FDA Fast Track and Priority Review Programs

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Summary

By statutory requirements and by regulation, guidance, and practice, the Food and Drug Administration (FDA) works with several overlapping yet distinct programs to get to market quickly new drug and biological products that address unmet needs. FDA most frequently uses three mechanisms for that purpose: Accelerated Approval, Fast Track, and Priority Review. The first two affect the development process before a sponsor submits a marketing application. Accelerated Approval allows surrogate endpoints in trials to demonstrate effectiveness and is relevant in fewer situations than the others. The Fast Track program encourages a sponsor to consult with FDA while developing a product. Unlike the others, Priority Review involves no discussions of study design or procedure; it relates only to an application's place in the review queue. Analysis of total approval time for *approved* applications under the Fast Track and Priority Review programs shows that for seven of the past nine years, Fast Track products have shorter median approval times than do all those applications assigned to Priority Review.

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It takes an average of 15 years from the moment a manufacturer first approaches the Food and Drug Administration (FDA) with an idea for a new drug to its final approval for marketing.[1] Steps in the development and approval of a drug or biologic (e.g., a vaccine) involve actions by both the manufacturer and FDA. First, a manufacturer (sometimes referred to as the sponsor) submits to FDA an Investigational New Drug (IND) application for permission to conduct clinical studies in humans. Second, the manufacturer completes Phase I, II, and III clinical trials to establish that a product is safe and effective for a specific purpose and population. Third, the manufacturer submits to FDA a New Drug Application or a Biologics Licensing Application (noted as NDA/BLA throughout this report) for permission to market the product. Fourth, FDA reviews the NDA/BLA for evidence of safety and effectiveness, a process that sometimes includes requests to the sponsor for additional information, the sponsor's response, and further FDA review. Finally, FDA decides whether to approve the application.

For drugs and biologics that address unmet needs or serious diseases or conditions, FDA regularly uses three formal mechanisms to expedite the development and review process: Fast Track product development, Priority Review, and Accelerated Approval.[2] This report briefly describes (in text and in **Table 1**) those mechanisms, including their intended effects and statutory and regulatory bases, and examines whether Fast Track accomplishes two goals: making approval more likely and shortening approval time.

Mechanisms to Expedite the Development and Review Process

Accelerated Approval

For the treatment of a serious or life-threatening illness, FDA regulations, promulgated in 1992, allow "accelerated approval" of a drug or biologic product that provides a "meaningful therapeutic benefit ... over existing treatments." The rule covers two situations. The first allows approval to be based on clinical trials that, rather than using standard outcome measures such as survival or disease progression, use "a surrogate endpoint that is reasonably likely ... to predict clinical benefit." The second situation addresses drugs whose use could be deemed safe and effective only under set restrictions that could include limited prescribing or dispensing. FDA usually requires postmarketing studies of products approved this way.[3] Accelerated Approval involves different concerns than do the other programs designed to speed the normal process for important new products, and therefore this paper will not discuss it further.

[1] Pharmaceutical Research and Manufacturers of America (PhRMA), at http://www.phrma.org.

[2] Other options fit very limited situations and support shorter times from idea to approved public use. The Animal Efficacy Rule (21 CFR 314 Subpart I and 21 CFR 601 Subpart H) allows submission of data from animal studies of effectiveness as evidence to support applications of certain new products "when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible." The Project BioShield Act of 2004 allows the HHS Secretary to authorize the emergency-use of products that do not yet have FDA approval in certain circumstances (21 U.S.C. 360bbb-3); also, see CRS Report RS21507, *Project BioShield: Purposes and Authorities*, by (name redacted).

[3] Regulations for the accelerated approval of new drugs for serious or life-threatening illnesses are at 21 CFR 314 Subpart H, and for biological products at 21 CFR 601 Subpart E.

Fast-Track Mechanism

The Food and Drug Administration Modernization Act of 1997 (FDAMA, P.L. 105-115) directed the Secretary to create a mechanism whereby FDA could designate as "Fast Track" certain products that met two criteria. First, the product must concern a serious or life-threatening condition; second, it has to have the potential to address an unmet medical need. Once FDA grants a Fast Track designation, it encourages the manufacturer to meet with the agency to discuss development plans and strategies before the formal submission of an NDA/BLA. The early interaction can help clarify elements of clinical study design and presentation whose absence at NDA/BLA submission could delay approval decisions. However, FDA makes similar interactions available to any sponsor who seeks FDA consultation throughout the stages of drug development. A unique option within Fast Track is the opportunity to submit sections of an NDA/BLA to FDA as they are ready, rather than the standard requirement to submit a complete application at one time.[4]

Priority Review

Unlike Fast Track or Accelerated Approval, the Priority Review process begins only when a manufacturer officially submits an NDA/BLA. Priority Review, therefore, does not alter the timing or content of steps taken in a drug's development or testing for safety and effectiveness. For products believed to address unmet needs, however, it shortens the average amount of time from completed application until approval decision from 10 months to 6 months. Although Priority Review is not explicitly required by law, FDA has established it in practice, and various statutes, such as the Prescription Drug User Fee Act (PDUFA), refer to and sometimes require it.[5]

[4] FDAMA created Section 506, Fast Track Products, in the Federal Food, Drug, and Cosmetic Act. See FDA, *Guidance for Industry: Fast Track Drug Development Programs—Designation, Development, and Application Review*, at http://www.fda.gov/cber/gdlns/fsttrk.pdf.

[5] FDA Center for Drug Evaluation and Research (CDER), Manual of Policies and Procedures (MAPP) 6020.3, revised July 18, 2007; Center for Biologics Evaluation and Research (CBER), Manual of Standard Operating Procedures and Policies (SOPP) 8405, revised September 20, 2004; and "Oncology Tools: Fast Track, Priority Review and Accelerated Approval," at http://www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm.

Table 1. Comparison of Mechanisms to Hasten Product Availability

	Accelerated Review	Priority Review	Fast Track
Authority	1992 *Rule*: 21 CFR 314 and 601. (In 1997, FFDCA 506(b).)	1996 *Agency Procedure*: CDER MAPP 6020.3; and CBER SOPP 8405.	1997 *Statute*: FFDCA 506(a).
Procedure	[Not specified; presumably manufacturer would request and FDA would determine whether to grant.]	Clinical team leader of FDA review team, upon receipt of application, makes recommendation.	Any time before marketing approval, manufacturer requests designation; FDA grants if criteria are met.
Qualifying 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.
	Adequate and well-controlled studies supporting use of surrogate outcome.	n.a.	
Benefit during development	Adjusted trial outcome requirements	n.a.	Close communication with FDA.
Benefit during review	n.a.	Additional attention; expedited review.	Rolling review.
Postapproval requirement	Studies to extend results from surrogate to clinical outcome.	n.a.	

Notes: FFDCA = Federal Food, Drug, and Cosmetic Act; n.a. = not applicable.

Measures of Program Effectiveness

Approval Rates

Are products that receive Fast Track designation more likely to have their NDA/BLA approved by FDA than products that receive no such designation? The answer is we don't know, because, while FDA provides statistics on the products it designates as Fast Track, it does not make public information on the NDA/BLAs it receives unless and until the product is approved/licensed.

What we do know from material on the FDA website:

- Manufacturers have requested Fast Track designation for 569 drugs and 195 biological products since the Fast Track program was set into law.
- FDA granted the designation to 74.5% of those drug requests and 63.6% of those biologics requests.

- Of products with Fast Track designation, FDA eventually approved 10.6% of the drugs and licensed 17.7% of the biologics.[6]

What that means is obscured by what we do not know:

- For what percentage of products with Fast Track designation do sponsors submit NDA/BLAs? How many NDA/BLAs submitted each year are for Fast Track products? With only the numerator (approved products), one cannot calculate the percentage of NDA/BLA submissions that are approved among Fast Track products.

FDA receives approximately 100-130 applications a year, and has stated that "close to 80 percent of all filed applications will eventually be approved."[7] The 10.6 and 17.7% figures for Fast Track are not a comparable statistic because they include the apparently large, but unquantified, number of product development attempts that manufacturers discontinue (for safety problems, lack of effectiveness, business decisions, competing projects). A useful analysis would account for the percentage of Fast Track and non-Fast Track products of which FDA is aware (e.g., that have INDs) that result in submitted NDA/BLAs.

Length of Decision Times for Approval

How long it takes from the time a sponsor applies for marketing permission to the moment FDA makes its decision varies greatly. The length matters to the sponsor and its stockholders, to potential consumers and healthcare providers, and to FDA. Two factors contribute to longer review times: review staff constraints at FDA, and the quality and completeness of applications when they are first submitted. PDUFA and its three reauthorizations have addressed the staffing issue by authorizing industry user fees to support FDA reviewers.[8] FDA's Web pages on the use of its Fast Track and Priority Review programs provide the review times for successful applications.

Table 2 compares the review times, by year and type of review procedure, for all 787 approved NDA/BLAs applications that were submitted from FY1998 through FY2006. These applications received either a *Standard Review* or a *Priority Review,* and the review times for these two procedures are summarized in the first two pairs of data columns in the table. The third pair of columns summarizes review times for approved NDA/BLA applications for products that received a Fast Track designation. As discussed below, most, though not all, of these 55 applications received a Priority Review and thus are counted in the Priority Review columns; the remainder are captured in the Standard Review data. The final pair of columns provide data on Priority Review times for NDAs of *New Molecular Entities (NMEs)* and *New BLAs*. These applications represent a subset of all those subject to Priority Review, and are the group of products most similar to Fast Track products.

[6] FDA, "CDER Fast Track Products Approved Since 1998 through 3/31/07," "Fast Track Designation (FY1998-FY2006), updated through 9/30/2007," "CDER Response to Request for 'Fast Track' Designation FY2007, updated through 9/30/2007," and "CBER Fast Track Designation Request Performance, 3/1/98 through 12/31/07," all at http://www.fda.gov.

[7] FDA, PDUFA FY2006 Performance Report to Congress, at http://www.fda.gov/pdufa/report2006.

[8] See CRS Report RL33914, *The Prescription Drug User Fee Act (PDUFA): History, Reauthorization in 2007, and Effect on FDA*, by (name redacted).

Each row of **Table 2** corresponds to approved applications submitted during a specific year. The *total approval time* includes the time FDA spends to review an application, plus the time the sponsor takes to respond to questions, if necessary, plus the time FDA spends on any additional review. The table provides the *median* approval time for each submission year group, which is the value at the mid-point of times in a group. FDA uses the median in its reports, stating, "It provides a truer picture of our performance than average time, which can be unduly influenced by a few very long or short times."[9]

Table 2. Number and Total Approval Time (in months) of Approved NDAs and BLAs, by Fiscal Year of Submission, and by Review Procedure

	Category of Review Procedure							
	All Standard NDAs & BLAs		All Priority NDAs & BLAs		Fast Track		Priority NMEs & New BLAs	
FY of submission[a]	No.	Median Approval Time	No.	Median Approval Time	No.[b]	Median Approval Time	No.[c]	Median Approval Time
1998	65	12.0	25	6.4	5	5.8	16	6.2
1999	55	13.8	28	6.1	2	5.1	19	6.9
2000	78	12.0	20	6.0	4	4.8	9	6.0
2001	56	14.0	10	6.0	8	16.0	7	6.0
2002	67	15.3	11	19.1	2	12.4	7	16.3
2003	58	15.4	14	7.7	7	9.0	9	6.7
2004	90	12.9	29	6.0	9	5.0	21	6.0
2005	58	13.1	22	6.0	9	6.0	15	6.0
2006[d]	80	13.0	21	6.0	9	6.0	10	6.0
Total	**607**		**180**		**55**		**113**	

Sources: All data are from the FDA website at http://www.fda.gov. Fast Track data calculated from "CDER Fast Track Products Approved Since 1998 through 3/31/07," and PDUFA annual performance reports, FY1999 through FY2006. Priority NME and new BLA from "CDER Approval Times for Priority and Standard NMEs and New BLAs, Calendar Years 1993-2006." Priority and Standard NDA and BLA from "CDER Approval Times for Priority and Standard NDAs and BLAs, Calendar Years 1993-2006."

a. FDA tallies review times by the year the NDA/BLA was submitted, not the year it was approved or denied.

b. Includes Fast Track reviews of original NDA/BLAs only; does not include 11 reviews of supplemental NDA/BLAs.

c. Priority NMEs and New BLAs are included also in the All Priority column.

d. Each annual PDUFA Performance Report adjusts the number and duration of reviews completed for earlier years' submissions. For example, the FY2006 report included completed reviews of 15 FY2006 submissions, 14 FY2005 submissions, and 1 FY2004 submission.

Fast Track submissions in theory differ from routine NDA/BLA submissions because they address unmet needs in the treatment of life-threatening or serious conditions. Similar criteria

[9] FDA, "CDER Data Briefing 1996-2006 Accessible Version," at http://www.fda.gov/cder/reports/CDERDataBriefing1996-2006accessible.htm.

apply to drugs that FDA gives Priority Review status. In fact, 80% of Fast Track NDA approvals were also given Priority Review, as were all of the approved Fast Track BLAs. Again, FDA makes public detailed data only regarding the products that it approves/licenses.

Using the data in **Table 2** to determine the impact Fast Track designation has on approval time is complicated by limitations in the data available. These include the following: *Inadequate data:* Available FDA tables aggregate applications by year and present only the median approval time value for each year. This precludes using the individual application times in subsequent calculations. *Missing data:* Data available for analysis come from *approved* applications. Inclusion of numbers of applications and total time to review decision (approval or not) would allow examination of additional aspects of the Fast Track program that may provide advantages that do not affect total approval time. *Unavailable documentation of decisions:* Without detailed documentation of the many decisions embedded in the FDA summary tables, accuracy or consistency in assignment to year of submission rather than year of approval cannot be assessed. If an application is assigned to one year in the Fast Track column and to another in the All Priority column, for example, relying on the annual median approval times could distort the comparisons. *Overlapping categories:* The All Priority and All Standard groups sum to the total number of approved applications in each submission year. The other categories, however, overlap. By definition, the Priority NMEs and New BLAs category is a subset of the All Priority NDAs and BLAs. For the Fast Track NDAs, at least 87% are counted in the Priority NDA group and at least 68% are also counted in the Priority NME group. (FDA lists some Fast Track NME applications as assigned to Standard Review.)

As expected, based on program goals, times are shorter for Priority Review than for Standard Review. For seven of the nine years, median Fast Track times were shorter than Priority Reviews, suggesting that Fast Track may have reduced time-to-market beyond the shortening of review time afforded by Priority Review. A more detailed analysis of individual application data might indicate how group differences may be due to obvious exceptions, different procedures or application completeness or quality, or unknown factors or chance. For example, how does the wide range of approval times—from 2.4 to 34.1 months—for the eight Fast Track product NDA/BLAs submitted in 2001 affect group averages? Finally, review time from submission to approval is only one measure of Fast Track effect. If a Fast Track designation enables a sponsor to submit a completed NDA/BLA sooner than it would otherwise, that advantage would not be evident in this comparison of review times that begins with submission.

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