Understanding FDA Review Pathways

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FDA Programs for Expediting Drug Review & Development

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Accelerating the Pace of Innovation

Washington, DC-based Think Tank & Advocacy Organization

A unique model to create a path to better drug development and approval through scientific, regulatory, and legislative solutions.

Develops groundbreaking partnerships:
- Federal Agencies (FDA, NIH, NCI)
- Academic Research Centers
- Professional Societies
- Industry
- Advocacy Organizations
Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe

ABSTRACT The US Food and Drug Administration is often criticized as inefficient compared to its European counterpart, the European Medicines Agency. This criticism is especially common in the field of oncology, where severely ill patients have few therapeutic options. We conducted a direct drug-to-drug comparison of the two regulatory agencies’ approvals of new oncology drugs. We found that contrary to public assertions, the median time for approval for new cancer medicines in the United States was just six months—and that these new anticancer medicines are typically available in the United States before they are in Europe. Our findings reinforce the need for strong financial and public support of the Food and Drug Administration, so that such medicines can continue to be made available speedily to patients in need.

In recent years, the scientific understanding of the basic biology of cancer has undergone a major transformation. With the advent of bioinformatics, it is now possible to elucidate the molecular pathways involved in cancer development and to design drugs to specifically target these pathways. Examples of such breakthroughs include Herceptin (trastuzumab), which blocks the effects of a protein that transmits growth signals to breast cancer cells, and Celecox (celecoxib), which inhibits the enzyme that is active in chronic inflammatory processes. This new era of scientific discovery has the potential to lead to new anticancer medicines with greater efficacy and reduced toxicity, allowing patients to live longer and healthier lives.

Despite these breakthroughs, some critics argue that given the advances in basic science, we should be able to develop new oncology drugs more quickly than we do. One reason cited for the slower-than-expected pace is a regulatory environment that is not sufficiently equipped with the resources and scientific foundation needed to evaluate new approaches to cancer treatment. Some critics specifically have characterized the Food and Drug Administration (FDA) as slow and inefficient at reviewing drugs in comparison to its European counterpart, the European Medicines Agency (EMA). Furthermore, some have claimed that the FDA has become so risk-averse, it is increasingly difficult to obtain approval for effective drugs in the United States.

To examine the quality of how the FDA responds to new anticancer medicines, we analyzed new oncology drug approvals by the FDA and the EMA. We describe our methods and results below.

Study Data And Methods We compared review times at the FDA and the EMA for 110 oncology drugs in the period 2003–2010. Our data came from the publicly available drug databases on the FDA and EMA websites; they represent only initial approvals, not supplemental applications. In addition, we investigated only active treatment drugs, not drugs for supportive care, such as pain relievers or antiemetics.

For each new drug in the United States, we collected the date of the first New Drug Application (NDA) or Biologic License Application submission
Approved NMEs in Oncology 2003-2010
FDA vs EMA
FDA Programs for Expediting Drug Review & Development

The FDA expedites the review of drugs treating serious conditions with the potential to provide significant improvements in safety or effectiveness over existing therapies:

- Priority Review
- Fast Track
- Accelerated Approval
- Breakthrough Therapy Designation
Priority Review

In 1992, the Prescription Drug User Fee Act set up specific goal times for review New Drug Applications (NDA) Priority Review cuts the time in which the FDA aims to take action on a drug’s application from ten months to six months.

Requirements:

• To be considered for Priority Review, a drug must address a serious condition and the drug must demonstrate, through clinical trial data or other scientifically valid information, the potential to provide a significant improvement in safety or effectiveness over existing treatments.

When to Submit a Request:

• Because Priority Review only impacts the marketing application review, which takes place late in the FDA approval process, drug sponsors generally submit requests either alongside or as a post-submission addition to a Biologics License Application (BLA) or New Drug Application (NDA).

Features:

• The FDA aims to take action on a drug sponsor’s marketing application in six months, compared with ten months for standard review.
Established as part of the Food and Drug Modernization Act (FDAMA) in 1997, Fast Track is a process to increase communication between drug sponsors and the FDA throughout the development and review process for drugs that address an unmet medical. Fast Track addresses a broad range of serious conditions.

Requirements:

• To be considered for Fast Track designation, a drug must address a serious or life-threatening condition and the drug must demonstrate the potential to address unmet medical need.

• Depending on how far a drug is into development, this can mean mechanistic rationale, evidence of activity in a nonclinical model, pharmacological data, or clinical data indicating that the drug either treats a condition for which there exists no other treatment or provides some benefit over existing treatment.

When to Submit a Request:

• Fast Track designation can be requested at any point in the development process—as early as Investigational New Drug Application (IND) application submission and generally prior to Biologics License Application (BLA) or New Drug Application (NDA) submission.

Features:

• FDA may consider rolling review, allowing early review of portions of a drug sponsor’s marketing application before the complete application has been submitted.
The Accelerated Approval regulations were first instituted by the FDA in 1992 in order to speed the availability of new drugs to treat HIV/AIDS.

Requirements:

- To be considered for Accelerated Approval, a drug must address a serious or life-threatening condition and
- The drug must demonstrate effect on an intermediate clinical endpoint (or surrogate endpoint)—a result that is reasonably likely to predict clinical long-term benefit and can be measured earlier than that benefit (e.g. tumor shrinkage can be used as an endpoint to predict survival benefit in some instances of cancer).

When to Submit a Request:

- Accelerated Approval impacts clinical trial design and post-market planning, so drug sponsors are generally advised to discuss it with FDA during development.

Features:

- A drug granted Accelerated Approval is approved based on evidence of impact on a surrogate endpoint rather than evidence of impact on the actual clinical benefit the drug is intended to provide.
- This approval is generally conditional on a sponsor’s agreement to demonstrate the drug’s long-term safety and efficacy in post-approval trials. If a sponsor fails to do this, either by refusing to conduct a trial or by conducting a trial that finds the drug to be unsafe or ineffective, FDA may withdraw approval.
But critics of the trials argue that the new science behind the drugs has eclipsed the old rules — and ethics — of testing them. They say that in some cases, drugs under development, PLX4032 among them, may be so much more effective than their predecessors that putting half the potential beneficiaries into a control group, and delaying access to the drug to thousands of other patients, causes needless suffering.
Getting Breakthrough Therapies to Patients

• The 2011 Conference included a panel entitled: Development Paths for New Drugs with Large Treatment Effects Seen Early.

• The workgroup proposed scientific strategies to ultimately expedite FDA approval for a drug showing dramatic responses in the early stages of development while maintaining drug safety and efficacy standards.

Goals of Breakthrough Therapy Designation

Goal 1: Expedite drug development process for products that show remarkable clinical activity early

Goal 2: Minimize the number of patients exposed to a potentially less efficacious treatment
Developing Standards for Breakthrough Therapy Designation

Charles L. Saunders, Chair; Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center; Investigator, Howard Hughes Medical Institute.

Daniel A. Haber, Director, Cancer Center, Massachusetts General Hospital; Investigator,

PANEL 4
Development Paths for New Drugs with Large Treatment Effects Seen Early

Thomas Fleming, Professor, Biostatistics, University of Washington

Mikhail Sokratos, Director, Leukemia Program, Associate Professor of Medicine, Cleveland Clinic

Cezary Liberzon, Director, Biostatistics, Genentech

Edward Kerr, Mathematical Statistician, Biometric Research Branch, National Cancer Institute

Wyndran Wilson, Senior Investigator, Chief, Lymphoma Therapeutics Section, NCI

Janet Woodcock, Director, Center for Drug Evaluation and Research, U.S. FDA

Rajeshwar Sridhar, Director, Division of Biostatistics V, CDER, U.S. FDA

June Perlmutter, President and Founder, Gemini Group

12TH CONGRESS
20 SESSIONS

S. 2236

To provide for the expedited development and evaluation of drugs designated as breakthrough drugs.

IN THE SENATE OF THE UNITED STATES

MARCH 26, 2012
Mr. HUNTS (for himself, Mr. HAYES, and Mr. BRUNI) introduced the following bill, which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

A BILL

To provide for the expedited development and evaluation of drugs designated as breakthrough drugs.

1 Be it enacted by the Senate and House of Representa-
2 tives of the United States of America in Congress assembled,

3 SECTION 1. SHORT TITLE.

4 This Act may be cited as the “Advancing Break-
5 through Therapies for Patients Act of 2012”.

6 SEC. 2. BREAKTHROUGH THERAPIES AND FAST TRACK

7 PRODUCTS.
President Obama signs Breakthrough Product designation into law as part of the Food and Drug Administration Safety and Innovation Act

“While people like to talk about polarization and gridlock in Washington, this bill is a victory for both bipartisanship and for the millions of American who rely on medicines and medical devices.”—Sen. Tom Harkin (D-IA) and Sen. Michael Enzi (R-WY)
Breakthrough Therapies

Established in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA), the Breakthrough Therapy Designation is given to drugs for which early evidence indicates a potentially transformative effect.

Requirements:
• A Breakthrough Therapy drug must address a serious or life-threatening condition and
• The sponsor must show a high magnitude of clinical activity indicating that the drug may demonstrate substantial improvements over existing therapies.

When to Submit a Request:
• Because the Breakthrough Therapy designation impacts clinical trial design, sponsors benefit most from pursuing it early in the development process—as early as Investigational New Drug Application (IND) submission and ideally prior to the end-of-Phase II meeting.
Breakthrough Therapies (2)

Features:

• Drug sponsors get extra opportunities to meet with the FDA and discuss study design, safety and efficacy requirements, dose-response concerns, use of biomarkers, and other critical development issues.

• FDA may consider rolling review, allowing early review of portions of a drug sponsor’s marketing application before the complete application has been submitted.

• Due to their large early clinical effect, Breakthrough drugs can sometimes skip portions of the standard FDA review process without compromising safety and efficacy standards.

• Drug sponsors get increased exposure to FDA senior managers, experienced review staff, and cross-disciplinary experts to help coordinate internally and aid in efficient development and review of clinical and non-clinical components of the application.

• Because Breakthrough drugs have early ability to benefit patients, the FDA aims to collaboratively examine a Breakthrough drug’s entire development program and take scientifically appropriate steps to minimize the number of patients receiving placebos or less efficacious treatment as part of the testing process.
Current Breakthrough Therapies

Breakthrough Designations by Therapeutic Category

- Cancer: 49.1%
- Cardiovascular: 2.8%
- Infectious Disease: 14.2%
- Rare Inherited Disorders: 13.2%
- Other: 20.8%

Breakthrough Therapy Designation Requests: 334
Breakthrough Therapy Designation Granted: 109
Indications Approved with Designation: 34
Expedited Development and Review Programs

• **Priority Review:** Cuts a drug’s FDA review period from ten months to six
  − Unlike the Fast Track Designation or Accelerated Approval, the Priority Review process begins only when a manufacturer officially submits a new application. It does not alter the timing or content of steps taken in a drug’s development or testing for safety and effectiveness. It can be given to products believed to address unmet need or offer major advances in treatment.

• **Fast Track:** Sponsors gain access to rolling review, wherein portions of their marketing application may be reviewed before the complete application has been submitted

• **Accelerated Approval:** Allows approval based on surrogate endpoints—more easily measured outcomes that are reasonably likely to predict clinical benefit. Sponsors are required to confirm a drug’s efficacy in post-market clinical trials

• **Breakthrough Therapy:** Requested as early as IND application and preferably prior to end-of-Phase II meeting
  − Breakthrough drugs must show early clinical evidence of substantial improvement over existing therapies
  − Due to their large early clinical effect, Breakthrough drugs can sometimes skip portions of the standard FDA review process without compromising safety and efficacy standards

*Programs are not exclusive of each other*
Drug Discovery and Development Timeline

Pre-Discovery

Drug Discovery

Preclinical

Clinical Trials

FDA Review

Scale-Up to Mfg.

Post-Marketing Surveillance

~ 5,000 – 10,000 COMPOUNDS

FT

2

5

FT

AA

ONE FDA-APPROVED DRUG

AA

BROKENTHROUGH THERAPY

IND SUBMITTED

20-100
100-500
1,000-5,000

IND SUBMITTED

6 – 7 YEARS
0.5 – 2 YEARS
INDEFINITE

Courtesy of the American Association of Cancer Research 2011 Cancer Progress Report