VIEWPOINT

Accelerated Approval Is Not Conditional Approval
Insights From International Expedited Approval Programs

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Accelerated approval was developed in the US in 1992 as an expedited regulatory approval pathway for drugs and biologics in response to the AIDS crisis. Since then, the US Food and Drug Administration (FDA) has granted the majority of accelerated approvals in oncology, leading to earlier availability of promising therapies for patients with cancer, a median of 3.4 years before completion of the confirmatory trials that would have been necessary for regular marketing approval.[1] Success of the US accelerated approval program has prompted other international regulatory health authorities (RHAs) to develop similar expedited approval programs (**Table**[2]). Although they share a goal of providing earlier access to potentially lifesaving therapies, critical differences exist, which we compare herein.

Accelerated Approval in the US

Accelerated approval was instituted in 1992 by regulation and was codified into law under the FDA Safety and Innovation Act in 2012.[3] This law allows for "approval of a product for a serious or life-threatening disease or condition …[that] 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."[3] Most accelerated approvals granted in oncology have relied on overall response rate as a primary end point.[1] However, overall response rate is not limited to accelerated approval and has been used to support regular approvals, particularly in rare disease settings, in those with long survivorship, and in cases where observed high response rates in initial trials would render subsequent randomized trials impractical owing to the loss of equipoise b ecause of this prior efficacy data.

The FDA Safety and Innovation Act also specifies that accelerated approvals "may be subject to" the requirement "that the sponsor conduct appropriate postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit."[3] Several factors can affect the successful completion of these studies, including enrollment challenges and the rapidly evolving treatment landscape in oncology, which were addressed recently by an Oncologic Drugs Advisory Committee meeting in April 2021.[4] Typically, if clinical benefit is verified by these postmarketing trials, then a regular approval is granted. However, if they are not conducted with due diligence or fail to verify clinical benefit, FDA may withdraw the accelerated approval indication, which can involve a lengthy process and include a public hearing if the applicant does not remove the indication voluntarily.[3] This process has lasted up to 11 months (eg, first-line bevacizumab in combination with paclitaxel for treatment of metastatic *ERBB2* [formerly HER2]-negative breast cancer). To date, 15 of 167 (8.9%) oncology indications granted accelerated approval have been withdrawn voluntarily (n = 14) or by FDA (n = 1).[5]

Promoting the timely completion of confirmatory trials can be a challenge after accelerated approval. In a recent analysis, the median time to verification of benefit was 3.4 years, whereas withdrawal took 8.8 years. Having an ongoing confirmatory trial at the time of accelerated approval was associated with a shorter median time to verification of benefit (3.1 vs 5.5 years).[1]

International Expedited Approval Programs

Since development of the US accelerated approval program, expedited approval programs have been implemented by several international RHAs (Table). Most rely on end points that are likely to predict clinical benefit; however, conditional marketing authorization (CMA) in the European Union (EU) and UK relies on a benefit-risk assessment. This has led to relatively few approvals based on single-arm clinical trial data by the EU (52% for all indications).[6] Another notable feature of programs in the EU, Switzerland, and UK is that only new molecular entities are considered for expedited approval. This contrasts with the US and others, which may also grant expedited approval for supplemental applications.

Additionally, unlike accelerated approval in the US, the expedited approvals granted by the EU, UK, Australia, and Switzerland are time limited and expire. In the EU and UK, CMA expires yearly and must be renewed with an application and interim report on outstanding obligations submitted at least 6 months before expiration.[6,7] Evaluation of each renewal application includes the risk-benefit assessment as well as the time frame for completion of the specific obligations determined at the time of CMA. The mean time from granting CMA until conversion to a standard marketing authorization in the EU is 3.5 years.[8] Similar to CMA, provisional approval in Australia expires after 2 years and may be extended for additional 2-year periods up to a maximum of 6 years. A fixed deadline may exclude trials with slow enrollment that require a long time to complete. In prior analyses of accelerated approvals and EU CMAs, the time from expedited approval to subsequent action was greater than 6 years in 21% and 27%, respectively.[1,6] Temporary authorization in Switzerland also expires after 2 years and may be extended in exceptional cases. These programs in Australia and Switzerland were implemented recently (2018 and 2019, respectively), and data on time to verification are not yet available.

The expiry periods for conditional and provisional approval programs place the onus of timely completion of confirmatory trials and verification of benefit on the applicant in the EU, UK, Switzerland, and Australia. This contrasts with expedited programs elsewhere that place responsibility on

Table. Comparison of International Expedited Approval Programs[a]

Regulatory health authority (country/union)	Expedited program (year initiated)	Eligible applications[b]	Postmarketing requirements	Approval expiration
US Food and Drug Administration (United States)	Accelerated approval (1992)	New molecular entities and supplements	Confirmatory trial that verifies the clinical benefit in the same or a related population	No
Health Canada (Canada)	Notice of Compliance with conditions (1998)	New molecular entities and supplements	Confirmatory trial(s) that verify the clinical benefit	No (annual progress reports required until the conditions have been met or removed)
			Annual progress reports of confirmatory trials and other ongoing trials	
			Postmarketing surveillance	
European Medicines Agency (European Union)	Conditional marketing authorization (2006)	New molecular entities	Complete specific obligations to confirm positive benefit-risk balance	Yes (valid for 1 y, must renew)
Pharmaceuticals and Medical Devices Agency (Japan)	Conditional approval (2017)[c]	New molecular entities and supplements	Confirmatory studies or other clinical data (including database-based studies) that reaffirm the clinical efficacy and safety in the target population	No
Therapeutic Goods Administration (Australia)	Provisional approval (2018)	New molecular entities and supplements	Continuation of trials	Yes (must be renewed every 2 y and completed in 6 y)
			Submission of confirmatory efficacy and safety data required for full registration within the provisional registration period	
Swissmedic (Switzerland)	Temporary authorization (2019)	New molecular entities	Fulfillment of conditions determined at the time of approval	Yes (valid for 2 y, may be extended in exceptional cases)
Medicines and Healthcare Products Regulatory Agency (United Kingdom)	Conditional marketing authorization (2021)	New molecular entities	Complete specific obligations to confirm positive benefit-risk balance	Yes (valid for 1 y, must renew)

[a] Adapted from Friends of Cancer Research.[2]

[b] US Food and Drug Administration categories used for consistency.

[c] Regenerative medicine products (cell and gene therapy) are considered under the program Conditional, time-limited approval.

the RHA to initiate a resource-intensive withdrawal process. Overall, these time-limited approaches may limit public exposure to stale claims of effectiveness that cannot be expeditiously substantiated. Conversely, as reasonable trial completion times are often indication specific, flexibility may be necessary in implementing such postmarketing time limits.

Conclusions

The accelerated approval pathway in the US has allowed earlier access to lifesaving therapies for patients with cancer and has created a model for other RHAs to develop similar expedited approval programs. More recently, the FDA Oncology Center of Excellence, through Project Orbis, has led efforts to coordinate regulatory processes between international RHAs to benefit patients with cancer worldwide.[9] Future discussions of the accelerated approval program in the US can continue to build harmony between these agencies and strengthen this approval pathway by considering the differences between expedited programs, including recent innovations by international RHAs.

ARTICLE INFORMATION

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