FDA's Latest Thinking on Accelerated Approval Program for Drugs and Biologics

On December 6, 2024, the U.S. Food and Drug Administration ("FDA" or the "Agency") issued a draft guidance for industry on accelerated approval of drugs and biologics for serious conditions (the "Draft Guidance"). The Draft Guidance sets forth FDA's proposed guidance addressing which products qualify for accelerated approval, the applicable standards for granting accelerated approval, and the process for withdrawing products previously granted accelerated approval.

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미국 보건복지부 법무실에서 변호사 경력을 시작해, 이후 저명한 글로벌 로펌들의 제약, 바이오, 헬스케어 자문팀 일원으로 활동했다. 한국에서는 글로벌 분자진단 기업인 씨젠에서 사업개발 및 법무 총괄 임원으로 재직하였으며 현재는 덴톤스 리 법률사무소의 생명과학 헬스케어 팀을 이끌며 제약·바이오, 진단, 의료기기, 헬스케어 자문 업무를 수행하고 있다. 제약·바이오 분야 제품 수명주기 전 단계 자문과 기술 라이선싱 및 협업 거래를 중점적으로 다룬다.

The Draft Guidance, when finalized, will supplement the accelerated approval policies and procedures portion in the final guidance for industry that was issued on May 30, 2014 (the "2014 Final Guidance"). Except for the contents on serious condition, available therapy and unmet medical need defined and described in the 2014 Final Guidance, the Draft Guidance will replace the rest of the accelerated approval content in the 2014 Final Guidance.

Background

Accelerated approval program is part of FDA's suite of expedited approval programs intended to facilitate the approval of new drugs and biologics developed for the treatment of serious or life-threatening diseases or that provide significant improvement over the existing therapies.

Designed to expedite the approval process in order to make the therapies available to patients quicker based on the adetermination that the therapies' benefits outweigh their risks, there are four expedited approval programs, and they are priority review, accelerated approval, fast track, and breakthrough therapy.

These programs are distinct with overlapping criteria and features. Below table contained in the 2014 Final Guidance summarizes main features of the expedited approval programs.

FDA's accelerated approval program has a long history. First implemented by FDA in 1992, the accelerated approval program was codified into law in 1997 by U.S. Congress in the Food and Drug Administration Modernization Act of 1997 which was subsequently amended in 2012 to allow FDA to base accelerated approval on a surrogate or an intermediate clinical endpoint.

While the 2014 Final Guidance provided details on the administration of the accelerated approval program, there have been concerns over the

2014 Final Guidance

	Fast Track Designation	Breakthrough Therapy Designation	Accelerated Approval Pathway	Priority Review Designation
Qualifying criteria	• A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR • A drug that has been designated as a qualified infectious disease product	• A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	• A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND 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)	• An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR • Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A OR • An application for a drug that has been designated as a qualified infectious disease product OR • Any application or supplement for a drug submitted with a priority review voucher
When to submit request	• With IND or after • Ideally, no later than the pre-BLA or pre- NDA meeting	• With IND or after • Ideally, no later than the end-of-phase 2 meeting	• The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials, which should usually be already underway at the time of approval	• With original BLA, NDA, or efficacy supplement
Features	• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Other actions to expedite review	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	• Shorter clock for review of marketing application (6 months compared with the 10-month standard review)
Additional consi derations	• Designation may be rescinded if it no longer meets the qualifying criteria for fast track	• Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy	• Promotional materials • Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit • Subject to expedited withdrawal	• Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

Source 2014 Final Guidance

years that the sponsors that have been granted accelerated approval on their drugs fail to complete the confirmatory trials to confirm the clinical benefit.

In 2022, Office of Inspector General ("OIG") of the U.S. Department of Health and Human Services issued a report highlighting the concerns(the <2022 OIG Report>). OIG found that the industry's utilization of the accelerated approval pathway has increased over time but more than one-third of the applications have incomplete confirmatory trials. Of the 278 accelerated approval pathway approved drugs from 1992 to 2021, reviewed in the 2022 OIG Report, 104 approved drugs had incomplete confirmatory trials.

In the same report, OIG also found that the government funded Medicare and Medicaid programs spent more than $18 billion in a four-year period from 2018 to 2021 for accelerated approval drugs with incomplete confirmatory trials past their planned completion date, alarming the U.S. government that Medicare and Medicaid programs are spending billions of taxpayer money on therapies that have yet to verify a clinical benefit.

> Due diligence means that sponsors should commit sufficient resources to conduct the clinical trials that are necessary to verify the clinical benefit.

Faced with criticism, U.S. Congress in 2022 expanded FDA's authority in accelerated approval pathway by enacting a new legislation, the Food and Drug Omnibus Reform Act of 2022 ("FDORA," part of the Consolidated Appropriations Act).

FDORA requires FDA to establish the following, mainly: (1) conditions for post-approval confirmatory trials no later than the date of accelerated approval, (2) evidentiary standards for granting accelerated approval, and (3) new process for expedited withdrawal of accelerated approval. FDORA also requires FDA to publish a guidance for the industry, and the Draft Guidance is FDA's interpretation of FDORA mandated improvements to the accelerated approval pathway.

Accelerated Approval Endpoints

The Draft Guidance provides two types of endpoints that can be relied upon for accelerated approval determination: (1) a surrogate endpoint that is reasonably likely to predict clinical benefit and/or (2) a clinical endpoint that is likely to predict an effect on irreversible morbidity or mortality ("IMM") or other clinical benefit.

❶ Surrogate Endpoints

The Draft Guidance defines a surrogate endpoint as a biomarker that predicts clinical benefit but is not itself a measure of clinical benefit. According to FDA, a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit would be an endpoint that would support accelerated approval while a surrogate endpoint proven to predict clinical benefit would be appropriate for traditional approval, not accelerated approval.

FDA then explains that a surrogate endpoint that lacks the evidence to predict clinical benefit cannot be used for either traditional or accelerated approval pathway. In such a situation, FDA advises the sponsor to consult with the appropriate review division within FDA about the path forward for expedited approval.

The Draft Guidance provides examples of a surrogate endpoint, including sputum culture conversion from positive to negative during treatment of pulmonary tuberculosis and an increase in hemoglobin that has been determined likely to predict improvements in sickle cell disease patients.

❷ Intermediate Clinical Endpoints

According to the Draft Guidance, an intermediate clinical endpoint is "a measurement of a therapeutic effect that can be measured earlier than an effect on IMM" and may support accelerated approval when it is likely to predict the drugs' effect on IMM or other clinical benefit. FDA suggests the demonstrated therapeutic effect on the intermediate endpoint alone would be sufficient for traditional approval. Accelerated approval based on intermediate clinical endpoint, on the other hand, will be considered "only when it is critical to confirm the effects on IMM or other clinical benefit.

The Draft Guidance identifies the following two circumstances in which intermediate clinical endpoints can be used to support accelerated approval: (1) a study for a short term benefit where a longer duration of effect is necessary for clinically meaning benefit and the short term benefit observed is likely to predict a longer duration of effect, and (2) an intermediate clinical endpoint showing clinical benefit on a less serious symptom of a serious disease but the benefit observed is likely to predict a favorable disease outcome.

In the Draft Guidance, FDA advises that early consultation with the FDA review team is critical if a sponsor plans to use a novel surrogate or intermediate clinical endpoint to support its accelerated approval. Because FDA may require additional preclinical or clinical data in connection with the proposed novel endpoints, early interaction with FDA is strongly recommended. FDA explains that it has established processes for early consultation on new surrogate endpoints and sponsors are advised to engage with FDA early.

Evidentiary Criteria for Accelerated Approval

The Draft Guidance makes it clear that the same standards for safety and effectiveness that are applicable to those drugs granted traditional approval are applied to the accelerated approval program.

For effectiveness, FDA requires substantial evidence produced through adequate and well-controlled clinical study. For safety, FDA requires sufficient information that indicates the drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling.

In addition, FDA emphasizes that accelerated approval application should include "adequate evidence that a proposed surrogate endpoint or an intermediate clinical endpoint is reasonably likely to predict the intended clinical benefit" of the drug or biologics.

FDA acknowledges that determining whether an endpoint predicts clinical benefit is a matter of judgment and will depend on "the biological plausibility of the relationship between the disease, the endpoint, and the desired effect, and the empirical evidence to support that relationship."

FDA states that evidence of pharmacologic activity alone is not sufficient, and the clinical data needs to be shown to support a conclusion that an endpoint is predictive of the intended clinical benefit.

In the Draft Guidance, FDA outlines the following three factors it will consider when assessing whether a surrogate endpoint can be used for accelerated approval. First, FDA states that the extent to which the surrogate endpoint's relationship to the underlying mechanism of the disease is well understood is important. If the relationship of the surrogate endpoint to the disease is not well understood, FDA will likely conclude that the surrogate endpoint is unlikely to be predictive of a meaningful clinical effect.

Second, FDA will assess whether there is "reliable and consistent evidence supporting correlation between the surrogate endpoint and the clinical outcome of interest" and will consider the source and nature of the evidence as important.

Third, FDA will assess whether a surrogate endpoint has been shown to predict a clinical benefit with another drug based on clinical trial data. FDA adds that this factor would be more persuasive "if the drug is in the same or a closely related pharmacological class."

The Draft Guidance explains that FDA's assessment of a surrogate endpoint will be "context-dependent." FDA uses a rare disease context as an example and explains that it may not be feasible to obtain data from other drug trials which show a relationship between drug effects on the surrogate endpoint and drug effects on the clinical endpoint.

In such context, it would be important to develop a strong understanding of the role of the surrogate endpoint in the pathophysiology of the disease. FDA further adds that whether a drug effect on a surrogate endpoint will support accelerated approval will depend on the magnitude and duration of the effect on the surrogate endpoint.

Confirmatory Trials

Sponsors are required to conduct confirmatory trials post-approval in order to verify the effect on IMM or other clinical benefit. The Draft Guidance provides that FDA will require confirmatory trials to be initiated prior to accelerated approval and completed with due diligence. By due diligence, FDA means that sponsors commit sufficient resources to conduct the trials that are necessary to verify the clinical benefit, the purpose of which is to determine as soon as possible that the drug provides the expected clinical benefit. As part of this process, FDA again stresses early engagement with the relevant review division of the Agency.

The Draft Guidance provides that in order to ensure interpretable results are obtained, FDA's agreement on the design and conduct of the confirmatory trial will be important. Thus, the sponsor should submit to FDA the protocol for the confirmatory trial as soon as possible, specifying the timelines for patient enrollment and trial completion.

FDA repeatedly emphasizes the importance of engaging with the Agency early in the drug development program, and confirmatory trial should proceed at the time the accelerated approval application is submitted to the Agency.

The Draft Guidance sets forth conditions for the progress of confirmatory trial, no later than the date of accelerated approval, including "enrollment targets, the target date of study completion, or other milestones," in order to ensure that the confirmatory trial is completed in a timely manner.

FDA again emphasizes the importance of sponsors dedicating resources to this endeavor. In addition to the timely completion of confirmatory trial, FDA further emphasizes the importance of high retention of patients in confirmatory trials.

The Draft Guidance provides that the confirmatory trial generally would evaluate a clinical endpoint for measuring the clinical benefit in the same disease population that supported the accelerated approval. The Draft Guidance suggests that FDA may accept a confirmatory trial involving a different but related patient population to verify the predicted clinical benefit, e.g., "in a population with a different stage of the same disease." FDA also mentions that, instead of using a clinical endpoint, it may be appropriate to conduct additional evaluation of the surrogate endpoint used for accelerated approval in the same population. Additionally, the Draft Guidance suggests that FDA is open to considering novel trial designs such as "adaptive designs, enrichment strategies, trials with pragmatic elements, or decentralized trials" to verify clinical benefit. FDA requires the submission of progress reports on confirmatory trials approximately every 180 days. FDA cautions that sponsors considering a novel trial design should consult with the Agency early in the drug development process.

Other Conditions of Accelerated Approval

As part of the accelerated approval process, FDA will require that sponsors submit to FDA copies of all promotional materials during the pre-approval review period. FDA will require that for a drug approved under accelerated approval pathway, the drug label must describe the limitation of the drug and any uncertainty about the potential clinical benefit. In the drug label, there must also be a statement that the drug was approved based upon accelerated approval and the availability of the drug may be contingent on verification of the clinical benefit in a confirmatory trial. FDA emphasizes that sponsors seeking approval under accelerated approval should assume that all regulatory marketing requirements, including post-marketing and recordkeeping and safety reporting requirements are applicable to accelerated approval drugs.

Withdrawal of Accelerated Approval

Until FDORA, it has been challenging for FDA to revoke an approval. Now based on the authority granted under FDORA, the Draft Guidance specifies four conditions for which FDA will use the expedited procedure to withdraw a previously granted accelerated approval: (1) the sponsor fails to conduct any required post-approval study, (2) the study fails to verify and describe the clinical benefit of the product, (3) other evidence shows the drug product is not safe or effective, and (4) the sponsor disseminates false or misleading promotional materials.

The Draft Guidance provides that one of the FDA centers (e.g., CBER or CDER) that approved the drug through accelerated approval will issue a withdrawal of the accelerated approval. Depending on the circumstance and discourse between FDA and the sponsor of the affected accelerated approval, either the sponsor will voluntarily withdraw the accelerated approval or FDA will take a regulatory action.

FDA repeatedly emphasizes the importance of engaging with the Agency early in the drug development program, and confirmatory trial should proceed at the time the accelerated approval application is submitted to the Agency.

If FDA has concerns that a drug that has been granted accelerated approval does not appear to meet the criteria for accelerated approval, the responsible center will convene an advisory committee for consultation on whether one of the conditions for withdrawal has been met. If the center concludes that a condition has been met, the center will issue a proposal to withdraw the accelerated approval, which will trigger the withdrawal process mandated by FDORA.

To begin the expedited withdrawal of accelerated approval, FDA is required to provide the sponsor with (1) due notice, (2) an explanation for the proposed withdrawal, (3) an opportunity to meet with the FDA's Commissioner or a designee of the Commissioner, (4) an opportunity for written appeal to the Commissioner, or to a designee who has not participated in the proposed withdrawal, and (5) opportunity for an advisory committee meeting. As part of this process, FDA must make this process public by providing an opportunity for public comment on the withdrawal proposal and publishing on its website public comments received and FDA's response to such comments.

Conclusion

FDA's industry guidance documents such as the 2014 Final Guidance and the proposed Draft Guidance are important because FDA uses them to inform the industry of its current thinking on a topic and approaches to enforcing the laws for which the agency is responsible.

The new legal requirements mandated by FDORA and as interpreted in the Draft Guidance will become important to improving the administration of accelerated approval pathway.

The new requirements aim to reduce risk to patients by requiring more stringent evidence of safety and efficacy when the Agency reviews whether a drug is appropriate for accelerated approval. Confirmatory trials are now required to be underway before granting of accelerated approval, and sponsors are required to devote resources to their timely completion. Significantly, FDA is now empowered to withdraw the granted accelerated approval when clinical benefit is not shown. These reform measures will help to address the concerns identified in the 2022 OIG Report and lead to greater transparency in and more predictable administration of accelerated approval pathway.

Public can submit comments to the FDA on the Draft Guidance, and comments are due by February 4, 2025.