogate or clinical endpoint that can be measured earlier) that is reasonably likely to predict an effect on clinical benefit but removed the initial requirement for an AA drug to “generally provide meaningful

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advantage over available therapies.” Although FDA’s regulations and guidance have not yet been modified to reflect the later language change, the modified language in FDASIA nonetheless reduced some ambiguity regarding which products may qualify for accelerated approval. By explicitly incorporating a more comprehensive benefit–risk assessment in FDA communications regarding an AA, along with outcomes measured by a surrogate or intermediate clinical endpoint, stakeholder confusion related to AA could be further reduced.

The AA pathway broadly applies to all drug classes and is used across clinical divisions within the FDA. However, AA has been most frequently used in oncology. In the past 10 years (2010–2019), 84% of FDA’s accelerated approvals were granted for oncology indications.<sup>5</sup> The robust experience of AA in oncology, which is unique given an extensive infrastructure for conducting research and aggregating data, can be used to inform the use of AA in other indications. This white paper will explore the impact of AA, identify challenges, and pose improvements both broadly and within the context of, and informed by, learnings from applications of AA in oncology. For a discussion of other expedited programs used by the FDA see the companion white paper “[Modernizing Expedited Development Programs](#).”

## Why is AA Important for Patients?

Since its creation by FDA in 1992, 148 new drugs or biologics to treat serious or life–threatening illnesses have been approved through the AA program.<sup>5</sup> One assessment of oncology treatments concluded that therapies receiving AA were made available a median of 3.4 years earlier than would be achievable if confirmation of clinical benefit based upon a primary endpoint, such as overall survival, was required.<sup>6</sup>

AA has extended or, in certain cases, saved patients’ lives by providing earlier access to novel therapies than would have been possible using the traditional FDA approval pathway. Specifically, for multiple myeloma, access to new therapies that are used as single agents, and are now being used in combination, have been accelerated, extending the time of disease stabilization when, in the absence of the AA drug, patients would have experienced debilitating symptoms, progressed, or died.

As more transformative treatments are developed that extend survival by years or even decades, the ability to quantify overall survival will become increasingly difficult or impossible within the context of a clinical trial. Specifically, for patients with a terminal illness or those that lack other treatment options, randomization to a control arm to determine overall survival (OS) is, in many cases, unethical. Further, as treatments become more highly targeted to smaller populations or subsets of diseases, traditional measures of benefit will become more difficult to employ where large numbers of patients are needed to statistically quantify OS as compared to surrogate measures of clinical benefit such as response rate. Enhancements to the AA pathway will help to ensure continued benefit from this program as medicines and drug development evolve. For example, where a confirmatory trial for an AA therapy would traditionally verify clinical benefit measured by a surrogate endpoint, communication of a preliminary benefit–risk assessment that includes but is not limited to consideration of outcomes of a surrogate endpoint, may better reflect a more holistic consideration of factors that are important to patients

in an approval determination. In other words, the confirmatory trial would be conducted to verify the totality of evidence of a drug, including magnitude and duration of benefit and safety, and whether the benefits received from a drug justified the risk rather than focus only on confirmation of a primary endpoint. A framework to encourage greater patient input on the determination of benefit-risk is important to amplifying the patient voice in drug development.

Finally, although the benefits of a drug may outweigh the risks in a clinical trial population, it is important to characterize the benefit-risk profile in the real-world population. The information provided by clinical trials is based upon a highly selected, homogenous, patient pool (typically younger patients with fewer comorbidities) that is less reflective of the general population. A patient cannot make truly informed decisions regarding treatment choices without adequate data to provide a complete picture of the benefits and risk of a therapy. For this reason, the importance of Phase IV confirmatory studies, which examine the benefit of a therapy and the toxicities in a broader population or in the real world through real-world studies, cannot be overemphasized. The AA pathway could supplement post-approval required trials with such real-world assessments to capitalize on all mechanisms of data generation to produce the most robust benefit-risk assessment possible.

## Surrogate Endpoint vs Benefit-Risk Assessment

Since the AA Program was codified in the US, analogous regulatory pathways have been implemented by other regulatory bodies, including the European Medicines Agency (EMA) and Health Canada, with the intent of expediting access to new therapies intended to treat serious diseases in those settings (Table 1). While implemented for a similar purpose, a comparison of each pathway also reveals important differences. For example, Conditional Marketing Authorisation (Conditional Approval), the pathway implemented by the EMA is distinctive with respect to its use of an initial benefit-risk analysis of a drug as a basis for a Conditional Approval as opposed to evaluation of an drug's effect on a surrogate endpoint that is used as the basis for AA by FDA and many of the other programs. Further, Conditional Approval by EMA is valid for only one year with the option of sponsor application for renewal. It is also important to note that regulatory approval in the EU does not necessarily translate to immediate patient access to new drugs as in the US because European countries also require a health technology assessment once a drug is determined to be safe and effective before reimbursement is awarded.

There is some discrepancy, particularly in oncology, regarding the clinical and regulatory context in which a surrogate endpoint is used to grant traditional approval and when a surrogate endpoint is considered reasonably likely to predict benefit to support AA. This can create confusion over distinctions between traditional and accelerated development programs. For example, objective response rate (ORR) is considered a surrogate endpoint used for AA in oncology. However, FDA can also grant traditional approval based on this surrogate endpoint in single-arm trials when the ORR is substantial and durable. As another example, responses of fungating skin lesions were considered evidence of direct clinical benefit to support traditional approval of vismodegib for advanced basal cell carcinoma.<sup>7</sup> Consequently, the use of the same surrogate in different contexts necessitates greater clarity regarding the level of evidence necessary for and how various endpoints are considered across development programs when a

drug can be granted traditional approval based upon an endpoint that is also used for AA.

Similar to the use of a benefit-risk assessment to support conditional approval by the EMA, drug development through the AA pathway in the US could be enhanced if communication about an AA were shifted away from a focus solely on predictive endpoints and toward a discussion about overall benefit-risk considerations. FDA already uses a standard framework for benefit-risk considerations when making approval decisions. The elements of FDA's benefit-risk framework include Analysis of Condition, Current Treatment Options, Benefit, and Risks and Risk Management.<sup>8</sup> Greater clarity regarding how FDA considers benefit-risk could be helpful, particularly regarding the magnitude of effect and potential toxicities of a drug. For example, when considering magnitude of effect, a substantial outcome in a surrogate endpoint may be a superior outcome vs a less impactful outcome as measured in a traditional endpoint. Additionally, potential toxicities should be considered within the context of importance to a patient's quality of life and may contribute to determining the "availability" of treatments. It may be appropriate to award AA to a drug with a lower ORR if the drug is less toxic or has a positive impact on patient-reported outcomes or function—and a confirmatory trial would aim to verify that benefit vs risk was maintained in the post-market setting.

## Challenges and Solutions

### Pre-approval setting

Prioritization of the benefit-risk framework for drug review would facilitate a more holistic assessment of new therapies. It is within the context the above considerations, regarding the benefit-risk assessment in regulatory determinations, that we suggest additional considerations to improve AA within the benefit-risk framework.

**Defining an "available therapy."** The statute for AA, as amended by FDASIA, establishes eligibility for an AA and requires FDA to take "into account the availability or lack of alternative treatments." Patient access to treatments through AA has benefited from the clinical judgement that FDA reviewers have been afforded and the ability to account for confounders when considering an "available therapy." However, challenges remain when interpreting the definition of available therapy in certain situations. First, it is not always clear whether the existence of an FDA approved drug with an FDA approved indication in the disease of interest should necessarily be considered an available therapy. For example, over time and as the standard of care improves, some drugs become less relevant, or not used at all, in clinical practice at the time of a new AA and should not be considered an available therapy when assessing a new drug application in the same indication. Second, the use of published literature to establish an available therapy is highly discretionary but could benefit from additional clarity. For example, FDA has considered drugs for first-line lung cancer as an "available therapy" for lung cancer patients when determining eligibility for AA. When AA was awarded for crizotinib for metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements (ALK+), platinum doublet chemotherapy in first-line and docetaxel in second-line were considered available therapies. The crizotinib AA was based upon two single arm trials compared to published literature of ORR for platinum doublet chemotherapy and docetaxel.<sup>9</sup> However, benefit was confirmed in a randomized confirmatory trial. Last, an emerging consideration is how to define available therapy for molecular

indications. When considering a biomarker positive population, it may not be appropriate to consider an FDA approved drug with an expansive indication, which would include the biomarker positive population, but was never studied in that subpopulation, as an available therapy. A standardized approach to the definition of an “available therapy” in the context of a specific disease setting or population/subpopulation, including biomarker positive and novel refractory disease states (e.g., PD-(L)1-refractory populations), should be considered to provide greater clarity and consistency in application of AA.

**Surrogate endpoint.** Surrogate or intermediate endpoints such as duration of response or ORR are tumor-based endpoints, and there is no consistency in the magnitude of improvement in response rates that would constitute a change in other endpoints such as overall survival. Further, ORR from historic literature may not be as accurately assessed as compared to ORR in a modern registrational clinical trial, which typically requires blinded independent central radiology review. It is difficult to assess the level of evidence needed to establish that a surrogate endpoint fulfills the requirement of “reasonably likely to predict clinical benefit.” Standardization or additional guidance for qualitative metrics of surrogate or intermediate endpoints would be helpful to provide more clarity and predictability for development programs without reducing flexibility for regulatory decision-making. Expectations and transparency in how FDA will consider magnitude of surrogate measures could be further clarified in design of confirmatory trials.

Another consideration in the use of surrogate endpoints is a better understanding of how the intermediate endpoint is weighted in a benefit-risk assessment. Different considerations may need to be taken for response rate vs duration of response and the magnitude of each. For example, tazemetostat was unanimously recommended by an Oncology Drug Advisory Committee (ODAC) based upon a 11–15% ORR for patients with metastatic or locally advanced epithelioid sarcoma with a lack of available therapies being a key consideration.<sup>10</sup> In oncology, a high response rate with a duration of response that lasts more than one year is preferable, but less substantive outcomes will require more nuanced consideration, including the rarity of the patient population.

**Heterogeneity in populations.** There has emerged a phenomenon of “excellent responders” in the context of immunotherapies, where there may be less than 10% of patients that respond to a therapy but those minority of patients that do respond exhibit dramatic and long term responses. In these cases, the overall trial for the general population may fail to demonstrate a benefit, but treatment may still be appropriate for those “excellent responders.” It may be appropriate to award AA in that “excellent responder” subpopulation, despite failure of the trial to demonstrate benefit in the overall population, followed by post-market confirmatory requirements. How FDA considers surrogate endpoints in a benefit-risk assessment could be further clarified in guidance including how to appropriately design a statistically powered trial to identify efficacy in these sub-populations. This may need to include considerations for the objective or definition of a confirmatory trial. For example, a “confirmation of benefit” may be less about demonstrating superior survival of a therapy in the overall population and it may be more important to identify those patients that are “exceptional responders” based upon response measured in a biomarker-positive population.

**Development of surrogate endpoints.** More research is needed to develop new surrogate endpoints or provide more substantial evidence of likelihood to predict clinical benefit in support of AA. Surrogate endpoints that can clarify benefit in patients who achieve disease stabilization, such as changes in circulating tumor DNA, may be an important tool for drug development and clinical decision making. FDA could create a formal process, or expand upon the Drug Development Tool (DDT) Qualification Program, for sponsors to submit key data variables and patient outcomes from clinical trials used to support accelerated approval and traditional approval to help validate endpoints that predict clinical benefit. FDA considers clinical outcomes assessments to be a DDT and has issued draft guidance to inform the qualification of these metrics.<sup>11</sup> This evidence could be aggregated through a collaborative community or independently of FDA through precompetitive consortia to provide a publicly available database of evidence to support benefit-risk assessments that include evidence based upon a surrogate endpoint.

**External control arms to support clinical trials.** Clinical trials, from Phase I dose-finding and safety trials to Phase III randomized trials examining efficacy, form the backbone of the drug development pipeline and inform regulatory approvals. Single-arm clinical trials are now used to support regulatory approval, particularly important for AA, in settings where ethical concerns or challenges with feasibility of deploying a concurrent control arm exist, such as rare diseases or populations with unmet needs where randomization to a placebo or active comparator (for refractory settings) would be inappropriate and/or not feasible. While single-arm trials alone may yield important safety and efficacy signals and can be relied on for regulatory decision making in these clinical and regulatory contexts, real-world evidence (RWE), such as external controls (sometimes referred to as synthetic controls) may provide additional context and supplementary evidence. For example, in 2017, avelumab received AA for Merkel cell carcinoma on the basis of an 88-patient single arm Phase II trial. Real-world evidence (RWE), contributed by external data from a registry, was used as supportive evidence, but the regulatory approval was based primarily on data from the Phase II trial.<sup>12</sup> Expanding the use of external controls to other difficult-to-study indications may reduce patient burden where research may be slowed or uninterpretable due to the use of a concurrent randomized control. The latter may be the case with some confirmatory trials of medical products made available through the accelerated approval pathway where the control arm may be compromised by early discontinuation or treatment crossover to the investigational therapy made available by an AA.<sup>13</sup>

### **Post-approval challenges and solutions**

Although awarding of an AA to market a new therapy is contingent upon continued generation of evidence to verify and describe drug effectiveness, enrollment in confirmatory trials once a drug is already on the market may pose challenges. Certainly, once a drug is widely available, the incentive for a patient to participate in a clinical trial, and risk randomization to a placebo or an active control that is perceived as inferior, is reduced. This situation can be further exacerbated where a substantial improvement in overall survival is expected, as in the case of AA and breakthrough therapy designated drugs, and there may be loss of equipoise for conducting a randomized trial with a less effective therapy for confirmation of clinical benefit following AA. Further, it may not be ethical to take advantage of access barriers outside of the US, where the therapy is not yet available, to accrue patients to a trial that otherwise would be unlikely

to accrue patients within the US. The confirmatory evidence deemed necessary by the FDA to assess the benefit-risk of the therapy is nevertheless critical to ensure patient safety and benefit and different approaches to generating this information are needed, along with consideration of how evidence generated from confirmatory trials inform changes to labeled indications.

**Initiation of confirmatory studies in pre-market setting.** Confirmatory trials could be required to be initiated and have enrolled a pre-determined number of patients when the marketing application (NDA or BLA) is filed. This would require additional and earlier communication between FDA and sponsor to facilitate, including, more real-time access for the FDA to the necessary data that would inform design of a confirmatory trial, including guidance to determine how a “minimum number of patients accrued” would be defined across different drugs and disease settings. Access to data could be provided to FDA on a similar timeframe as a drug manufacturing and formulation program. This could not only inform confirmatory trial design earlier but also facilitate use of more pragmatic trial designs by aligning the patient population pre-approval to the initial study to give greater confidence in results of the confirmatory trial. Further, it could promote the awarding of AA based on an “intermediate data review,” in line with a benefit-risk assessment as opposed to a surrogate endpoint.

**Consideration of subsequent confirmatory studies.** Sponsors can conduct a confirmatory trial in different populations or settings than the initial trial for which AA was awarded for numerous reasons, including low accruing trials and loss of equipoise, and there are examples where this has occurred. Most commonly, this is used for AA based upon substantial response rate in a single-arm trial with a monotherapy in a refractory population, the confirmatory trial, then, utilizes a randomized design in an earlier line setting. For rare populations where randomized trials are not feasible, confirmatory trials, with a single-arm design consisting of more patients and/or longer follow-up for duration of response may be considered.

A randomized design approach, however, can become problematic if the confirmatory trial that utilizes a different population than the initial trial, fails to confirm benefit in the subsequent population. These results are not necessarily a reflection of the effectiveness of the drug but are likely reflective of trial design related issues such as inability to accrue sufficient patients, high drop-out or crossover rates that impact the statistical power of the study, or enrolling the wrong patient population. Gefitinib, approved in non-small-cell lung cancer, is an example in which the confirmatory trials failed and ultimately lead to a withdrawal of AA.<sup>14</sup> However, subsequent trials were able to identify an appropriate patient population, leading to a subsequent approval in EGFR-mutant lung cancer.<sup>15,16</sup> In similar instances, FDA may be hesitant to remove an AA for a therapy due to concerns that the treatment may meet an unmet medical need in a certain subpopulation while still recognizing that additional clinical trials are needed to confirm benefit in that subpopulation. Indeed, the impact of withdrawal of AA for gefitinib on unmet medical need was mitigated by the availability of another therapy, erlotinib, which remained on the market. Without the availability of an alternative therapy, access issues for that particular population would have been of concern. By allowing the sponsor to retain AA for the drug after the initial confirmatory trial failed and conduct additional post-market trials allows the FDA to address both concerns. Further, FDA could host a public discussion at an ODAC to discuss the failed trial and to consider whether other confirmatory trials or withdrawal may be appropriate. This public



format would facilitate a transparent discourse that bolsters patient input in the decision-making process and prioritizes benefit-risk assessments in the post-market setting. FDA currently has a withdrawal process for removing AA, but this is an onerous and time-consuming process, making it an ineffective method for withdrawing AA in a timely manner when the company does not agree with the withdrawal. The withdrawal process will also require improvement to facilitate opportunities for subsequent confirmatory trials, where appropriate and necessary, to ensure a robust AA pathway. The FDA should consider ways in which this pathway can be made more nimble and improve this mechanism as an enforcement mechanism for required confirmatory studies. Additional changes to the AA Program could be considered. For example, analogous programs to AA implemented by other regulatory agencies, such as the EMA, are valid for one year after approval with the option to renew annually. The FDA could be given authority to require an annual update of post-market requirements and review of new data to ensure post-market commitments are met in a timely manner.

**Real-world evidence to support confirmation of benefit.** RWE is increasingly becoming utilized in drug development, including in the post-market setting. Recent legislative and regulatory policies focused on RWE, such as the 21st Century Cures Act, Prescription Drug User Fee Act (PDUFA) Reauthorization of 2017, and FDA Framework on Real-World Evidence, highlight the interest in using RWE applications across the drug development life cycle.<sup>17-20</sup> While the centrality of clinical trials remains, the homogenous patient populations included to produce rigorous data limit the generalizability of clinical trial-related drug safety and efficacy to its broader use in clinical practice.<sup>21</sup> Real-world datasets, on the other hand, can be assembled that produce robust analyses that complement those of clinical trials. RWE can reflect broader, more diverse patient populations than are typically included in traditional clinical trials and can be applied across multiple use cases, including to answer timely clinical questions, assess endpoints measures, perform comparative effectiveness research, and study long-term drug safety. Within the context of a benefit-risk assessment for AA, additional evidence from RWE could be used to supplement confirmatory trial results and contribute to a more complete understanding of drug efficacy and safety.

## Conclusions

The AA pathway has proved to be an extremely important mechanism to promote development of and access to therapies for serious or life-threatening illnesses. It is important to continue to improve on this mechanism to maximize the benefit achievable through this pathway for patients. This white paper provides several possible recommendations to achieve this goal.

## Glossary

**Clinical benefit:** a positive therapeutic effect that is clinically meaningful in the context of a given disease. The clinical benefit must be weighed against a treatment's risks to determine whether there is an overall benefit for patients (i.e., a positive benefit-risk profile).<sup>3, 22</sup>

**Clinical endpoint:** a characteristic or variable that directly measures a therapeutic effect of a drug—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives.<sup>3, 22</sup>

**Intermediate clinical endpoint:** a measurement of a therapeutic effect that can be measured earlier than an effect on irrecversible morbidity or mortality (IMM) and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit.<sup>3, 22</sup>

**Reasonably likely surrogate endpoint:** surrogate endpoint that is supported by strong mechanistic and/or epidemiologic rationale, but the amount of clinical data available is not sufficient to show that they are a validated surrogate endpoint.<sup>22</sup>

**Surrogate endpoint:** a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Depending on the strength of the evidence supporting the ability of a marker to predict clinical benefit, the marker may be a surrogate endpoint that is known to predict clinical benefit (a validated surrogate endpoint that could be used for traditional approval), a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit (and that could therefore be used as a basis for accelerated approval), or a marker for which there is insufficient evidence to support reliance on the marker as either kind of surrogate endpoint (and that therefore cannot be used to support traditional or accelerated approval of a marketing application).<sup>3, 22</sup>

**Validated surrogate endpoint:** surrogate endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit.<sup>22</sup>

## References

1. 21 CFR part 314, subpart H
2. 21 CFR part 601, subpart E
3. Food and Drug Administration. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. May 2014. <https://www.fda.gov/media/119293/download>. Accessed online 10/7/2020.
4. Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA.
5. US Food and Drug Administration. CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint As of June 30, 2020. <https://www.fda.gov/media/88907/download>. Accessed online 10/1/2020.
6. Beaver JA, Howie LJ, Pelosof L, et al. A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review. *JAMA Oncol.* 2018;4(6):849–856. doi:10.1001/jamaoncol.2017.5618. Accessed online 10/1/2020.
7. Media release. FDA approves Erivedge (vismodegib) capsule, the first medicine for adults with advanced basal cell carcinoma. Roche Group Media Relations. Basel, 30 January 2012. <https://www.roche.com/media/releases/med-cor-2012-01-30.htm>. Accessed online 10/1/2020.
8. US Food and Drug Administration. Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA VI Implementation Plan (FY 2018–2022) accessed on 10/27/2020. <https://www.fda.gov/media/112570/download>
9. Kazandjian D, Blumenthal GM, Chen HY, et al. FDA approval summary: crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. *Oncologist.* 2014;19(10):e5–e11. doi:10.1634/theoncologist.2014-0241. Accessed online 10/8/2020.
10. Media Release. FDA Approves Tazemetostat for Epithelioid Sarcoma. Onclive. January 23, 2020. [tps://www.onclive.com/view/fda-approves-tazemetostat-for-epithelioid-sarcoma](https://www.onclive.com/view/fda-approves-tazemetostat-for-epithelioid-sarcoma). Accessed online 10/1/2020.
11. Food and Drug Administration. Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff. DRAFT GUIDANCE. December 2019. <https://www.fda.gov/media/133511/download>. Accessed online 10/7/2020.
12. Cowey, C. L. et al. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. *Futur. Oncol.* 13, 1699–1710 (2017).
13. Friends of Cancer Research. Exploring Whether a Synthetic Control Arm can be Deriving from Historical Clinical Trials that Match Baseline Characteristics and Overall Survival Outcome of a Randomized Control Arm. (2018). Available at: [https://www.focr.org/sites/default/files/SCA White Paper.pdf](https://www.focr.org/sites/default/files/SCA%20White%20Paper.pdf).
14. Food and Drug Administration. AstraZeneca Pharmaceuticals LP; Withdrawal of Approval of a New Drug Application for IRESSA. (77 FR 24723, April 25, 2012).

15. Pircher A, Ploner F, Popper H, Hilbe W. Rationale of a relaunch of gefitinib in Caucasian non-small cell lung cancer patients. *Lung Cancer*. 2010 Sep;69(3):265-71. doi: 10.1016/j.lungcan.2010.01.017. Epub 2010 Feb 18. PMID: 20167388. Accessed online 10/7/2020.
16. Kazandjian D, Blumenthal G, Yuan W, He K, Keegan P, Pazdur R. FDA Approval of Gefitinib for the Treatment of Patients with Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer. *Clin Cancer Res* 2016;22:1307-1312. doi: 10.1158/1078-0432.CCR-15-2266. Accessed online 10/7/2020.
17. US Food and Drug Administration: PDUFA reauthorization performance goals and procedures fiscal years 2018 through 2022. <https://www.fda.gov/media/99140/download>
18. US Congress: 21st Century Cures Act. P.L. 114-255, 2016.
19. US Congress: Prescription Drug User Fee Act. P.L. 102-571, 1992.
20. Food and Drug Administration. Framework for FDA's Real-world Evidence Framework. December 2018. <https://www.fda.gov/media/120060/download>. Accessed online 10/26/2020.
21. Elting L, Cooksley C, Bekele B, Frumovitz M, Avritscher E, Sun C, Bodurka D. Generalizability of cancer clinical trial results: prognostic differences between participants and nonparticipants. *Cancer* 2006; 106(11):2452-2458. DOI 10.1002/cncr.21907
22. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Glossary. 2016 Jan 28 [Updated 2020 Aug 4]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK338448/> Co-published by National Institutes of Health (US), Bethesda (MD).

Table 1: Comparison of AA Programs Across Nations

Regulatory Agency	Program Name	Date Initiated	How do you qualify?	How is drug evaluated?	Post-marketing Requirements	References/Notes
FDA - US	Accelerated Approval	1992	A drug that treats a serious condition <b>AND</b> generally provides a meaningful advantage over available therapies <b>AND</b> demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	<ul style="list-style-type: none"> <li>- <b>Surrogate Endpoint:</b> a marker that is thought to predict clinical benefit, but is not itself a measure of clinical benefit</li> <li>- <b>Intermediate Clinical Endpoint:</b> a measurement of a therapeutic effect that can be measured earlier than an effect on IMM and is considered reasonably likely to predict the drug's effect on IMM</li> </ul>	<ul style="list-style-type: none"> <li>- Postmarketing confirmatory trial that evaluates a clinical endpoint that directly measures clinical benefit</li> <li><b>OR</b></li> <li>- A confirmatory trial conducted in a different but related population that is capable of verifying the predicted clinical benefit</li> </ul>	<ul style="list-style-type: none"> <li>• 21 CFR part 314, sub-part H</li> <li>• 21 CFR part 601, sub-part E</li> <li>• Section 506(c) of the FD&amp;C Act, as amended by section 901 of FDASIA</li> </ul>

<b>EMA - EU</b>	Conditional Marketing Authorisation	2006	Medicinal products that aim at the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, or medicinal products to be used in emergency situations in response to public health threats	(a) the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive; (b) it is likely that the applicant will be in a position to provide the comprehensive clinical data; (c) unmet medical needs will be fulfilled; (d) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required	<ul style="list-style-type: none"> <li>- The holder will be required to complete <u>specific obligations</u> (ongoing or new studies, and in some cases additional activities) with a view to providing comprehensive data confirming that the benefit-risk balance is positive</li> <li>- Valid for one year, and renewable afterwards</li> </ul>	Regulation (EC) No 507/2006
<b>PMDA - Japan</b>	Conditional Early Approval System	2017	<ul style="list-style-type: none"> <li>- No standard existing therapy or superior clinical usefulness as compared with the existing products in terms of quality of life of patients, efficacy, or safety</li> <li>- Applicable to serious diseases or orphan drug designation</li> <li>- Confirmatory clinical trials are difficult to conduct or take a long time due to a limited number of patients</li> <li>- Clinical trials other than confirmatory trials have shown a certain degree of efficacy and safety</li> </ul>	<ul style="list-style-type: none"> <li>- Clinical trials that use a justified surrogate endpoint</li> <li>- Show the safety and efficacy of the drug in some other way</li> </ul>	<ul style="list-style-type: none"> <li>- Post-marketing surveillance period extended</li> <li>- Surveillance or clinical studies must be conducted as a post-marketing requirement (recent examples indicate that post-marketing comparative studies are not necessary and post-marketing surveillance is acceptable)</li> </ul>	Pharmaceutical and Medical Device Act

<b>NMPA - China</b>	The Green Channel	2014	Fills 1 of 8 criteria: - Drug applications for products with “significant clinical value,” such as innovative drugs and those with advanced formulations; - Clinical trial applications for generic drugs submitted three years before the patent expires on the reference product; - Clinical trial applications for new drugs undergoing parallel review in the U.S. and EU; - Registration applications for drugs undergoing parallel review in the U.S. and EU using the same production line; - Registration applications for new drugs developed under Chinese national research programs; - Registration applications for drugs to treat AIDS, tuberculosis, viral hepatitis, rare diseases and cancer, as well as pediatric and geriatric drugs; - Registration applications for drugs in short supply approved by China’s National Health and Family Planning Commission and the Ministry of Industry and Information Technology; and - Registration applications for pediatric drugs that have been approved in the U.S., EU and “surrounding areas” of China, backed by compelling clinical data	- Phase 1 and Phase 2 data if reviewers can reasonably predict or determine the clinical benefit has a significant advantage versus existing treatments - Trial applicants with less convincing Phase 1 and 2 data still may request an abbreviated Phase 3 trial to speed the drug to market	- Will still need to complete Phase III trials that show clinical benefit	CFDA Order [2014] No. 13  <a href="https://www.fdanews.com/IPRM0325162">https://www.fdanews.com/IPRM0325162</a>  Updated in 2019.  <a href="https://regulatory.usc.edu/regulatory-updates-special-report-china-september-2019/">https://regulatory.usc.edu/regulatory-updates-special-report-china-september-2019/</a>
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<b>TGA – Australia</b>	Provisional Approval	2018	<ul style="list-style-type: none"> <li>- New prescription medicine or new indications medicine</li> <li>- For treating a serious condition</li> <li>- Favorable comparison against existing therapeutic goods</li> <li>- Major therapeutic advance</li> <li>- Evidence of a plan to submit comprehensive clinical data</li> </ul>	<ul style="list-style-type: none"> <li>- Less comprehensive clinical data</li> <li>- Surrogate endpoints with justification: the ability to predict benefit based on evidence, the strength of the evidence, the certainty of the prediction, and why remaining uncertainties are considered acceptable</li> </ul>	<ul style="list-style-type: none"> <li>- Company must agree to continue clinical trials and submit comprehensive evidence for review</li> <li>- The validity of approved provisional determinations will lapse six months after the determination is granted. Sponsors may apply to the TGA for an extension of determination validity for a further six months</li> </ul>	<a href="https://www.tga.gov.au/provisional-approval-pathway-prescription-medicines">https://www.tga.gov.au/provisional-approval-pathway-prescription-medicines</a>
<b>Health Canada</b>	Notice of Compliance with Conditions	1998	Provide access to promising new drugs for patients suffering from serious, life-threatening or severely debilitating diseases or conditions for which no drug is presently marketed in Canada or for which a significant increase in efficacy or a significant decrease in risk is demonstrated in relation to an existing drug marketed in Canada	<ul style="list-style-type: none"> <li>- Trials with surrogate markers that require validation;</li> <li>- Phase II trials that would require confirmation with Phase III trials consistent with the normal course of development of a therapeutic entity; or</li> <li>- Phase III trials where a single small to moderately sized trial would require confirmation of either the efficacy or safety of the agent under question. These trials should be replicates of the pivotal trials or trials of different design where the outcomes are congruent with, and complimentary to, those of the original trial</li> </ul>	<ul style="list-style-type: none"> <li>- Confirmatory trials that verify the clinical benefit of the drug</li> <li>- Annual progress reports of confirmatory and other ongoing trials</li> </ul>	Guidance on the notice of compliance with conditions