**Expedited Drug Review Processes for Approval in US and EU** **with Consequences and Case Reports**

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**Abstract:** Expedited approval processes push new drugs to the market faster than ever. Regulatory Authorities of US and EU are using different approval pathways to cut down the time it takes to conduct a clinical review. Conventional drug discovery is a costly and time-consuming process. A study found that pharmaceutical industries spend an average of $3 billion in R&D activities, and more than 10 years are required to develop and market one new drug. Patients can hardly wait 10 years for a lifesaving drug. For this reason, in the field of new drug discovery, Regulatory authorities and pharmaceutical companies are pursuing a strategy that expedites the approval of certain drugs that treat severe conditions and address unmet medical needs. Expedited approval processes could attract attention as a solution to dramatically reduce the time and cost required for the new drug discovery.  However, expediting new drug approvals raises concerns, because of lack of important safety and efficacy information, potentially heightening the risk of patient harm. Some of the products which are approved through the expedited process have gone unpredicted and withdrawn from the market because of inadequate review time and lack of long-term safety studies. In this article, it is presented with different expedited approval processes and case reports that support the consequences that occurred through these speedy approval processes.

**Keywords:** Expedited Approval, Fast Track Approval, Accelerated Approval, Breakthrough Therapy, Priority Review, Priority Medicines

**1 Introduction**

Expedited approval processes are intended to facilitate and expedite the development and approval of new drug products to treat serious or life-threatening diseases and address an unmet medical need [[1](https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf)].Regulatory Authorities like FDA and EMA are following different methods to accelerate both the drug discovery and review process timelines to treat serious diseases and fill an unmet medical need. In order to speed up the availability, regulatory authorities of the US and EU have created rapid review and approval pathways. These pathways can provide significant economic benefits to drug developers by reducing the cost of some premarket studies and allowing early market access. Compared to the standard approval process, these pathways also comprise different types and levels of clinical evidence of efficacy.

**2 Rationale for expedited approval process**

In 1988, AIDS had reached epidemic proportions in the US. A crowd gathered in front of the US Food and Drug Administration (FDA) in Rockville, Maryland. "42,000 patients died with AIDS,” the protestors chanted. “Where was the FDA?” The Center for Disease Control and Prevention concluded that over 62,000 people in the united states had died from AIDS by the end of 1988.

The protestors demanded the FDA, “Stop placebo-group studies in clinical trials investigating AIDS drugs to speed up the availability of new drugs to the patients that showed efficacy.” A few days after the protest, the FDA announced that it would begin to consider approving drugs for serious or life-threatening diseases based on Phase Ⅱ clinical trial results [[2](https://www.the-scientist.com/bio-business/picking-up-the-pace-34262)].

**Table 1 Comparison of Standard and Expedited Approval Process**

|  |  |  |
| --- | --- | --- |
| Parameters | Standard Approval Process | Expedited Approval Process |
| Early access | Not possible | Possible |
| Average timeline | 10 years | 4.8 years |
| Approval is based on | Clinical endpoint | Surrogate endpoint |
| Can be approved | After phase Ⅲ clinical trials | As early as post phase Ⅰ |
| Safety issues | Very less | More often |
| Criteria for use | All diseases | The drug must be intended to treat life threatening disease and when there are no alternative therapies |

**3 Expedited Approval Processes in US**

In US, there are four regulatory pathways have been put in place from 1992 onwards, such as the “Fast Track Approval” (1988), “Accelerated Approval” and “Priority Review” (1992), and “Breakthrough Therapy” (2012) to expedite the development, approval and, enrich the productivity of novel drugs to treat serious or life-threatening diseases. These pathways use a range of approaches, including frequent interactions between companies and FDA staff, greater clinical trial design flexibility, and shortened timelines for review of applications [[3](file://D:\Admin\Downloads\3)New%20Drug%20Therapy%20Approvals%202019%20%5bInternet%5d.%20U.S.%20Food%20and%20Drug%20Administration.%202020%20%5bcited%2011%20September%202020%5d.%20Available%20from:%20https:\www.fda.gov\drugs\new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products\new-drug-therapy-approvals-2019)].

* 1. **Fast Track Approval**

The United States Food and Drug Administration (USFDA) defines Fast Track is a process that facilitates the development and expedites the review of drugs to treat serious or rare diseases and fill an unmet medical need. The Fast-Track approval process was introduced in 1988.  Sponsors typically request Fast Track Designation during the IND phase of drug development. FDA reviews the request and makes a decision within 60 days. The main purpose is to get new drugs to the patients earlier. Fast Track approval addresses a broad range of serious conditions. AIDS, Cancer, Alzheimer’s, and Heart failure are evident examples of serious conditions. However, diseases such as Diabetes, Epilepsy, and Depression are also considered to be serious conditions. Filling an unmet medical need is defined as providing therapy or treatment where none exists [4].

**Eligibility for Fast Track Designation** [5]

Fast Track designation can be given based on non-clinical or clinical data and may be available with relevant, pre-clinical data prior to clinical benefit in human clinical studies. A drug must show some advantage over available treatment in order to get a fast-track designation, such as

* Showing superior efficacy than existing therapies
* Avoiding serious adverse effects of an available therapy or treatment
* Improving the diagnosis of a serious or life-threatening disease where early diagnosis results in an improved outcome
* Decreasing clinically significant toxicity of an existing therapy
* Addressing an emerging public health need

**Benefits of Fast Track Designation**

A Fast-Track designated drug is eligible for some or all of the following

* More frequent meetings to discuss development plan with FDA
* More frequent written correspondence
* Eligibility for Accelerated Approval and Priority Review, if relevant criteria are met
* Rolling Review, which means that a drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, instead of waiting until every section of the BLA or NDA is completed. BLA or NDA review usually begins after the drug company has submitted the complete application to the FDA
  1. **Breakthrough Therapy**

Breakthrough Therapy designation is a process that accelerates the development and review of drugs that are intended to treat serious or life-threatening diseases. Preliminary clinical evidence must be needed to show substantial improvement over available treatment on a clinically significant endpoint(s). Breakthrough Therapy was introduced in 2012. The sponsor requests a Breakthrough Therapy designation, and the FDA will respond to the request within 60 days. The request should be received by the FDA no later than the end of phase Ⅱ clinical trials [6].

**Qualifying Criteria for Breakthrough Therapy Designation**

* If the drug is for a serious or life-threatening disease
* Preliminary clinical evidence is essential
* May demonstrate substantial improvement on clinically significant endpoint(s)

**Primary considerations for Breakthrough Therapy Designation** [7]

The FDA relies on three primary considerations

* The quantity and quality of the clinical evidence being submitted in a designation request
* The available therapies that the drug is being compared to can be provided
* The magnitude of the treatment effect is shown

**Benefits of Breakthrough Therapy Designation**

* All Fast-Track designation features can be applicable for Breakthrough Therapy.
* Intensive guidance on an efficient drug development program, beginning as early as Phase Ⅰ
* Organizational commitment involving experienced review staff and senior managers
  1. **Accelerated Approval**

When studying a new drug molecule, it can take many years to learn whether a drug provides a real therapeutic effect on patient survival rate and functions. A positive therapeutic effect that is clinically meaningful in the context of a proposed disease is known as "Clinical Benefit." In 1992, FDA introduced the Accelerated Approval regulations and amended them in 2012. These regulations allowed drugs for earlier approval of drugs that treat serious conditions that filled an unmet medical need based on a surrogate endpoint [8]. Drugs approved through FDA Accelerated Approval Program still need to be verified in clinical trials using endpoints that demonstrate clinical benefit, and those studies are known as phase Ⅳ confirmatory trials. If the drug later proves incapable of demonstrating clinical benefit to patients, then FDA may withdraw an Accelerated approved drug [9].

**Eligibility for Accelerated Approval Designation**

* If there is a serious condition
* Meaningful advantage over available therapy
* Sponsors must agree to conduct adequate and well-controlled post-marketing confirmatory studies that validate the surrogate endpoint

**Benefits of Accelerated Approval**

* Discussions with reviewing division early in the development process (pre-IND meeting)
* Drugs under Accelerated Approval can be approved based on an unestablished surrogate endpoint.
* Shortens overall development time
  1. **Priority Review**

A Priority Review is an expedited program introduced in 1992 that will direct overall attention and resources to the evaluation of priority drug applications that, if approved, would play a major role in the increased safety or effectiveness of the Diagnosis, treatment, or prevention of serious conditions when compared to standard applications [10].

**Eligibility for Priority Review Designation**

* The proposed drug must treat a Serious Disease or Condition.
* Demonstrating the potential to be a significant improvement in safety or effectiveness

**Benefits of Priority Review**

A drug review process can be completed in 6 months instead of 10 months under standard review.

**Figure No. 1:** Bar graph representation of number of Fast Track Approval & Breakthrough Therapy Designation requests from January 1, 2015 to September 30, 2020 [11, 12, 13, 14]

**Figure No. 2:** Pie chart representation of Accelerated Approvals& Priority Review Approvals from 2015 to 2019 [15, 16, 17, 18, 19]

**4 Expedited Approval Processes in EU**

In the EU, The European Medicines Agency (EMA) is the central regulatory body providing authorization to speed up the development and approval of new medicinal products in situations of unmet medical need to treat serious or life-threatening diseases. EMA provides various expedited routes for early patient access to new medicines that address public health needs such as PRIME (Priority Medicines), Accelerated Assessment, Conditional Marketing Authorisation, Compassionate Use, Exceptional Circumstances [20].

**4.1 PRIME - Priority Medicines** [21]

EMA launched the PRIME scheme in March 2016. The scheme focuses on drug products that show a greater therapeutic advantage over existing treatments or benefit patients with no available treatments.  PRIME provides enhanced scientific and regulatory support to optimize development and enable accelerated assessment of drugs that can address patients' unmet medical needs.

**Eligibility for PRIME Designation**

* When the drug is for serious life-threatening disease or condition where there is no major therapeutic efficacy over existing treatments or no available medication to treat a patient
* A medicinal product should demonstrate the potential to benefit patients with unmet medical needs based on early clinical data

**Benefits of PRIME approval**

* PRIME helps developers of promising new drugs to optimize development plans
* Initial Marketing Authorization (MA) and Centralized procedure
* PRIME eligible products may also qualify for Conditional Marketing Authorization (CMA)
* It fosters early dialogue with EMA to facilitate robust data collection and high-quality marketing authorization applications
* It speeds up an evaluation so that patients and their families have long been hoping for earlier access to safe treatments for their unmet medical needs, such as AIDS, Cancer, Alzheimer's disease
* Early Rapporteur appointment from the Committee for Medicinal Products for Human Use (CHMP) or the Committee for Advanced Therapies (CAT), to deliver continuous support and help to build knowledge ahead of Marketing Authorization Application (MAA)
* Organizes an initial kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts from working parties and relevant EMA scientific committees
* Issues preliminary guidance on a company’s overall development plan and regulatory approach
* Assign a dedicated EMA contact person
* Provides scientific advice during the development stage
* Medicines eligible for PRIME are also potentially eligible for accelerated assessment at the time of an application for marketing authorization

**4.2 Accelerated Assessment**

The Accelerated Assessment was introduced in November 2005 by the revised EU pharmaceutical legislation. This regulatory tool aims to speed up patients' access to new medicines of major public-health interest by reducing the review time of a Marketing Authorisation Application. According to Article 14 (9) of Regulation (EC) No 726/2004, when an application is submitted for marketing authorization in respect of medicinal products for unmet medical needs or constitutes a significant improvement over the existing methods of diagnosis, treatment, and prevention of a serious condition human use which are of major interest from the point of view of public health, the applicant or companies can request an Accelerated Assessment procedure [22]. The European Medicines Agency's Committee for Medicinal Products for Human Use reviews a Marketing Authorization Application for Accelerated Assessment [23].

**Eligibility for Accelerated Assessment**

* Medicinal products can be eligible for Accelerated Assessment if the CHMP decides the product is of major interest for public health and therapeutic innovation
* Accelerated assessment requests should be made at least two to three months before submitting the MAA
* EMA strongly recommends that applicants can request a pre-submission meeting six to seven months before final submission to prepare for evaluation under Accelerated assessment

**Benefits of Accelerated Assessment**

* Evaluating a MAA under a Centralized Procedure can take up to 210 days. On request, the CHMP can reduce the timeline to 150 days if the applicant provides appropriate justification for an Accelerated Assessment
* Accelerated Assessment pathways use both clinical and surrogate endpoints
* For products undergoing Accelerated Assessment based on surrogate endpoints, the real clinical benefit of the products approved for marketing may never be established because there is no consistent requirement for confirmatory post-marketing studies [24].

**4.3** **Conditional Marketing Authorisation** [25]

The EMA introduced conditional Marketing Authorisation (CMA) in 2005 as an early access pathway for medicines that address unmet medical needs and treat patients' life-threatening or rare diseases. In the interest of public health, applicants may be granted a CMA for such medicinal products where the benefit of immediate availability outweighs the risk based on less comprehensive data than usually required. The marketing authorization holder will submit complete clinical data at a later stage. CMA is valid for one year and can be renewed annually.

**Eligibility for Conditional Marketing Authorisation**

CMA can be granted if the CHMP finds that all the following requirements are met

* When the anticipated benefits justify the risks
* The applicant is invited to notify the EMA about his intention to request a CMA as part of the “Letter of Intent” to be sent to the EMA in advance about the submission of MAA
* The applicant will likely be able to provide comprehensive data after marketing authorization
* Unmet medical needs of the patients will be fulfilled
* The benefit to public health of the medicinal product’s immediate availability on the market outweighs the risks
* Medicines designated as orphan drugs are also eligible for CMA

**Benefits of Conditional Marketing Authorisation**

* CMA can speed up earlier patient access to new medicines.
* Once comprehensive data on the drug product have been submitted, the marketing authorization may be converted into a standard marketing authorization. Initially, this is valid for five years but can be renewed for unlimited validity.
* For medicinal products deemed suitable for CMA, applicants are also encouraged to request an Accelerated Assessment.

**4.4** **Compassionate Use**

Compassionate Use is a treatment option that permits the use of unauthorized medicine. Under strict conditions, products in the development phase can be made available to seriously ill patients who have a disease with no available treatments. EMA provides recommendations through the CHMP, but these do not create a legal framework. Compassionate use programs are coordinated and implemented by the Member States, which set their own rules and procedures [26].

**Eligibility for** **Compassionate use**

* Compassionate use programs are only put in place if the medicinal product is expected to help patients suffering from life-threatening, long-lasting, or seriously debilitating diseases or illnesses, which cannot be treated satisfactorily with any currently authorized medicine
* Every member state of the European Union has developed its own legislation for Compassionate use programs based on the EMA recommendations and legal framework. Therefore, it is necessary for stakeholders such as health professionals, pharmaceutical companies, patients and patient organizations, and policymakers to be informed of legislation and processes that facilitate early access to innovative medicines

**Benefits of Compassionate use** [27]

* Compassionate Use Programme (CUP) benefits patients unable to participate in clinical trials who fail to fulfil the eligibility criteria. Participation in clinical trials is a difficult choice for patients with life-threatening, long-lasting diseases
* Patients get early access to investigational drugs or drugs that have not yet received marketing authorization in the European Union
* Patients have access to promising drugs at an earlier stage during the life cycle, for instance, post phase II. Otherwise, patients have to wait for a considerable amount of time until the drug is authorized and is on the market
* The market authorization holders in the EU get the opportunity to resolve any product-related issues and can overcome challenges or issues encountered by pre-approved drugs through early access

**4.5 Exceptional circumstances**

In 1993, the European Union introduced an instrument to approve drugs under Exceptional Circumstances (ECs). Early market access could be granted to drug products where the applicant is unable to provide complete data on the efficacy and safety under normal conditions of use because the condition to be treated is rare or collection of full information is not possible or is unethical. The sponsors need to perform further studies to meet specific obligations after obtaining marketing approval [28]. Drugs that are approved under Exceptional Circumstances are reviewed annually to reassess the risk-benefit balance. Approval under Exceptional Circumstances is a unique type of approval to the European Union, and a drug cannot be authorized under both Exceptional Circumstances and Conditional Approval.

**Eligibility for Approval under Exceptional Circumstances**

Exceptional Circumstances designation is a type of marketing authorization in the European Union that is granted on the basis of one of the following criteria

* Medicinal products for which the applicant is unable to provide comprehensive efficacy and safety data due to the rarity of the indication
* If it is considered unethical to collect the comprehensive safety and efficacy data for a standard approval
* Inability to provide comprehensive data due to the present state of knowledge and the applicant should explain what scientific knowledge would be needed to conduct such trials, justify the lack of such knowledge and that such scientific knowledge cannot reasonably be expected to be developed by the applicant

**Benefits of Approval under Exceptional Circumstances**

* Accelerated Assessment can be requested for products that are approved under Exceptional Circumstances.
* Marketing authorization of medicinal products under Exceptional Circumstances may be varied with the addition of new indication(s). In such cases, the marketing authorization will still remain under Exceptional Circumstances.

**Figure N0. 3:** Bar graph representation of CMA, Accelerated Assessment, Exceptional Circumstances, & PRIME from 2017-2019 [29, 30, 31]

**5 Expedited Approval Processes in India**

To fulfil the objective to accelerate the accessibility of new drugs and encourage clinical research in India, the Union Ministry of Health and Family Welfare, India has introduced the "New Drugs and Clinical trials Rules, 2019" on 25th March 2019. The permission to conduct local clinical trials is within 30 days and 90 days for global clinical trials. Suppose no communication has been received from the Central Licencing Authority to the applicant regarding the grant of permission or rejection within the said period. In that case, the permission to conduct a clinical trial shall be deemed to have been granted by the Central Licencing Authority, and such permission shall be deemed to be legally valid to initiate a clinical trial [32]. Accelerated approval and expeditious review process may be allowed for new drugs intended to be used in life-threatening or serious disease conditions or rare diseases and addresses unmet medical needs. In such a case, the approval of the new drug is based on a surrogate endpoint, and post marketing trials shall be performed to validate the anticipated clinical benefit [33].

**6 Provisions intended to expedite the drug approval process**

When investigating a new drug, it can sometimes take many years to learn whether a drug actually provides a real clinical effect on how a patient survives, feels, or functions. Expedited approval programs accelerate the clinical investigation based on a surrogate endpoint. A surrogate endpoint used for accelerated approval is a laboratory measurement, a marker, radiographic image, physical sign, or other measures that are believed to predict clinical benefit but are not itself a measure of real clinical benefit. Similarly, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered likely to predict the clinical benefit of a drug. The use of surrogate or intermediate clinical endpoints instead of traditional endpoints for measurement of drug efficacy enabled the regulatory authorities to approve these drugs faster. For example, instead of having to wait to learn if a drug actually extends survival for cancer patients, the FDA and EMA may approve a drug based on evidence that the drug product shrinks tumour’s because shrinkage of the tumour is considered reasonably likely to predict a real clinical benefit. The drug company must conduct Phase Ⅳ confirmatory trials to validate that tumour shrinkage actually predicts that patients will live longer [34].

Biomarkers increase the success rate of drug development programs and thereby accelerate the availability of new therapeutics by reducing the time and cost of clinical trials while maintaining patient protections. Biomarkers are defined characteristics that are measured as indicators of health, disease, or a response to an exposure or intervention, including therapeutic interventions. These Biomarkers can help diagnose a disease, or predict future disease outcomes, like measurements of Blood Pressure as an indicator of Cardiovascular risks or measurements of blood sugar as an indicator of Diabetes. Biomarkers are also used to find the best treatment for a patient, to monitor the safety of drugs, or to identify if treatment is having the desired effect on the body [35]. A recently published analysis of clinical trials evaluating therapies for advanced Non-Small Cell Lung Cancer (NSCLC) has proved that the cumulative success rate for new agents for advanced NSCLC is lower than the industry-estimated rate [36]. However, the study also demonstrated that biomarker and receptor-targeted therapies (such as Crizotinib, Bevacizumab, and Erlotinib) substantially increased the clinical trial success rate. (refer to Illustration of Expedited Approval timeline of Crizotinib)

In the United States, Priority Review reduces the targeted marketing application review timeline from 10 months to 6 months, and in the European Union, Accelerated Assessment (AA) reduces the standard 210‐day MA application review time to a 150‐day review time

**Illustration of Expedited Approval timeline of Crizotinib**

XALKORI (Crizotinib) for Non-Small Cell Lung Cancer (NSCLC).

**Trade names:** XALKORI, Crizonix

**Sponsor:** Pfizer, Inc.

Crizotinib is an oral drug indicated for the treatment of NSCLC. The drug is developed and manufactured by Pfizer. Crizotinib is designed to block a protein called ALK (Anaplastic Lymphoma Kinase), which is involved in Cancer cell growth and survival. NSCLC is usually caused by smoking. It also occurs in people who work near asbestos, products using chloride and formaldehyde, certain alloys, paints, pigments, and preservatives. Symptoms of NSCLC include coughing up blood, shortness of breath, wheezing, chest pain, loss of appetite, losing weight without trying, and fatigue.

**2007:** ALK was first recognized as a molecular target in Non-Small Cell Lung Cancer [37].

**September 13, 2010:** Crizotinib obtained Orphan drug designation from the US FDA [38].

**December 6, 2010:** FDA granted Fast Track designation for Crizotinib [39].

**January 11, 2011:** Initiated the Rolling submission of a New Drug Application (NDA) to the US Food and Drug Administration (FDA) for Crizotinib [40].

**March 30, 2011:** Crizotinib New Drug Application (NDA) was submitted [41].

**May 16, 2011:** NDA for Crizotinib was accepted for filing and granted Priority Review status by the US Food and Drug Administration (FDA) [42].

**July 28, 2011:** Pfizer submitted MAA to the European Medicines Agency for XALKORI through the Centralized Procedure [43].

**August 26, 2011:** Crizotinib received Accelerated approval to treat certain late-stage (locally advanced or metastatic) Non-Small Cell Lung Cancers that express the abnormal anaplastic lymphoma kinase gene by the US Food and Drug Administration. The early approval Crizotinib was based on trial data of 255 patients enrolled in two clinical trials, namely Phase II Profile 1005 and Phase I Study 1001 have demonstrated significant activity and impressive clinical benefit [44].

**October 23, 2012:** The European Commission has given conditional marketing authorisation valid throughout the European Union for XALKORI [45].

**November 20, 2013:** Crizotinib received regular approval based on an improvement in progression-free survival in patients with metastatic ALK-positive NSCLC previously treated with one platinum-based chemotherapy regimen [46].

**April 21, 2015:** The USFDA granted Breakthrough Therapy designation to XALKORIfor the treatment of patients with ROS1-positive Non-Small Cell Lung Cancer [47].

**October 8, 2015:** Pfizer submitted a supplemental New Drug Application (sNDA) to the US food and drug administration [48].

**December 8, 2015:** FDA accepted and granted Priority Review for sNDA to Crizotinib [49].

**March 11, 2016:** The USFDA approved Crizotinib capsules for the treatment of patients with metastatic non-small cell lung cancer whose tumours are ROS1-positive. XALKORI is the first and only FDA-approved treatment indicated for two Biomarkers, ALK and ROS1, in metastatic NSCLC [50].

Crizotinib serves as a model for expedited development, review, and approval of novel, highly efficacious and the clinically meaningful drug that demonstrates the potential to address unmet needs for such a life-threatening disease or condition.

**7 Post marketing risks**

Post-marketing surveillance programs in the US and EU are capable of monitoring the overall quality, safety, and efficacy of drug products, and responding to public health risks which can help protect citizens from the threats posed by falsified medicines. Post-marketing surveillance is fundamental to the effective regulation of medicines and includes all regulatory activities that monitor the long-term adverse effects of innovative new drugs after launching into the market.

A drug approved by expedited approval programs based on less robust evidence produces more adverse effects than a molecule that has been subjected to the standard drug review process [51]. some of the expedited approved drug products have gone unpredicted and withdrawn from the market. Increased cardiovascular events from selective cox-2 inhibitors Rofecoxib and Valdecoxib, Alosetron-induced Ischemic Colitis, Rapacuronium-induced Bronchospasm, Hepatotoxicity from Cerivastatin, and Troglitazone were grievous. Lack of efficacy is also exemplified by some Fast-Track products such as Mibefradil, Moxalactam, Drotrecogin Alfa, and Cefonicid [52].

In the case of Vioxx tragedy, it was approved by the FDA in 1999 but withdrawn five years later, i.e., in 2004, when it was linked to increased cardiovascular risks. Nearly 107 million prescriptions for Rofecoxib were dispensed in the US between 1999 and September 2004 [53]. Merck spent more than $160 million on advertising this product to consumers [54]. Physicians did not know about potential cardiovascular risks associated with the long-term use of Vioxx. Research later published in the medical journal Lancet estimates that 88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them have died [59]. (refer to case study).

On April 19, 2012, The US Department of Justice announced that American pharmaceutical company Merck Sharp & Dohme was sentenced by a federal district court in Boston to pay a criminal fine of nearly $322 million.  In December 2011, Merck pleaded guilty to violating the Food, Drug, and Cosmetic Act (FDCA) by illegally marketing the painkiller Vioxx. The fine was imposed because of Merck's off-label marketing, or "misbranding," of Vioxx for rheumatoid arthritis before the FDA approved the drug for that disease. The FDA approved Vioxx in 1999 to reduce inflammation and pain caused by Osteoarthritis, acute pain in adults, and the treatment of menstrual pain but did not approve it for Rheumatoid Arthritis until April 2002. Nonetheless, Merck promoted Rofecoxib for Rheumatoid arthritis during that three-year interim period, despite a warning letter issued by the FDA in September 2001 [55].

**Case study**– Withdrawal of Vioxx (Rofecoxib) for Osteoarthritis

**Trade names:** Vioxx, Ceoxx, Ceeoxx, others

**Sponsor:** Merck & Co., Inc

Rofecoxib is a COX-2 selective Non-Steroidal Anti-Inflammatory Drug (NSAID). It was marketed by Merck & Co. to treat Osteoarthritis, Rheumatoid Arthritis, acute pain in adults, and painful menstrual cycles, Migraine, and Dysmenorrhea.

**In 1994**, Scientists working in a Merck research lab in Montreal discovered the Rofecoxib molecule, a cox-2 inhibitor. Merck research laboratories in new jersey took this discovery and immediately began developing a selective NSAID painkiller [56].

**November 23, 1998:** Merck & Co has submitted a New Drug Application to the US Food and Drug Administration for its Anti-inflammatory, once-daily COX-2 inhibitor Rofecoxib for the treatment of Osteoarthritis and pain, having tested the drug on 5,400 subjects in eight studies [57].

**January 1999:**Merck launches the largest Vioxx Gastrointestinal Outcomes Research study (VIGOR). The study was intended to expand the drug’s approved indications by showing that it would have less gastrointestinal side effects than naproxen for the treatment of rheumatoid arthritis with more than 8,000 participants, Half take Vioxx, and the other half take Naproxen [53].

**May 20, 1999:**The USFDA approves Vioxx, making the drug available by prescription in the United States. Merck obtained FDA approval on Vioxx in approximately April 1999 via a New Drug Application on a Fast-Track, 6-month approval process [58].

**October 1999:**First meeting of the VIGOR study's Data and Safety Monitoring Board (DSMB). Study results as of Oct. 1, 1999, show that Vioxx patients have fewer ulcers and less gastrointestinal bleeding than patients taking Naproxen [59].

**November 18, 1999:**At the VIGOR's safety panel second meeting, the discussion focuses on heart problems. As of November 1, 1999, 79 patients out of 4,000 taking Vioxx have had serious Cardiovascular adverse experiences or have died, compared with 41 patients taking Naproxen. The panel votes to continue the study and to meet again in a month [59].

**December22, 1999:**The VIGOR study’s safety panel holds its last meeting and learns that as of December 1, 1999, the risk of serious heart problems and death among Vioxx patients is twice as high as those taking Naproxen [60].

**March 2000: VIGOR study ends. During the course of the 12-month study, 20 of the patients died because of taking Vioxx [60].**

**February 2001:** Complete VIGOR study results were presented to the FDA, including the heart attacks and data on other cardiovascular events. The FDA then began negotiating with Merck for a Vioxx label change [61].

**November 6, 2001:** Merck rejected the FDA's proposed labelling, and Merck countered with a different label change [61].

**April 11, 2002:** Vioxx label was changed to include information about increased heart-attack risk after several face-to-face meetings between FDA and Merck [62].

**September 30, 2004:** Merck & Co. announced a voluntary, worldwide withdrawal of Vioxx, its arthritis and acute pain medication, after a study showed patients taking the drug on a long-term basis were twice as likely to have a heart attack or stroke compared with patients receiving placebo [63].

**November 2007:** Merck agreed to pay $4.85 billion to settle 27,000 lawsuits over its painkiller Vioxx. The amount, to be paid into a so-called settlement fund, is believed to be the largest drug settlement as of 2007 [64].

**8 Conclusion**

Speeding the availability of new drugs that treat life-threatening diseases is in everyone's interest, especially when the drugs are the first available treatment or if the drug has advantages over existing treatments. However, these expedited new drugs may have uncertainty in the efficacy data or undetected serious toxicities at the time of approval. They are not identified until after on the market for several years. Although these drugs may have safety concerns, they were approved based on the determination that the benefits outweighed potential risks of the drug. All drugs have risks. FDA and EMA have efforts in place to minimize these safety risks, and there are still occurrences where drugs may come to market quickly and lead to safety concerns. The consequences are clear that safety can be assured only after the careful examination of post-marketing surveillance of such drugs. The finest quality medicines are frequently reaching patients only in a slow manner. Although, many drugs that treat life-threatening diseases or conditions have successfully been brought to market through these expedited pathways and have made a significant impact on disease progression. For example, a number of targeted cancer-fighting drugs and antiretroviral drugs used to treat HIV/AIDS entered the market via a speedy approval process and subsequently altered the treatment paradigm. These pathways can also significantly benefit drug developers by reducing the time and cost required for the new drug discovery.

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