Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 8 Issue 10 October 2024

Review Article

US-FDA Drug Approval Process: A Glimpse Through Regulatory Window

Pramod Kumar Sharma[1]* and Mamta Yadav[2]

[1]*Professor, Department of Pharmacology, Vyas Medical College and Hospital, Jodhpur, India*

[2]*Assistant Professor, Department of Pharmacology, Govt. Institute of Medical Sciences (GIMS), Greater Noida, India*

***Corresponding Author:** Pramod Kumar Sharma, Professor, Department of Pharmacology, Vyas Medical College and Hospital, Jodhpur, India.

Received: August 07, 2024

Published: September 13, 2024

Abstract

It is the right of every common man to have access to more safe and efficacious medicine as early as possible once approved by the regulators. To achieve such an ideal scenario the US regulatory body, the FDA has a structured mechanism for the drug approval journey to ensure that Americans have access to modern medicines without delay to address their treatment needs. Accordingly, depending upon the potential of a new drug for an intended disease or clinical condition, the FDA has adopted a versatile approach long back. The strategy of prioritizing and optimally utilizing resources and technology to support development is always a welcome move. Adopting such a strategy for a promising drug candidate appropriately and adequately addresses the inherent dilemma of the regulator where the focus should be concentrated. To achieve timely and sacrosanct approval of a potential drug candidate the FDA has a mechanism in place to provide different designations to these drug candidates. A hierarchy that the US FDA follows for giving such a designation depends on the potential benefit a candidate drug promises to offer over existing drugs. It also considers whether the drug in question is potentially better than available treatment, can treat a rare life-threatening disease or is helpful in case of unmet clinical need. Although regulators always work in the general public's interest, they are also not immune to flak and criticism. Few such strategies are being seen sceptically by the experts and have been condemned by them.

Keywords: FDA; CDER; Fast-Track Designation; Drug Approval; Break-Through Therapy; Priority Review

Introduction

It is mandatory to ascertain the drugs that are marketed in the United States are not only safe but effective also. This is the responsibility of the FDA's (Food and Drug Administration) Center for Drug Evaluation and Research (CDER) to make public access to safe and effective medicines. This is achieved by the CDER Office of Testing and Research which ensures drug quality, safety, and effectiveness by conducting limited research activity on drug products destined to be marketed. CDER reviews both prescription drugs and those available over the counter (OTC) without a prescription [1].

Early availability of safe, efficacious and advanced medicines is always a privilege that American consumers enjoy. Having said that I do not mean that it is an easy and straight path to make early access of new drugs to Americans. For a new, advanced drug slated to be marketed, the CDER acts as a consumer watchdog to ensure only safe and efficacious drugs reach the consumer [2].

CDER division of the FDA has multifaceted roles not limited to preventing quackery and making available relevant information that is necessary for the prescriber and the consumer for the judicious use of medicines. It also makes sure that drugs work in the

way they are supposed to and applies to both branded and generic medicines' health benefits without exposing consumers to unnecessary known risks [2].

FDA approves a drug when the data available on the drug's effects (good or bad) have undergone adequate review by CDER. The entire drug approval process in the FDA context takes place in a structured manner and is intended to prevent the population from potential risk.

There have been incredible efforts taken to improve and prolong people's lives using modern medicine. Still, the treatment of many diseases and health conditions is way far from reality [3].

Fostering research and development of new chemical or biological entities requires not only ancillary and supportive economic considerations but a conducive ecosystem i.e., governmental policy that can fuel innovative research for safe and efficacious molecules.

It is the sole responsibility of the sponsor to show that the drug is safe and effective to receive approval for marketing by the FDA [3].

Points of consideration before FDA approval [2].

At the outset, the FDA team reviews and critically analyzes the target clinical condition or disease against which the drug is claimed to be safe and efficacious. FDA meticulously weighs the current treatment armamentarium available for the said clinical condition. It thus helps the FDA judiciously weigh the drug's risks and benefits in the current therapeutic context.

- FDA team goes one step ahead and critically evaluates the ratio of risk versus benefit submitted for NDA (New Drug Application) by the sponsor after clinical studies as per guidelines if available. Usually results from two well-designed clinical trials are required to provide sufficient, credible and valid assurance that the findings of the first study could not be because of chance finding or influenced by any sort of bias.
- No drug is devoid of risk and risk is always inherent. It is the effort of the FDA to prepare a plan and strategy well in advance for how to detect risk and its subsequent management. Keeping this in view, the FDA mandates that the sponsor should take all necessary steps to implement a Risk Management and Mitigation Strategy (REMS) well in time.

The FDA sincerely exercises its genuine scientific efforts through the use of technology and repeated deliberation in cases where the benefits and risks of a drug in question are uncertain and may be difficult to reliably interpret or predict.

FDA approval strategies

- **Standard Review:** Review status is usually designated by the FDA to drugs that do not fulfil the criteria for the priority review consideration criteria. Even in the absence of an applicant for review request, the team responsible for review will designate each application as a priority or standard. The designation pertains to setting a timeline for initiating review activity on a new drug application. The timeframe for standard review is by default within 10 months of receipt of the application. Not only NDAs, and BLAs, but efficacy supplements are also provided with a review designation. No review designation is allotted for the applications that are not filed [4].
- **Priority Review:** To improve and speed up drug dossier review time the FDA adopted a two-tiered system. This was necessary for prioritizing the need for faster review for a potential molecule and when the sponsor has expressly requested it and is ready to pay as well. As a result, in 1992, the FDA launched the Prescription Drug User Fee Act (PDUFA) and agreed to expedite drug review time on payment of certain fees. The only difference from the standard review is that the review timelines of an application are reduced to 6 months in contrast to 10 months. The sponsor is expected to hear from FDA within 60 days of the receipt of an application. Priority review is more task intensive and involves full focus and resources for a valid evaluation. However, there would not be any compromise with the standard adopted for the approval or the quality, validity and credibility of the data required [5].

- **Accelerated Approval:** The strategy is meant to accelerate the quick and early availability of promising drugs to the general public for serious as well as life-threatening conditions. This could be made possible as the approval granted is based on a surrogate endpoint(s) that can abbreviate the trial duration [6]. FDA scrutinize all the evidence without any laxity for accelerated approval as in the case of a standard approval.

Since approval is based on an effect on a "surrogate endpoint" that is reasonable and likely to predict clinical benefit. There al-

ways remains an element of uncertainty that how well that surrogate endpoint will correlate with the desired clinical benefit for the indication the drug is meant for [7].

After the grant of accelerated approval, the FDA mandate requires the sponsor to perform confirmatory clinical studies that often begin before the approval. The ongoing approval is contingent on how the drug performs in confirmatory trials. If a confirmatory study reaffirms anticipated benefit, the FDA grants regular traditional approval. In the reverse scenario, or if there is an inordinate delay from the sponsor's end, the FDA may dictate the sponsor to voluntarily withdraw the drug or else the FDA withdraws approval.

Several targeted anti-cancer therapies have paved their way to the market through accelerated approval pathways [8].

The accelerated approval pathway attracted a lot of criticism for adopting substandard and has been criticized recently for employing lower regulatory standards than traditional drug approval, undue delays in withdrawing approvals of drugs for which studies have not confirmed clinical benefit, and confirmatory trials not being pursued with due diligence.

Fast track approval

The US FDA defines "Fast Track as a process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need" [9]. The unmet medical need may simply be elaborated as making therapy available for a disease where no treatment is available or providing an alternative drug that is a therapy which may be inherently superior to existing therapy [10]. If the sponsor wishes to submit a fast-track approval application it can be done as early as the stage of investigational new drug (IND) filing. The decision of fast-track consideration is communicated to the sponsor within sixty calendar days as per FDA policy.

The perceptible benefits of this process are that it provides opportunities for investigators to work in unison with the regulator to conduct and submit the relevant study data. The FDA can assign a drug the fast-track label based on a single phase 2 study [11].

Breakthrough-Therapy designation

Theoretically there is no appreciable difference between fast-track and break-through therapy designations. Both strategies require prioritizing and concentrating resources on the best therapeutic agent in the developmental phase for an ailment where no satisfactory therapy is available [12]. However, under such a strategy FDA allows more flexibility in terms of study designs for life-threatening rare diseases or uncommon cancers. The extent of flexibility depends on the diseases in question and not the designation. A flagrant example of design flexibility could be like conducting a clinical trial with a single group being compared with historical control. Such an approach may at times provide more than adequate or substantial evidence of treatment effectiveness. Adopting such an approach sometimes becomes an absolute requirement due to unavoidable ethical challenges posed in certain cases. This designation is usually reserved for a drug candidate that shows significant potential for benefit over and above available therapies.

It will be surprising to know that this designation has also been provided for the nonlabelled use of a drug or any surgical intervention if there is compelling evidence that undoubtedly proves their safety and effectiveness. The standard criteria that are uniformly followed by the FDA is that the candidate under question should support substantial improvement over available agents based on data derived from preliminary clinical studies [13].

Conclusion

Regulatory science cannot be considered in isolation and it is a mix of both scientific evidence and reasoning. The FDA review policies and processes to grant licenses to therapy is an ideal example of a regulatory framework for a country like India. The drug approval processes in India have been surrounded by a war of words on the majority of occasions. It could be in the form of rollbacks after approval, labelling revision, or frequent alteration in guidelines and recommendations. In India, a new drug gets marketing approval once it has undergone a phase III clinical trial on an adequate number of local patients from all over India as dictated by guidelines. India is a country with a diverse population, and ethnicity that necessitates the conduction of local studies to genuinely ascertain the safety and efficacy of a drug. In real scenarios, however, this criterion has also been bypassed many times. We think

that several efforts have been made in the recent past to align drug regulation in line with developed countries. However, the regulation-making process for new drugs is still not sufficiently mature and relies heavily on regulatory knowledge of other countries e.g., the US, the UK and EU.

Several exemptions from human-based trials are granted in India if the drugs are approved in more developed and advanced economies. Although it sometimes can be viewed as beneficial in terms of preventing unnecessary duplication of data, and saving cost and time but can sometimes be followed with consequences if such an exemption is based on erroneous judgement of the authorities. It should also be considered a welcome approach from the health perspective of the public at large. However, excess and disjoined dependence on other countries' regulatory sagacity, might, at times, hinder the learning of our regulatory staff and could prove a deterrent to the acquisition of new knowledge.

Financial Support and Sponsorship

None.

Conflicts of Interest

None.

Bibliography

1. Food and Drug Administration. How Drugs are Developed and Approved (2022).
2. U.S. Food and Drug Administration. Development and Approval Process | Drugs (2022).
3. Kepplinger EE. "FDA's Expedited Approval Mechanisms for New Drug Products". *Biotechnology Law Report* 34.1 (2015): 15-37.
4. MANUAL OF POLICIES AND PROCEDURES CENTER FOR DRUG EVALUATION AND RESEARCH. FDA (2013).
5. FDA. Priority Review (2018).
6. LII / Legal Information Institute. 21 U.S. Code § 356 - Expedited approval of drugs for serious or life-threatening diseases or conditions (2021).
7. Beakes-Read G., *et al*. "Analysis of FDA's Accelerated Approval Program Performance December 1992–December 2021". *Therapeutic Innovation and Regulatory Science* 56.5 (2022): 698-703.
8. Beaver JA and Pazdur R. "Dangling" Accelerated Approvals in Oncology". *The New England Journal of Medicine* 384.18 (2021): e68.
9. Chary KV. "Expedited drug review process: Fast, but flawed". *Journal of Pharmacology and Pharmacotherapy* 7.2 (2016): 57-61.
10. Vreman RA., *et al*. "Unmet Medical Need: An Introduction to Definitions and Stakeholder Perceptions". *Value in Health* 22.11 (2019): 1275-1282.
11. U.S. Food and Drug Administration. Fast Track (2018).
12. Sherman RE., *et al*. "Expediting Drug Development — The FDA's New "Breakthrough Therapy" Designation". *The New England Journal of Medicine* 369.20 (2013): 1877-1880.
13. Corrigan-Curay J., *et al*. "Breakthrough-Therapy Designation — An FDA Perspective". *The New England Journal of Medicine* 378.15 (2018): 1457-1458.