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Research Article

**REGULATORY REQUIREMENTS FOR APPROVAL
FASTTRACK DRUGS AS PER US GUIDELINES**V. Mallikarjun¹, V. Rajesh Babu², Sana Kusar¹, V. Rajkumar¹¹Chaitanya College of Pharmacy Education & Research, Hanamkonda, T.S.²MESCO College of Pharmacy, Hyderabad, Telangana State.**Abstract:**

Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. AIDS, Alzheimer's, heart failure and cancer are obvious examples of serious conditions. However, diseases such as epilepsy, depression and diabetes are also considered to be serious conditions. Any drug being developed to treat or prevent a condition with no current therapy obviously is directed at an unmet need. If there are available therapies, a fast track drug must show some advantage over available therapy.

Advancing the health of Americans through the development of safe and effective new drugs is an imperative at the heart of FDA's mission. The infusion of resources provided through industry user fees has enabled FDA to adapt to rapid advances in science and to dramatically cut drug review times to speed promising therapies to patients. In the 21st century, FDA is the fastest drug review agency in the world.

FDA has worked effectively to implement flexible review practices without lowering the agency's standard for drug efficacy. This flexibility has translated into a historically high proportion of drug approvals on the first regulatory review cycle, increasing predictability for drug developers. These changes resulted in faster drug review times relative to other regulatory authorities and an increasing proportion of new medicines being introduced in the U.S. first, allowing for earlier access to innovative treatments. Recently, rapid advances in our understanding of human biology and the underlying mechanisms of some diseases have offered many new potential targets for medical product development.

But we still have a long way to go in understanding the full range of diseases that confront Americans and in developing the scientific tools necessary to translate scientific discoveries into treatments and cures. Discussions are currently underway on how to close the gap between the discovery and delivery of innovative products. With so much progress already achieved at the product review stage, more attention is being focused on early stage development and the clinical trials process. While changes are appropriate and important, none should lower FDA's evidentiary standards, otherwise patients would be exposed to unreasonable and unnecessary risks associated with insufficient information. The agency looks forward to continuing to work with others, including Congress, industry, academia, patients and advocacy groups, on these issues.

Keywords: Fast track, FDA, AIDS, Alzheimer's, heart failure

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INTRODUCTION:

Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions. Determining whether a condition is serious is a matter of judgment, but generally is based on whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one. AIDS, Alzheimer's, heart failure and cancer are obvious examples of serious conditions. However, diseases such as epilepsy, depression and diabetes are also considered to be serious conditions. Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy which may be potentially better than available therapy. Any drug being developed to treat or prevent a condition with no current therapy obviously is directed at an unmet need. If there are available therapies, a fast track drug must show some advantage over available therapy, such as: Showing superior effectiveness, effect on serious outcomes or improved effect on serious outcomes, Avoiding serious side effects of an available therapy, Improving the diagnosis of a serious condition where early diagnosis results in an improved outcome, Decreasing a clinical significant toxicity of an available therapy that is common and causes discontinuation of treatment, Ability to address emerging or anticipated public health need.

A drug that receives *Fast Track* designation is eligible for some or all of the following:

- More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval
- More frequent written communication from FDA about such things as the design of the proposed clinical trials and use of biomarkers
- 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, rather than waiting until every section of the NDA is completed before the entire application can be reviewed. BLA or NDA review usually does not begin until the drug company has submitted the entire application to the FDA.

Fast Track designation must be requested by the drug company. The request can be initiated at any time during the drug development process. FDA will review the request and make a decision within sixty days based on whether the drug fills an unmet medical need in a serious condition. Once a drug receives *Fast Track* designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process. The frequency of communication assures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patient

In 1962, the United States was shocked by the news that thousands of babies were being born in Europe with terrible birth deformities, caused by a drug known as thalidomide, that was prescribed to European women during pregnancy. While the U.S. was spared this calamity by the refusal of the Food and Drug Administration to allow thalidomide's sale in this country, Congress saw the horrifying effects of inadequately reviewed drugs and unanimously enacted legislation directing the FDA to tighten the standard by which new drugs were approved for marketing – with a requirement for drug companies to submit solid and rigorous science-based evidence that new drugs were both safe and effective.

More recently, Congress has passed laws, including the 1992 Prescription Drug User Fee Act, designed to add a new focus - bringing important drugs to market more quickly and predictably, while still protecting Americans from unsafe and ineffective medicines. Congress' focus on optimizing speed of access as well as safety and effectiveness is challenging but necessary – both are critical to the health of American patients. And the success of the biopharmaceutical industry depends on both as well. Market strength depends on American and worldwide confidence in the quality and rigor of FDA's oversight of drug safety and effectiveness, while continued development of innovative new drugs is aided by a swift, predictable approval process. This white paper provides up-to-date information on FDA's drug approval process, demonstrating that FDA continues to review and provide Americans with access to innovative drugs more quickly than the EU and other developed countries. The paper also describes how FDA is using available tools to expedite drug development, including Accelerated Approval, flexible clinical trial designs, surrogate endpoints, Priority Review, Fast Track Designation, and Breakthrough Therapy Designation.

Criteria for qualification as a fast track drug development program:

Section 506(a)(1) of the Act states that a drug designated as a fast track product is intended for the treatment of a serious or life-threatening condition and demonstrates the potential to address unmet medical needs for the condition. The fast track classification thus does not apply to a product alone but applies to a combination of the product and specific indication for which it is being studied. The indication, for the purposes of this document,

includes both the condition for which the drug is intended (e.g., heart failure) and the anticipated or established benefits of use (e.g., improved exercise tolerance, decreased hospitalization, increased survival).⁴ It is therefore the development program for a specific drug for a specific indication that will receive fast track designation. Such a program is referred to in this document as a fast track drug development program and the criteria involved in designation. These criteria are more fully described below.

A drug that receives "fast track" designation is eligible to receive some or all of the following incentives:

- More frequent meetings with the FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval;
- More frequent written correspondence from the FDA about such things as the design of the proposed clinical trials;
- Eligibility for accelerated approval – i.e., approval on an effect on a surrogate, or substitute endpoint, reasonably likely to predict clinical benefit. For instance, a drug that promises to extend the survival of cancer patients can be approved even if it has only been shown to shrink tumors in a clinical trial. Shrinking tumors is a surrogate endpoint because it is a meaningful outcome in and of itself, and an indirect measurement of the drug's effectiveness. Final approval of a drug based on such endpoints is given on the condition that post marketing clinical trials verify the originally claimed benefit. If a confirmatory trial proves otherwise, the FDA can remove the drug from the market;
- Rolling review, which means that a drug company can submit completed sections of its New Drug Application for review, rather than waiting until every section of the application is finished; and
- Dispute resolution if the drug company is not satisfied with an FDA decision not to grant fast track status.

METHODOLOGY:

The **New Drug Application (NDA)** is the vehicle in the United States through which drug sponsors formally propose that the Food and Drug Administration (FDA) approve a new pharmaceutical for sale and marketing. The goals of the NDA are to provide enough information to permit FDA reviewers to establish the following:

- Is the drug safe and effective in its proposed use(s) when used as directed, and do the benefits of the drug outweigh the risks?

- Is the drug's proposed labeling (package insert) appropriate, and what should it contain?
- Are the methods used in manufacturing (Good Manufacturing Practice, GMP) the drug and the controls used to maintain the drug's quality adequate to preserve the drug's identity, strength, quality, and purity?

Before trials:

To legally test the drug on human subjects in the U.S., the maker must first obtain an Investigational New Drug (IND) designation from FDA. This

application is based on pre-clinical data, typically from animal studies after P1, that shows the drug is safe enough to test in humans. Often the "new" drugs that are submitted for approval include new molecular entities or old medications that have been chemically modified to elicit differential pharmacological effects or reduced side-effects.

Clinical trials:

The legal requirement for approval is "substantial" evidence of efficacy demonstrated through controlled clinical trials. This standard lies at the heart of the regulatory program for drugs. It means that the clinical experience of doctors, the opinion of experts, or testimonials from patients, even if they have experienced a miraculous recovery, have minimal weight in this process. Data for the submission must come from rigorous clinical trials. The trials are typically conducted in three phases:

- Phase 1: The drug is tested in a few healthy volunteers to determine if it is acutely toxic.
- Phase 2: Various doses of the drug are tried to determine how much to give to patients.
- Phase 3: The drug is typically tested in double-blind, placebo controlled trials to demonstrate that it works. Sponsors typically confer with FDA prior to starting these trials to determine what data is needed, since these trials often involve hundreds of patients and are very expensive.
- (Phase 4): These are post-approval trials that are sometimes a condition attached by the FDA to the approval.

The legal requirements for safety and efficacy have been interpreted as requiring scientific evidence that the benefits of a drug outweigh the risks and that adequate instructions exist for use, since many drugs are toxic and technically not "safe" in the usual sense. Many approved medications for serious illnesses (e.g., cancer) have severe and even life-threatening side effects. Even relatively safe and well understood OTC drugs such as aspirin can be dangerous if used incorrectly.

FDA Approvals:

It takes on average 12 years and over US\$350 million to get a new drug from the laboratory onto the pharmacy shelf. Once a company develops a drug, it undergoes around three and a half years of laboratory testing, before an application is made to the U.S. Food and Drug Administration (FDA) to begin testing the drug in humans. Only one in 1000 of the compounds that enter laboratory testing will ever make it to human testing. If the FDA gives the green light, the "investigative" drug will then enter three phases of clinical trials:

- Phase 1 uses 20-80 healthy volunteers to establish a drug's safety and profile. (about 1 year)
- Phase 2 employs 100-300 patient volunteers to assess the drug's effectiveness. (about 2 years)
- Phase 3 involves 1000-3000 patients in clinics and hospitals who are monitored carefully to determine effectiveness and identify adverse reactions. (about 3 years)

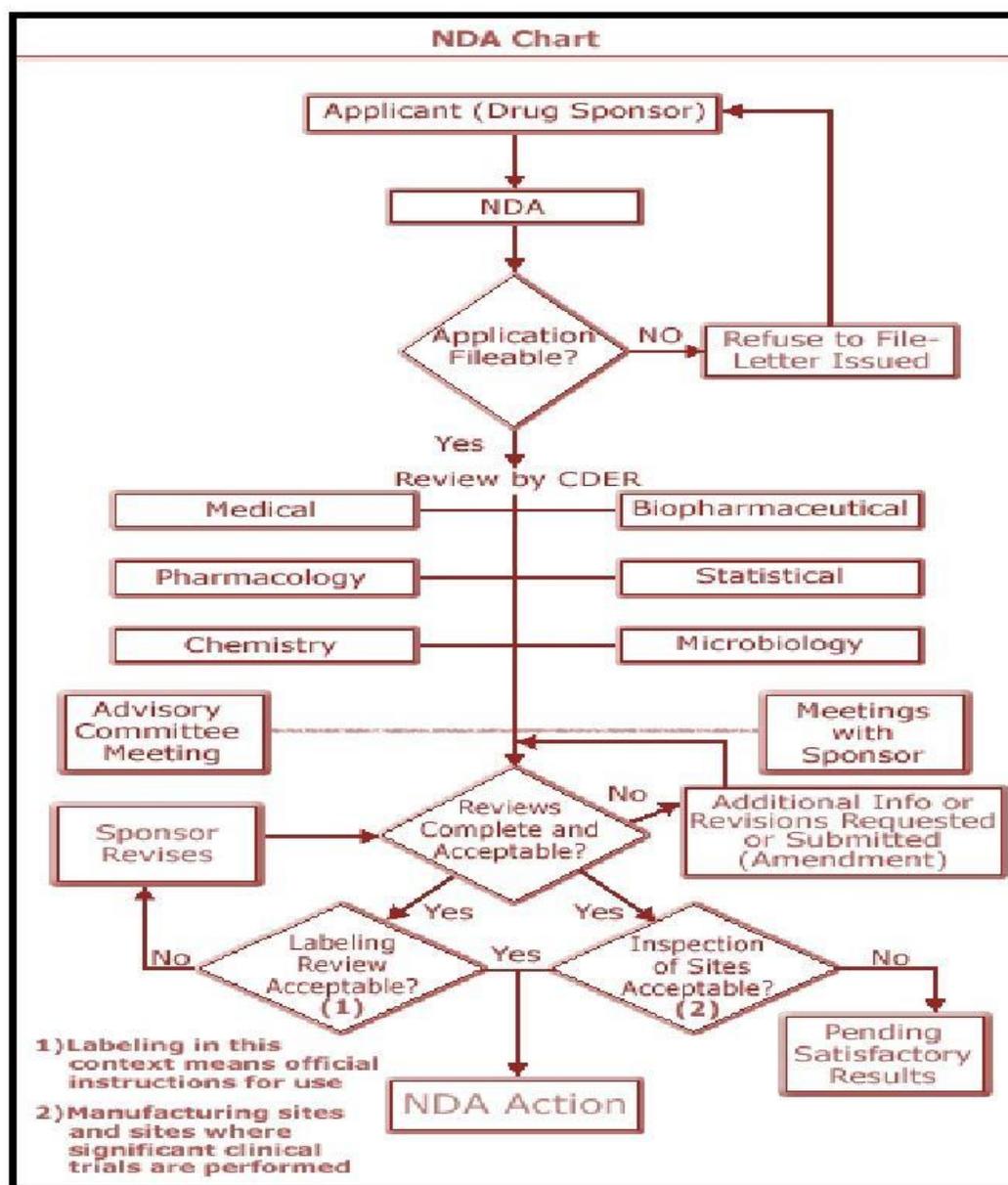


Fig.1: New drug approval process in US

FDA:

The Food and Drug Administration (FDA) has created three mechanisms to speed the approval of drugs that effectively treat serious diseases, especially those that are the first of their kind or those that provide increased benefit over existing treatments. Fast Track, Accelerated Approval, Priority Review—their names imply speed of the highest order, and it's tempting to assume that acquiring any of these designations will speed your

drug's approval and save you millions of dollars. That's certainly possible, but just like anything that sounds too good to be true, it's worth taking the time to understand the requirements and potential benefits of each, so you can make an informed decision about what's best for your drug development program.

The Food and Drug Administration (FDA) continued to bring life-saving drugs to patients in the U.S. quickly and efficiently in fiscal year (FY) 2012

(October 1, 2011-September 30, 2012). Matching its performance in FY 2011, FDA approved 35 novel medicines in FY 2012, often more quickly than it was done anywhere else in the world. At the same time, FDA continued to strengthen its ability to rapidly detect and analyze safety problems that emerge after a drug is marketed. FDA also broadened the actions it is taking to support innovation in drug development.

FDA expedited the review and approval of over half of these new medicines by using its several review authorities for important new drugs, including Fast Track, Priority Review, and Accelerated Approval. For example, of the 12 drugs that received a Fast Track designation, 75% were approved on the first cycle of review, and of the 10 Fast Track drugs for which FDA was able to make comparisons to approvals in other countries, 100% were approved in the U.S. first. Strengthened communication with drug companies early in development and flexible clinical trial designs for drugs for unmet medical needs also enabled drug companies to conduct shorter smaller, or fewer studies, reducing the length and cost of drug testing. Other FDA programs also played an important part in achieving these results.

TIMELINESS OF FDA REVIEW:

The timeliness of FDA approval of new drugs continues to compare favorably with other regulatory agencies around the world. While we are not in competition with them, we recognize the need to approve safe and effective drugs that offer new health benefits as quickly as possible. As in previous years, FDA's record in FY 2012 shows its commitment to helping patients get timely access to important new drugs.

FDA continues to lead the world in the first introduction of new active substances. This includes all new active substances launched world-wide, including those not approved in the U.S. Over the past decade, roughly half of the new active substances launched anywhere on the world market were first approved in the United States, and the percentage of first introductions in the U.S. is increasing. In 2011, 64% of new active substances were first launched in the U.S., approaching an all-time high for U.S. drug introductions. Looking only at the 35 NMEs that were approved in the U.S. in FY 2012, the great majority were approved earlier than in other countries. Of the 32 novel drugs for which FDA was able to make comparisons to approvals in other countries, 24 (75%) were approved by FDA before any other regulatory agency in the world, including the European Medicines Agency (EMA), the European Union's drug approval authority. (Three

additional drugs, an imaging agent and two cord-blood products, are manufactured by individual healthcare facilities—a hospital and two blood banks—and it was not possible to determine whether similar products were approved in other countries).

FDA EXPEDITES DRUG REVIEW:

FDA uses a range of tools to expedite the development, review, and approval of the most promising new therapies. These tools include Fast Track, Priority Review, and Accelerated Approval. Eighteen of the 35 novel drugs (51%) were reviewed under at least one of the Fast Track, Priority Review, or Accelerated Approval programs. FDA also allowed flexible clinical development programs, where appropriate, for drugs for unmet medical needs, such as for orphan drugs. In addition, FDA is beginning to use the "Breakthrough Therapies" provision that was added to FDA's authority this year in the Food and Drug Administration Safety and Innovation Act (FDASIA), but it was not available to expedite any of the drugs approved in FY 2012 Steps in New DRUG Application

Pre-Clinical Research:

New drugs may be developed by a variety of different people or organizations, including independent researchers, university medical centers, government centers, or other organizations. According to the FDA, there are several ways in which new drugs are developed. Some new drug research begins with studies of how the body functions in the broadest terms. From these studies, researchers develop ideas of new ways to treat illnesses and abnormalities. Researchers then begin to search for compounds that will help achieve the desired effect on the body. They may conduct laboratory tests (called assays) by adding compounds to enzymes, cell cultures, or cellular substances grown in the laboratory to determine whether the compounds produce an effect. This process can take a significant amount of time but is often accelerated with the use of computers or other technology. Another way scientists may develop drugs is to study natural compounds made by organisms such as fungi, viruses and molds.

Clinical Studies:

After short-term animal studies are completed (and often after some results from long-term animal studies can be obtained), the sponsor of the drug applies for approval from the CDER (Center for Drug Evaluation and Research) to continue testing the safety and effectiveness of the drug in human clinical trials. The sponsor submits an investigational new drug application (IND) to the CDER, which contains

the plan for the study. This IND process allows promising drugs to be studied extensively in expanded access protocols. The IND application is carefully reviewed by members of the CDER who specialize in medical, chemistry,

pharmacology/toxicity, and statistical fields to determine whether there are any flaws in the initial studies and whether the overall development plan is feasible.

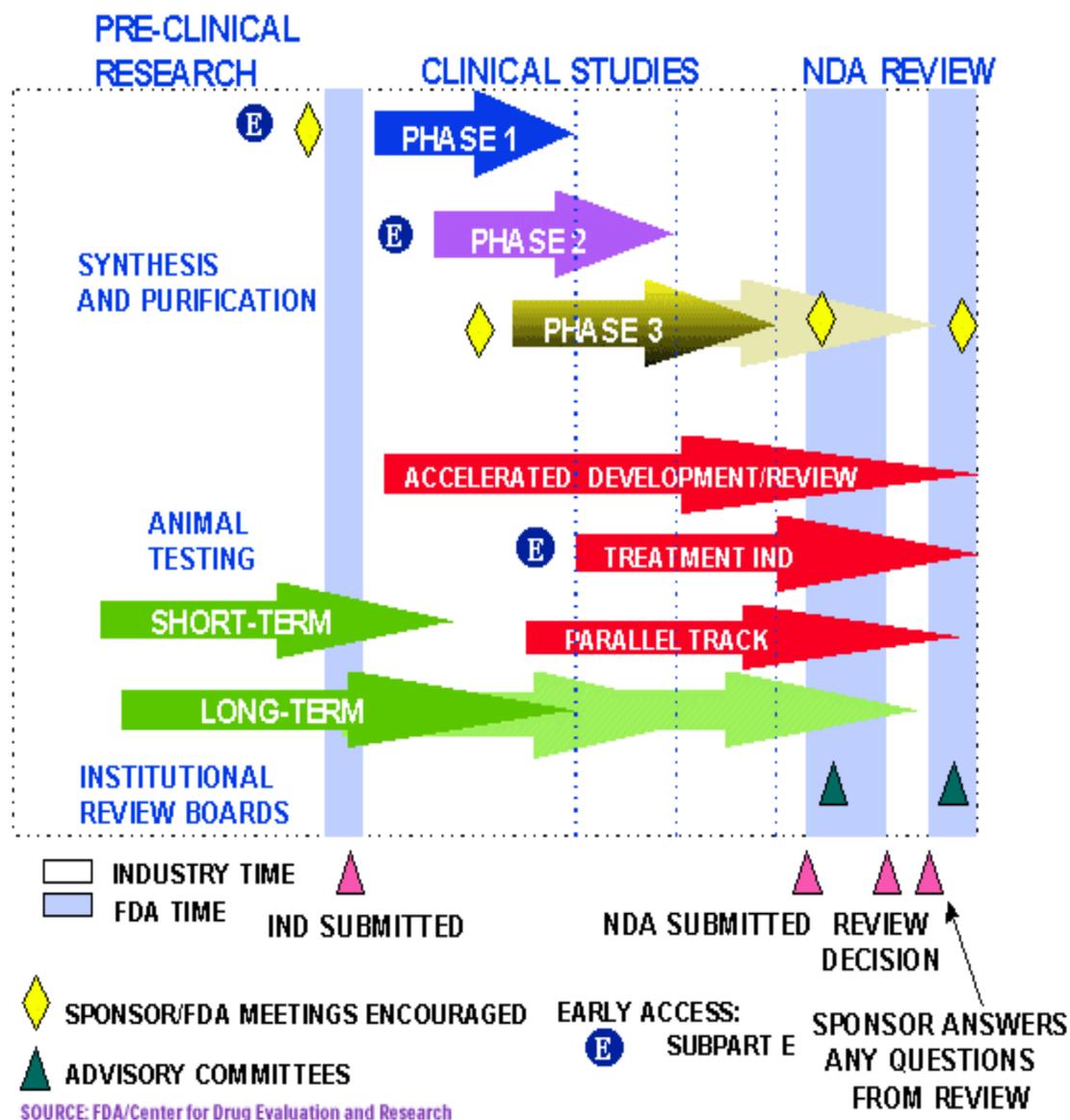


Fig. 2: Drug development and its phases

Government Review and Approval:

After clinical trials are complete, the drug sponsor submits a new drug application (NDA) for consideration by the CDER (Center For Drug Evaluation and Research). The NDA documents all study results, and the CDER requires samples of the drugs and its labels. Over the past few years, the CDER has significantly accelerated the time it takes

to review drug applications. On average, standard drug applications are reviewed in 12 months or less and priority drug applications are reviewed in six months or less. CDER primary reviewers and supervisory personnel evaluate the NDA. According to the CDER, final review is often based on two questions:

- Do the results of clinical studies provide substantial evidence of the drugs effectiveness?
- Do the results of clinical studies show that the drug is safe under the proposed labeling (that is, do the benefits of the drug appear to outweigh the risks)?

After the CDERs evaluation, the office will send an official letter to the drug sponsor that typically states one of the following: 1) the drug is approved for marketing, 2) the drug is approved provided that minor changes are made, 3) the drug is not approved because of significant problems (the sponsor can appeal this latter evaluation, withdraw the application, or resubmit an amended application at a later date). After the drug is approved, marketing, production, and distribution measures begin.

The FDA has four expedited programs for drug approval:

- Fast-track designation
- Breakthrough therapy designation
- Accelerated approval
- Priority review designation

FAST TRACK DESIGNATION:

Fast Track, which was developed by FDA, and codified into law in 2007, is a process designed to facilitate the development and expedite the review of drugs to treat serious or life-threatening diseases that will fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious diseases, including AIDS, Alzheimer's disease, unmet medical need is defined as providing a therapy where none exists or one that may be potentially superior to an existing therapy. Once a drug receives Fast Track designation, FDA offers the sponsor early and frequent communications to facilitate an efficient development program. The frequency of communications ensures that questions and issues are resolved in a timely manner, often leading to earlier drug approval. Fast Track drug sponsors are also eligible for "rolling review" of applications, allowing earlier submission and initiation of review. More than a third (12/35) of the 35 drugs were given a Fast Track designation. Of the 12 drugs that received a Fast Track designation, 9 (75%) were approved in the first review cycle. Of the 10 Fast Track drugs for which FDA was able to make comparisons to approvals in other countries, 100% were approved in the U.S first.

Fast Track is "a process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need."

This sounds great for anyone with faster drug approval on the brain, but in reality, Fast Track designation does very little to accelerate the approval process for your drug.

1. More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval.
2. More frequent written correspondence from FDA about such things as the design of the proposed clinical trials.
3. Eligibility for Accelerated Approval, i.e., approval based on a surrogate or substitute endpoint reasonably likely to predict clinical benefit.
4. Rolling Review, which means that a drug company can submit completed sections of its New Drug Application (NDA) for review by FDA, rather than waiting until every section of the application is completed before the entire application can be reviewed.
5. Dispute resolution if the drug company is not satisfied with an FDA decision not to grant Fast Track status. However, the following should also be noted regarding Points 1 through 5.
6. Regular meetings are already allowed by FDA (pre-IND, EOP2, pre-NDA, etc). In addition, FDA is very willing to provide follow-up meetings and additional technical meetings for products.
7. FDA will provide you adequate correspondence to move quickly with your development program, especially if your product is for a life-threatening disease with no existing therapy.
8. Any drugs or biologics that meet the appropriate requirements (see below for more information) are eligible for Accelerated Approval, regardless of Fast Track designation.
9. Rolling Reviews have always been allowed for NDAs. Agreement must be confirmed by the reviewing Division. However, the Fast Track Designation does provide for rolling reviews of BLAs.
10. Dispute resolution is a standard FDA process already.

Qualifying Criteria for Fast Track Designation:

Fast track designation applies to the drug (either alone or in combination with other drugs) and the specific use for which it is being studied. The term drug refers to the combination of two or more drugs if the combination is the subject of the fast track designation or request. Where appropriate, FDA may grant designation to the development of a new use of an approved drug.

Demonstrating the Potential to Address Unmet Medical Need:

The type of information needed to demonstrate the potential of a drug to address an unmet medical need will depend on the stage of drug development at which fast track designation is requested. Early in development, evidence of activity in a nonclinical model, a mechanistic rationale, or pharmacologic data could be used to demonstrate such potential. Later in development, available clinical data should demonstrate the potential to address an unmet medical need

Features of Fast Track Designation:

Actions to Expedite Development and Review There are opportunities for frequent interactions with the review team for a fast track product. These include meetings with FDA, including pre-IND meetings, end-of-phase 1 meetings, and end-of-phase 2 meetings to discuss study design, extent of safety data required to support approval, dose-response concerns, and use of biomarkers. Other meetings may be scheduled as appropriate (e.g., to discuss accelerated approval, the structure and content of an NDA, and other critical issues). In addition, such a product could be eligible for priority review if supported by clinical data at the time of BLA, NDA, or efficacy supplement submission. Fast Track addresses a broad range of serious conditions. The purpose is to get important new drugs to the patient earlier

BREAKTHROUGH THERAPY:

Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). To determine whether the improvement

over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

For purposes of Breakthrough Therapy designation, clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint
- An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
- A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

ACCELERATED DEVELOPMENT:

An overview of the 3 types of accelerated development mechanisms is below in Table 1. The overlap in benefit and use in development or review is obvious. However, further analysis is provided below as to how to appropriately use the designations to best meet the needs of your development program.

Table 2: Comparison of Accelerated Development Mechanisms

Review Type	Accelerated Approval	Priority Review	Fast Track Designation
Authority	1992 Rule: 21CFR 314 and 601 (In 1997,FFDCA 506b)	1996 Agency Procedure: CDER MAPP 6020.3; and CDER SOPP 8405	1997 statute: FFDCA 506(a)
Procedure	At time of clinical studies, product sponsor requests(during meetings). Division-specific decisions.(resource availability dependent)	Upon receipt of application, clinical team leader of FDA review team makes recommendation. Division specific decision.	Any time before marketing approval, Product sponsor requests designation; FDA grants if criteria are met(with in 60 days)
Criteria	Serious or life threatening illness.	n.a.	Serious or life threatening condition.
	Potential to address unmet medical need	Major advance in treatment or treatment where no adequate therapy exists.	Potential to address unmet medical need.
Benefit During Development	Adjusted trial requirements	n.a.	More frequent FDA Communication
Benefit During Review	n.a.	Expedited review (4-6 months compared with 10-12 months)	Rolling review (submit sections of BLA/CTD as completed)
Post Approval Requirement	Studies to extend results from surrogate to clinical outcome	n.a.	n.a.

ACCELERATED APPROVAL

The Accelerated Approval process, first created by FDA in 1992 and later codified in statute, allows approval of drugs that treat serious or life-threatening diseases and that may fill an unmet medical need, based on a surrogate endpoint that is reasonably likely to predict clinical benefit but is not fully validated to do so. In some cases, approval is based on an effect on a clinical endpoint other than survival or irreversible morbidity. A surrogate endpoint is a marker—a laboratory measurement, or physical sign—that is used in clinical trials as an indirect or substitute measurement for a clinically meaningful outcome, such as survival or symptom improvement. For example, viral load is a surrogate endpoint for approval of drugs for the treatment of HIV/AIDS. The use of a surrogate endpoint can considerably shorten the time to approval, allowing more rapid patient access to promising new treatments for serious or life-threatening diseases. Accelerated

Approval is given on the condition that sponsors conduct post-marketing clinical trials to verify the anticipated clinical benefit. If these trials fail to demonstrate the anticipated benefits, approval can be revoked. More than 80 new products have been approved under Accelerated Approval since the program was established, including 29 drugs to treat cancer, 32 to treat HIV, and 20 to treat other conditions such as pulmonary arterial hypertension, Fabry disease, and transfusion-dependent anemia. Two of the 35 NMEs approved in FY 2012 were approved under Accelerated Approval

PRIORITY REVIEW

In 1992, under PDUFA, FDA agreed to specific goals for improving drug review times and created a two-tiered system of review times—Priority Review and Standard Review. Priority review designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy

exists. FDA aims to review priority drugs more quickly, in six months versus 10 months for standard drugs. For example, in January 2012, FDA gave a priority review to Kalydeco, a breakthrough drug to treat patients with cystic fibrosis (CF) and who have a specific genetic defect. Kalydeco is the first medicine that targets the underlying cause of CF rather than its symptoms or complications. It was reviewed and approved by FDA in just over three months. Twelve of the 35 FY 2012 drugs received priority review. Of those 12, 11 (92%) were approved on the first cycle, and 10 (83%) were approved in the U.S. before any other country. Prior to approval, each drug marketed in the United States must go through a detailed FDA review process. In 1992, under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – *Standard Review* and *Priority Review*. A Priority Review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).

EXPEDITING DEVELOPMENT AND REVIEW:

It is important to distinguish between fast track designation itself and the specific programs that are available to a sponsor or applicant of a product in a fast track drug development program under section 506(a) of the Act. A sponsor or applicant may apply for fast track designation at any time in the development process from the original submission of an IND until the BLA or NDA is approved by the Agency. A product designated as being in a fast track drug development program would be eligible for consideration for some or all of the programs outlined below. It is also important to recognize that, with the exception of the submission of portions of a BLA/NDA before submission of the entire application: the programs described below have been established in regulations under authority separate from section 506 of the Act. Therefore, products that are not in drug development programs that have been designated as fast track may also be able to take advantage of these programs.

Meetings:

Appropriately timed meetings between the regulated industry and FDA are a critical aspect of efficient drug development. Sponsors of products in fast track drug development programs should be in regular contact with the appropriate reviewing division to ensure that the evidence necessary to support marketing approval will be developed and presented in a format conducive to an efficient review. Specifically, the following are strongly recommended:

- Pre-IND consultation so that (i) appropriate preclinical studies can be performed to demonstrate the potential to address unmet medical needs and to support introduction of the product into human trials, (ii) phase 1 studies can be optimally designed to support further product development, (iii) overall development strategy can be considered, and (iv) issues regarding the potential for fast track designation may be discussed.
- An end of phase 1 meeting because, as discussed in 21 CFR 312.82 (see Appendix 3), the first phase 2 controlled trials in life-threatening or severely debilitating illnesses may provide sufficient data on safety and effectiveness to support approval, with later development of more extensive safety data, dose response information, and other information in post marketing studies. It is critical that early trials with mortality/major morbidity endpoints be discussed before implementation to reach agreement on study design, including the statistical plan.
- An end of phase 2 meeting to ensure that agreement between FDA and the sponsor has been reached on the design of the principal controlled trials intended to provide evidence of safety and efficacy. As noted in the paragraph above (section A.2.), for some fast track drug development programs, a meeting with much the same purpose will occur at the end of early clinical testing and maybe referred to as "end of phase 1/2 meeting."⁷ Note that the standard of evidence applicable to principal controlled trials is set forth at 21 CFR 314.126 (see also the FDA guidance document, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May, 1998)).
- A pre-BLA/NDA meeting to discuss and achieve agreement on critical issues including: Whether preliminary evidence of effectiveness was seen in the principal controlled trials intended to provide evidence of effectiveness, Structure, content, and timing of submission of the BLA or NDA, Structure and content of any electronic submissions, Structure, content, and timing of submission of portions of an application for marketing approval, if such submission is appropriate. • Readiness for, and proposed timing of, preapproval

inspections, Potential for, and proposed timing of, advisory committee presentation if applicable.

- A meeting maybe scheduled to discuss labeling issues as early in the review process as appropriate.

Written Correspondence:

1. In addition to meeting minutes, described in CBER SOPP 8101.1 (Scheduling Meetings with Regulated Industry) and CDERMAPP4512. 1 (Formal Meetings Between CDER and External Constituents (March 7, 1996)), the following should be provided to the sponsor by FDA:

- Timely comments on the design of the proposed principal controlled clinical trials that are to provide the basis for the Agency's determination of the safety and effectiveness of the product.
- End of phase 1 and/or end of phase 2 letters commenting on the adequacy of phase 2/3 development plans.

2. In addition to the usual information contained in premeeting packages described in CBER SOPP 8101.1 and CDERMAPP4512. 1, the sponsor should provide the following to FDA:

- Responses to FDA questions about any clinical trials that are to form the basis for the Agency's determination of the safety and effectiveness of the product.
- At the earliest possible time, protocols of any clinical trials that are not being carried out under an IND (i.e., foreign studies) and that will form the basis for the Agency's determination of the safety and effectiveness of the product.
- In meeting packages for meetings held after initial fast track designation, a discussion of how

accumulated data and study plans continue to demonstrate that the product and the development plan meet the criteria for fast track designation. If submission of portions of an incomplete application is sought, a written request for this kind of submission and a proposed schedule for submission (see IV.C.2. below).

- As soon as possible, if there are plans to study a surrogate endpoint suitable for review under the accelerated approval provisions, a discussion of and support for the proposed endpoint.

C. Review Programs:

Sponsors of products in fast track drug development programs maybe considered for one or more of the following procedures regarding marketing applications.

1. Priority review of BLAs and NDAs

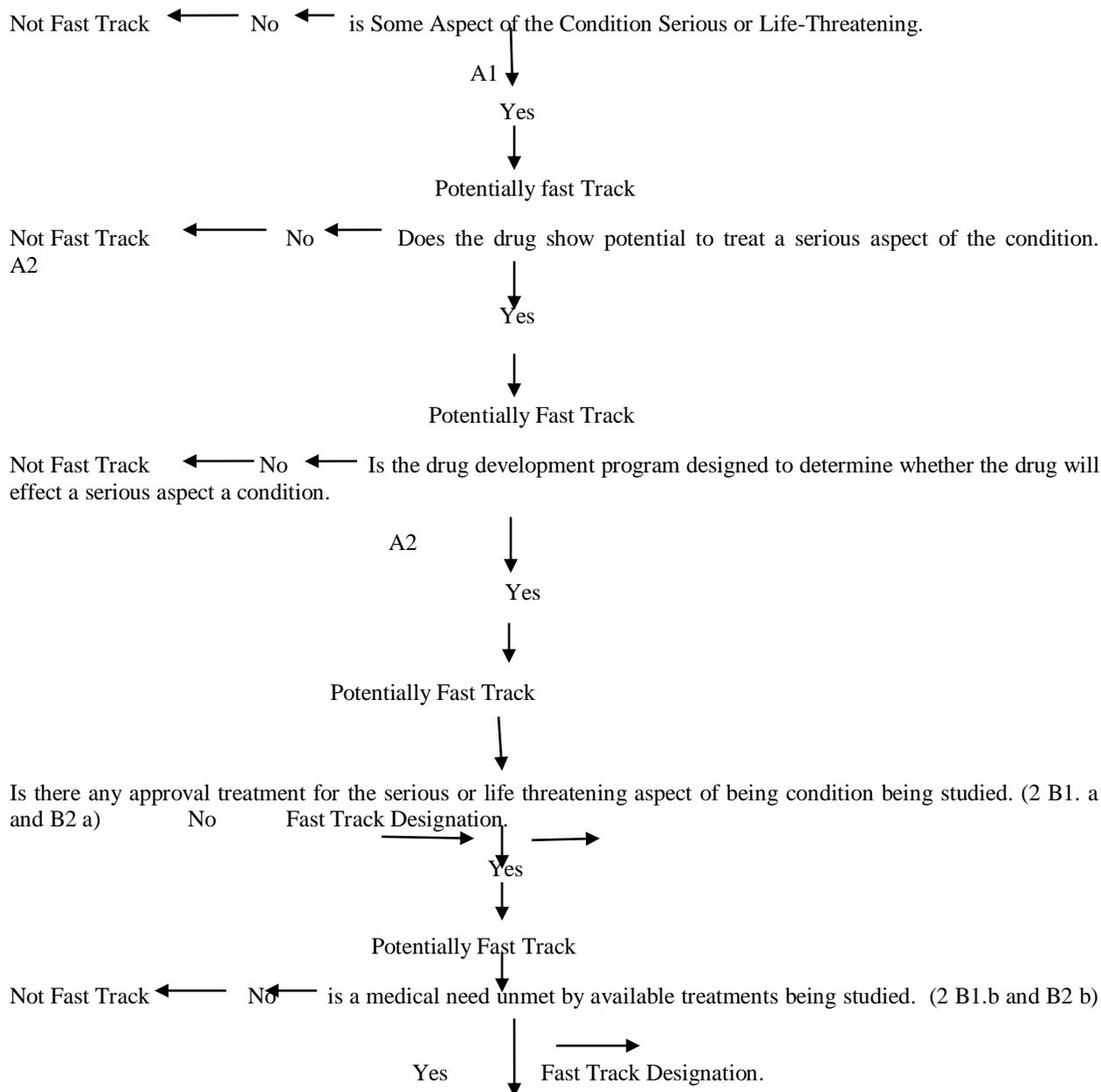
Because fast track products are intended to treat serious or life-threatening conditions and must demonstrate the potential to address unmet medical needs for such conditions, a BLA or NDA for a product in a fast track drug development program ordinarily will be eligible for priority review.

2. Submission of portions of an application

a. Submitting portions of a BLA/NDA

Section 506(c) of the Act provides that FDA may consider for review portions of a marketing application before the complete BLA or NDA is submitted. Filing may only occur if the applicant provides a schedule for submission of information necessary to make the application complete and pays any fees that may be required under section 736 of the Act (i.e., user fees).

Scheme for Determining Fast Track



FDA Fast Track Development Program

The **FDA Fast Track Designation** is a designation of the United States Food and Drug Administration (FDA) that facilitates the development, and expedites the review, of drugs which treat a serious or life-threatening condition and fill an unmet medical need. Fast Track designation must be requested by the drug company. The request can be initiated at any time during the drug development process. FDA will review the request and attempt to make a decision within sixty days.

Purpose

The purpose of Fast Track designation is to get important new drugs to the patient earlier.

Requirements

As stated, fast track designation is designed to aid in the development, and expedite the review, of drugs which show promise in treating a serious or life-threatening disease and address an unmet medical need. Serious Condition: Determining whether a

disease is serious is a matter of judgment, but generally is based on whether the drug will have an 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.

Unmet Medical Need: For a drug to address an unmet medical need, the drug must be developed as a treatment or preventative measure for a disease that does not have a current therapy. The type of information necessary to demonstrate unmet medical need varies with the stage of drug development: early in development, nonclinical data, mechanistic rationale, or pharmacologic data will suffice; later in development, clinical data should be utilized. If there are existing therapies, a fast track eligible drug must show some advantage over available treatment, such as:

- Showing superior effectiveness
- Avoiding serious side effects of an available treatment
- Improving the diagnosis of a serious disease where early diagnosis results in an improved outcome
- Decreasing a clinically significant toxicity of an available treatment
- Addressing an expected public health need

Incentives

A drug that receives Fast Track designation is eligible for some or all of the following:

- More frequent meetings with FDA to discuss the drugs development plan and ensure collection of appropriate data needed to support drug approval
- More frequent written correspondence from FDA about such things as the design of the proposed clinical trials
- Accelerated Approval or priority review if the requisite criteria are met. Accelerated approval is meant for drugs that demonstrate an effect on a surrogate, or intermediate endpoint reasonably likely to predict clinical benefit. Priority review shortens the FDA review process for a new drug from ten months to six months, and is appropriate for drugs that demonstrate significant improvements in both safety and effectiveness of an existing therapy. A fast track application is automatically considered for both of these designations.
- Rolling Review, which means that a drug company can submit completed sections of its

New Drug Application (NDA) for review by FDA, rather than waiting until every section of the application is completed before the entire application can be reviewed. NDA review usually does not begin until the drug company has submitted the entire application to the FDA

FDA Response:

FDA will respond to fast track designation requests within 60 calendar days of receipt of the request.

A. Designation letter

If the Agency determines that the criteria for designation as a fast track drug development program have been met, the designation letter will:

- State that fast track designation is granted for development of the product for use in treating the specific serious condition
- Point out that the sponsor should design and perform studies that can show whether the product meets an unmet medical need
- Alert the sponsor to the need for the drug development program to continue to meet the criteria for fast track designation

B. Non designation letter

If the Agency determines that a fast track designation request was incomplete or that the drug development program failed to meet the criteria for fast track designation, the Agency will send an on designation letter to the sponsor. The non designation letter will state that fast track designation is not granted and explain the reasons for the Agency's decision.

RESULTS AND DISCUSSION:

FDA and Drug Development Not only has the FDA drastically reduced its review time, it has also worked with industry to reduce overall drug development time by engaging earlier with the developer to discuss flexible approaches to developing data needed for approval. FDA's review time represents a small fraction of total drug development time; the process of discovery and testing takes far longer. In the 1970s and 1980s, when patients and industry were concerned about a drug "lag" with Europe, FDA's drug review program was so modestly funded that the agency could do little more than await a company's application for approval and place it into a queue for eventual review. Today, thanks to staffing increases supported by industry user fees and new regulatory authority, FDA is quicker and more nimble. Additional resources have enabled FDA to contribute insight and expertise to accelerate drug

development and assist and encourage new drugs sponsors.

New initiatives adopted concomitantly with the introduction of user fees are further reducing drug review times and substantially lowering drug development times: Accelerated Approval – This program, begun in the early 1990s, enables FDA to speed new treatments for serious or life-threatening illnesses for which there are no adequate therapies. Accelerated Approval is usually based on a “surrogate endpoint” -- that is, a “biomarker” that is “reasonably likely... to predict clinical benefit.” Clinical benefit will be verified through additional studies conducted after approval. More specifically, a surrogate endpoint is a marker of drug effect (e.g., an effect on blood pressure, a lab value, or tumor size) that does not directly represent an improvement in how a patient feels or functions, but is expected to predict such a benefit. The earliest surrogate endpoints included tumor shrinkage in cancer patients and an increase in certain white blood cells (“CD4” cells) in AIDS patients. Accelerated Approval was designed to speed the delivery of new drugs to patients with serious conditions -- and limited treatment options -- with verification of clinical benefit provided in “Phase 4” post-approval testing. Since its creation, the accelerated approval program has been used to approve over 90 new drugs and biologics, about a third for AIDS, a third for cancer, and a third for a variety of other serious conditions.

Priority Review – Drugs that hold the promise of delivering a significant improvement over existing therapy for serious or life-threatening illnesses can be designated for “priority” review, and a shortened six-month FDA review goal. From January 2008 through December 2013, 86 new drugs and biologics approved by FDA received priority status.

Fast Track Designation – FDA can provide Fast Track Designation to drugs for serious or life threatening illnesses for which there is an unmet need, including no approved treatments. Once designated, FDA works more closely with drug sponsors to facilitate submission of acceptable drug development plans, clinical trial designs, and data collection methods to support FDA review of the products’ safety and effectiveness. Once the sponsor begins to develop its marketing application data, it can submit the data to FDA for “rolling review,” rather than the usual process of submitting the entire marketing application at once. From January 2008

through December 2013, 66 new drugs and biologics approved by FDA received Fast Track Designation.

Breakthrough Therapy Designation – In 2012, Congress directed FDA to establish another program for expediting the development and review of new drugs for serious conditions, where there is preliminary clinical evidence that the drug may provide substantial improvement over existing therapy. Drugs that receive “Breakthrough” designation receive intensive guidance on an efficient drug development program, beginning as early as Phase 1. FDA makes an organizational commitment to involve senior managers and experienced review and regulatory health project management staff in a proactive, collaborative, cross-disciplinary review for such drugs. Although this program is new, 13 new drugs and biological products that received the Breakthrough designation have already been approved by FDA. And as of December 31, 2014, 74 had been granted the designation across a range of needs – cancer, infectious diseases and orphan diseases. The concept is expected to be a significant additional tool for reducing development times for such high impact drugs.

Flexibility Regarding Evidence Required to Support Approval – The statutory requirement for approving a new drug is that it be shown to be safe and effective. Effectiveness must be based on substantial evidence from adequate and well-controlled clinical investigations. This requirement usually means evidence from at least two adequate and well-controlled studies, each convincing on its own, although a single study can be sufficient. The agency “exercise[s] the broadest flexibility in applying the statutory standard, while preserving appropriate guarantees for safety and effectiveness,” as its regulations state.

Rare Diseases Nowhere is the use of flexibility in drug development more evident – and impactful – than in the case of rare, or “orphan,” diseases that afflict a small percentage of the population and are, therefore, not as commercially attractive for product developers. Yet finding effective treatments for rare diseases is a public health priority, and FDA has brought to bear all of its drug review and technical assistance tools to assist the development of new treatments for these conditions. The data on FDA’s involvement with rare diseases largely speaks for itself: • As noted previously, the number of orphan drugs approved (21) and novel therapeutic biologic products approved in 2014 (21) have reached all-time highs; • 80% of drugs approved for orphan diseases from 2008 through 2013 utilized at least one of

FDA's expedited review programs; • 62% of the novel new drugs for orphan diseases were approved on the basis of just one clinical trial plus supporting evidence; and, • 25% of the new drugs for orphan diseases were approved on the basis of a novel endpoint, endpoints for which there had been no prior precedence for the basis of approval in any disease.

TAMIFLU APPROVAL:

The US Food and Drug Administration (FDA) has extended the approval of Roche's Tamiflu (oseltamivir phosphate) for the treatment of acute, uncomplicated influenza to include infants two weeks of age and older. Tamiflu is prescribed by doctors to help lessen the duration and severity of influenza by blocking the virus' ability to replicate in the body. The approval makes Tamiflu the only prescription oral antiviral medicine approved to treat people of all ages, from infants two weeks of age to elderly

people. Tamiflu was first approved in the United States over 13 years ago. We are very pleased that this approval provides parents with a medicine for children as young as two weeks old, particularly because the Centers for Disease Control advises against vaccinating infants less than six months of age," said Hal Barron, MD, Head of Global Product Development and chief medical officer for Roche.

Tamiflu (oseltamivir):

The FDA approval of Tamiflu was based on the results of two double-blind trials conducted in 1997-8 in the United States and internationally. The transcript of the advisory committee meeting is not yet available. However, the Division Director's Memorandum on the New Drug Application is unless otherwise specified, the following comments are based on the Division Director's Memorandum.

Important Considerations for Tamiflu:

- Tamiflu must be administered within 48 hours of the onset of influenza symptoms
- Tamiflu is administered orally (75mg BID) for 5 days
- The safety and efficacy of Tamiflu in high-risk patients with pulmonary disease has NOT been demonstrated.
- Tamiflu should not be viewed as an alternative to influenza vaccine administration except for those minority of patients where the use of the vaccine is not recommended.(e.g. immunocompromised patients, those with allergy to eggs)

Side Effects:

The most common side-effects experienced by participants in the study were nausea and vomiting. These symptoms were mostly mild to moderate and generally occurred within the first two days of administration of the drug. Other less-frequent side-effects included diarrhea, bronchitis, abdominal pain, dizziness, headache, cough, insomnia, vertigo, fatigue.

Do not take Tamiflu if you are allergic to oseltamivir phosphate or any other ingredients of Tamiflu. Before starting treatment, make sure your doctor knows about any other medications you may be taking, or if you have any form of kidney disease. The effects of Tamiflu on children (under the age of 18) and on human pregnancies have not yet been determined

Approval:

In December 2012, the FDA expanded the use of oseltamivir phosphate to include infants over two weeks old (FDA/Center for Drug Evaluation and Research [CDER], 2012). Previously, the drug was only approved for use in children one year of age and

older. In an application from the manufacturer of oseltamivir phosphate (Hoffman-La Roche, Inc./Genentech) to the FDA, a proposal was made to approve its use (FDA/CDER,2012). The document stated that previous testing in rats showing toxic levels of the drug in the neonatal brain tissue was proven to be erroneous, and subsequent animal studies done by the National Institutes of Health (NIH) showed no such effects (FDA/CDER, 2012). Further, a retrospective study was conducted by the National Institute of Allergy and Infectious Diseases (NIAID) and NIH to review charts of infants who were administered oseltamivir phosphate "off label" by their health care providers (FDA/CDER, 2012).

The AIDS epidemic:

In the 1980s, a new tragedy one that "typifies the diseases of the future: slow, subtle, complex, and rooted in lifestyles and genes" propelled changes in the new drug regulatory scheme to enable faster approval for certain new products. A series of cases of homosexual men suffering from rare diseases that typically afflicted the elderly led the medical community to identify a new syndrome, the Human Immunodeficiency Virus and Acquired Immune

Deficiency Syndrome (HIV/AIDS). For several years following this initial discovery period (roughly 1981 to 1984), HIV/AIDS patients had no scientifically established or FDA-approved treatments to halt the progression of the virus, leading society to view HIV/AIDS as lethal. Those suffering from the syndrome had a significantly lower risk threshold than the average American; in other words, sufferers were willing to take greater risks in the safety of treatments in the hopes of obtaining any therapeutic benefit. Patients began seeking out any therapy that had anecdotal evidence of benefit, joining black market buying clubs and cooking medicine themselves.

These patients and the pharmaceutical industry increasingly criticized FDA as being far too slow, conservative, and risk-averse in the circumstances. Indeed, the demands of the FDCA drug development process added significant challenges to the marketing approval of a new drug compound for HIV/AIDS. Individuals lived with HIV/AIDS for years without knowing of their infection until symptoms developed leading to a diagnosis. Under the traditional developmental framework, potential therapies, like zidovudine (better known now as AZT) could not meet the risk-benefit requirements, or show the lack of long-term toxic side effects quickly enough given the progression to mortality rate of HIV/AIDS. Ultimately, FDA collaborated with the sponsor to facilitate a focused development and review program that led to the approval of zidovudine in approximately two years.

Creation of Priority Review, Accelerated Approval, and Fast Track designation:

The activism of the often socially marginalized HIV/AIDS patients ultimately produced several reforms by FDA and Congress. FDA promulgated Subpart E in 1988, modeled on the zidovudine clinical development process. The regulations recognized the need for the “broadest flexibility in applying the statutory standards” and the altered risk-benefit threshold of patients with life-threatening and seriously debilitating diseases. They provided for early and close consultation between FDA and the drug product’s sponsor, listing “procedures such as pre-IND and end of Phase 1 meetings as methods to improve the efficiency of preclinical and clinical development, and focus on efforts...to reach early agreement on the design of major clinical efficacy studies. They further provided for the use of medical risk-benefit judgment in the approval decision, including the consideration of the severity of the disease and the lack of a satisfactory alternative.

CONCLUSION:

Accelerated Approval, Priority Review, Fast Track, and Breakthrough Therapy each have the potential to shorten the pre-market process. But, the Breakthrough Therapy designation may provide additional benefits to a qualifying compound above those already available through the other three expedited approval mechanisms, primarily by increasing the quantity and quality of the interaction between FDA and a sponsor. Notably, the pharmaceutical industry is embracing the new designation, outstripping FDA’s expectations. Yet, it remains to be seen whether FDA implements the tools in a way that adds efficiency to the process, while maintaining the standards of safety and effectiveness.

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