Battle of the Regulators: Comparing FDA’s Accelerated Approval and EMA’s Conditional Marketing Authorisation

Battle of the Regulators: Comparing FDA’s Accelerated Approval and EMA’s Conditional Marketing Authorisation: The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) offer various pathways that can expedite the development and review of new therapies to treat serious or life-threatening diseases or conditions that have an unmet medical need. The availability of these programs acts as an incentive to applicants because each provide unique guidance from regulatory authorities, ultimately resulting in expedited approvals that more rapidly provide public health benefits.

A current example includes the mitigation of COVID-19 worldwide using expedited product development pathways to address the global public health emergency. Specifically, the FDA’s Accelerated Approval pathway allows for use of surrogate endpoints in clinical investigations, and the EMA’s Conditional Marketing Authorisation pathway assesses a positive benefit-risk assessment for provisional approval. Both programs potentiate earlier approval of emerging therapies intended to treat serious diseases or conditions with unmet medical needs.

Accelerated Approval and Conditional Marketing Authorisation: What Are They?

Accelerated Approval

The Accelerated Approval pathway is intended for therapies that treat a serious or life-threatening condition and provides a meaningful advantage over available therapies. The therapy must also demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The program alternatively offers the use of a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, and that is reasonably likely to predict an effect on irreversible morbidity, mortality, or other clinical benefit (such as an intermediate clinical endpoint).
The Accelerated Approval pathway is primarily used in situations where the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug. This program is also potentially useful in acute disease settings where the intended clinical benefit can be confirmed only in a very large study because the demonstration of clinical benefit occurs rarely (such as a surrogate endpoint that shows acute clinical effect in a small number of patients, but a much larger study would be required to assess a clinical outcome such as survival).

Drugs granted Accelerated Approval must meet the same FDA standards for safety and effectiveness that are required for traditional approval. FDA carefully evaluates such evidence to ensure that any remaining doubts about the relationship of the effect on the surrogate-to-clinical benefit are resolved by additional post-approval studies or trials. Accelerated Approval applications should also include evidence that a proposed surrogate endpoint or an intermediate clinical endpoint is reasonably likely to predict the intended clinical benefit of a drug.

**Conditional Marketing Authorisation**

The Conditional Marketing Authorisation pathway also supports the development of therapies that address unmet medical needs for serious or life-threatening conditions. This type of authorization grants approval based on less comprehensive clinical data than normally required, such that the benefit of immediate availability of the therapy outweighs the inherent risk that additional data are still required for “standard” marketing authorization. Conditional Marketing Authorisation is valid for one year and can be renewed annually.

Once granted, the marketing authorization holder must fulfill specific obligations within defined timelines, such as completing ongoing or new studies or collecting additional data to confirm the therapy’s benefit-risk assessment remains positive. Conditional Marketing Authorisation can be converted into Standard Marketing Authorisation once the marketing authorization holder fulfills the obligations imposed and once complete data confirms that the therapy’s benefits continue to outweigh its risks. Standard Marketing Authorisation is no longer subject to the “specific obligations” and is valid for five years. It can then be renewed for unlimited validity.

**Battle of the Regulators: Comparing FDA’s Accelerated Approval and EMA’s Conditional Marketing Authorisation, What are the Criteria for Eligibility?**

**Accelerated Approval**

To qualify for Accelerated Approval, the proposed product must be indicated for a serious or life-threatening condition to address an unmet medical need. A “serious condition” is defined by the FDA as “a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is considered serious is a matter of clinical judgement, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a
more serious one”.

An unmet medical need is defined by the FDA as “a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs)”. If there is no available therapy for a serious condition, there is clearly an unmet need. If there are available therapies to treat a serious condition, the new treatment would be considered to address the unmet medical need if the treatment:

- Has an effect on the serious outcome of the condition that is not known to be influenced by available therapy (for example, an available therapy may treat symptoms of a disease but may not address the overall disability or disease progression);
- Has an improved effect on a serious outcome/outcomes of the condition compared with available therapy(ies);
- Has an effect on a serious outcome of the condition in patients who are unable to tolerate or have failed to respond to available therapy(ies);
- Can be used effectively with other critical agents that cannot be combined with available therapy(ies);
- Provides efficacy comparable to those of available therapy(ies) while:
  - Avoiding serious toxicity that occurs with available therapy
  - Avoiding less serious toxicity that is common and causes discontinuation of treatment
  - Reducing the potential for harmful drug interactions;
- Provides safety and efficacy comparable to those of available therapy, but as documented benefit (such as improved patient compliance) that is expected to lead to an improvement in serious outcomes; and/or
- Addresses an emerging or anticipated public health need, such as a drug shortage.

The FDA recognizes that it is preferable to have more than one treatment approved under the accelerated approval provisions because it is possible that clinical benefit may not be verified in post-approval confirmatory trials. The FDA will therefore consider products as addressing an unmet medical need if the only approved treatments were granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

**Conditional Marketing Authorisation**

To be considered for Conditional Marketing Authorisation, a therapeutic product must meet the following criteria:

1. The benefit-risk balance of the medicine is positive;
2. It is likely that the applicant will be able to provide comprehensive data post-authorization;
3. The medicine fulfils an unmet medical need; and
4. The benefit of the medicine’s immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.
Conditional Marketing Authorisation is used as the fast track authorization option during public health emergencies (such as COVID-19) to speed up approval, allowing marketing authorization to be granted as soon as sufficient data becomes available to demonstrate that a therapy’s benefits outweigh its risks.

**Battle of the Regulators: Comparing FDA’s Accelerated Approval and EMA’s Conditional Marketing Authorisation, What are the Benefits?**

The main common benefit of the FDA Accelerated Approval and EMA Conditional Marketing Authorisation pathways is that these pathways can enable faster access to new therapies for serious conditions that otherwise have no, or limited, treatment options.

Therapies that qualify for these pathways require less comprehensive data than is normally required when pursuing a traditional approval pathway and therefore can be approved on an accelerated timeline. This is particularly useful for chronic diseases (i.e., a long disease course) in which the determination of a clinical endpoint would otherwise take a long time. These pathways allow for mitigation of public health emergencies, positive impacts on patient quality of life, and/or improved survival of those impacted by serious conditions or diseases. Ultimately, Accelerated Approval and Conditional Marketing Authorisation allow for the protection of public health in the quickest and safest manner possible.

To learn more, [contact our team](#) of Regulatory experts today.