

FAST TRACK PRODUCT DESIGNATION UNDER THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT: THE INDUSTRY EXPERIENCE

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With the passage of the Food and Drug Administration Modernization Act (FDAMA), existing programs for expedited development and approval for treatments of serious or life-threatening diseases were codified and consolidated under the administrative rubric of fast track product designation. The four basic programs available with fast track designation have been categorized by FDA as consisting of meetings, written correspondence, review programs, and dispute resolution. Despite some early skepticism by industry, and even FDA, that the benefits of designation were not readily apparent since the individual programs are generally available without designation, there are indications that fast track designation will be the improvement Congress intended. Unlike the individual expedited development and approval programs, which affect only part of the drug development timeline, fast track designation has the potential to facilitate the entire process. Industry requests for fast track designation have dwarfed pre-FDAMA industry participation. Yet, the best predictor of the future success or failure of fast track designation is how well it is working now. In order to evaluate this, the authors surveyed the biotechnology and pharmaceutical sponsors of 32 fast track designated products identified from public information sources and present their findings in this paper.

Key Words: Fast track; Fast track designation; FDA Modernization Act; FDAMA; Food and Drug Administration; Expedited development; Accelerated approval; Rolling review; FDA-sponsor meetings; Priority review

INTRODUCTION

BEFORE PASSAGE OF THE FDA Modernization Act in late 1997, fast track was many

things to many people. To some, it meant FDA's expedited development and accelerated review programs, also commonly called by the section in which they appear in FDA drug regulations, Subpart E and Subpart H, respectively. To others, the term referred to the early "fast track review" available for high-priority New Drug Applications (NDAs) whose sponsors were allowed to submit so-called "rolling NDAs." To still others, it can refer just to any drug given "priority" status

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after the Prescription Drug User Fee Act (PDUFA) of 1992 implemented specific time-frames for the review of products for approval based on their therapeutic ratings. Some even consider drugs approved under FDA's expanded access programs such as Treatment Investigational New Drugs (INDs) and Parallel Track to be included under the rubric of fast track.

Under FDAMA, many of these fast track programs have been codified and consolidated under a comprehensive fast track product development designation designed to facilitate development and approval of drug and biological products intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical conditions. Fast track designation is granted to the sponsor of the development program for a specific indication of a specific drug or biological product. FDA has also emphasized that expanded access programs for investigational drugs such as the Treatment IND program should be considered distinct from fast track. Treatment INDs operate to increase access prior to marketing approval, rather than to expedite the product's path to market, as fast track does (1).

In a September 1998 guidance document, FDA describes the benefits of fast track designation in terms of what is provided by its four basic programs:

1. Meetings,
2. Written correspondence,
3. Review programs, and
4. Dispute resolution (1).

The meetings program focuses on regular, appropriately timed consultations between the agency and the fast track designee, especially at the following critical junctures during the drug development process: pre-IND, end-of-Phase I, end-of-Phase II, pre-NDA/Biologics License Applications (BLA), and early in the labeling process. Written correspondence consists not only of the information provided to FDA by the sponsor, but also the timely comments provided by FDA on the design of the principal trials and the

adequacy of the sponsor's Phase II or III development plans. Review programs refer to the opportunity for priority review of the NDA or BLA, a "rolling review" of portions of a marketing application before the full NDA/BLA is submitted, and accelerated approval. Dispute resolution means that FDA determinations made under the fast track program may be appealed first at the level of the reviewing division/office within its Center for Drug Evaluation & Research (CDER) or its Center for Biologics Evaluation & Research (CBER), and if needed, at a level beyond the reviewing division/office.

These are significant programs but are they new to fast track designation? With the exception of "rolling review," programs available under FDAMA's fast track designation are also generally available under existing regulations. It is no wonder that industry initially viewed the "benefits" of fast track designation somewhat circumspectly as being three-fold: FDA interaction effects (ie, presumably meetings), clinical endpoint-related effects (ie, surrogate endpoints) and late-stage benefits (ie, rolling review). Even these so-called benefits were considered "... soft and really not well-defined (2)." More open skepticism was expressed by an industry regulatory affairs specialist who added that he already worked closely with FDA and did not see the need to add another level of formality and bureaucracy (3). A senior official at FDA echoed this sentiment, commenting that he failed to see how fast track would change the way his division handled things (4). The Pharmaceutical Researchers and Manufacturers of America (PhRMA), an industry trade association, noted the vagaries in the use of surrogate endpoints (5), even as FDA pointed out that rolling review is not automatic for designated products but must be negotiated. FDA also emphasized that rolling review really means rolling submission, as the actual review may not necessarily commence prior to the receipt of the complete application (1). Other comments claimed that companies would seek designation merely to showcase their products or to show patient groups that they were

doing everything possible to expedite the development of needed therapies (2). Still others viewed fast track designation just as a way for biotechnology firms to boost stock prices (3).

This early skepticism by industry concerning the fast track designation seemed to beg the question: Does fast track designation actually “do” anything to facilitate product development? While the effects of fast track designation on total development time are not yet measurable less than three years after passage of FDAMA, the effects of its regulatory progenitors have been quantified. A study of the impact of Subpart E procedures from 1988 to 1993 indicated that there was “a substantial decrease in clinical development times and a lesser, although not insignificant, decrease in FDA review times,” for New Chemical Entities (NCEs) receiving a Subpart E designation compared to similarly rated NCEs without Subpart E designation that had been approved during the same period (6). Similarly, a review of the accelerated approval process from 1992 through mid-1997 showed that the time gained over the traditional approval process for 20 drugs and biologics ranges from an estimated minimum of 3 to 48 months (7). In addition, a study of NCEs approved from 1987 to 1995 showed that pre-IND meetings and end-of-Phase II conferences were associated with shorter clinical development times (8).

Clearly, fast track programs themselves have demonstrable benefits for product development, but the question that remains is whether fast track designation itself enhances these effects. One way to look at the potential advantage of fast track designation compared to individual fast track programs is to focus on the drug development timeline.

As shown in Figure 1, each of the fast track programs affects only a part of the drug development timeline. For example, priority review (given to products offering a significant improvement over those already on the market) affects the timeline only late in the process as the product enters the FDA approval stage. Rolling review becomes important somewhat earlier as the results of the

principal clinical trials are available toward the end of the clinical development period. Accelerated approval begins to have an impact further back on the clinical development timeline toward the end-of-Phase I when the drug or biological product has demonstrated safety and the potential utility of the unvalidated surrogate endpoints or indirect clinical benefits as predictors of ultimate clinical benefit. Subpart E designation has an effect early on in the clinical phase of development through its emphasis on early consultation and communication, as well as later through the compression of Phase III clinical trials into Phase II trials. However, its impact diminishes somewhat at the approval phase, even though any influence from the utilization of a more flexible risk-benefit analysis by FDA reviewers would be expected to occur at the approval stage.

Fast track designation, in contrast, can significantly impact the entire drug development timeline. It can be discussed with FDA as early as the pre-IND meeting and an actual designation decision may be available upon IND submission. Fast track designation continues to facilitate the entire clinical development period since it has essentially subsumed the procedures formally available only under the Subpart E regulations. It then expedites FDA review by serving as the regulatory gateway for rolling review (only review of the Chemistry, Manufacturing, and Controls [CMC] section of the NDA is now available outside of FDAMA), and achieving fast track designation means that a product “. . . ordinarily will be eligible for priority review (1).”

Another way to gauge the significance of fast track designation for product development is to assess the level of participation by developers. Recent numbers provided by FDA in public source information indicate that there have been 70 requests for fast track designation to CDER (9,10,11), and an estimated 44 to CBER as of early 2000 (9,10,12). At the current pace, we have projected that fast track designation requests will be well over 200 by the beginning of 2002, with about 60% going to CDER and the rest to CBER (Figure 2).

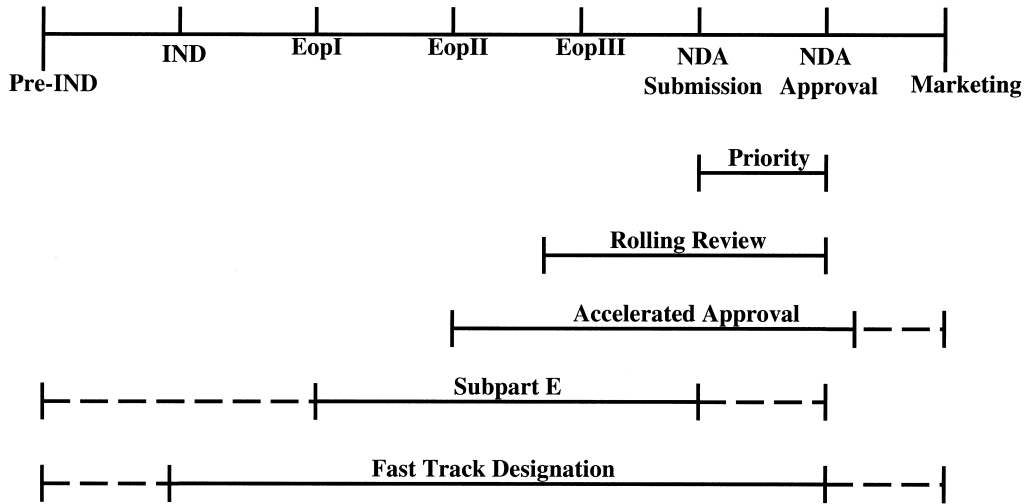


FIGURE 1. Impact of fast track programs versus designation on development timeline.
 Source: Tufts Center for the Study of Drug Development 2000

How does this compare to industry participation in fast track programs prior to FDAMA? There were more requests for fast track designations in the one year since the FDA issued the guidance document for the FDAMA fast track program in September 1998 than there were Subpart E and accelerated approvals in the whole 10 years prior to

FDAMA. If designation awards continue at the current rate of about 60% to 70%, there will be double the number of products fast-tracked in less than half the time under FDAMA than there were under the pre-FDAMA programs.

So far, what we know about fast track designation is that its impact could poten-

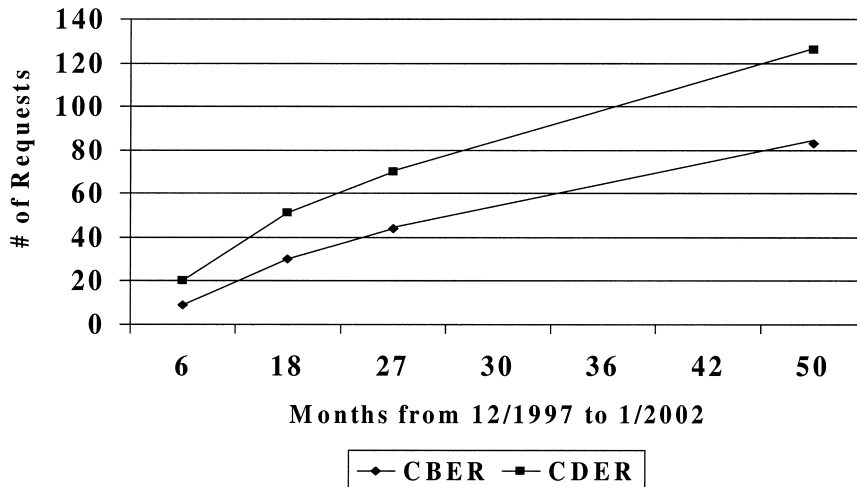


FIGURE 2. The pace of fast track requests.
 Note: Third data point (44 for CBER requests) had to be extrapolated because number given in public source information was not cumulative.
 Source: Tufts Center for the Study of Drug Development 2000

tially encompass the entire drug development timeline and that the level of industry participation in the designation program is high. The final approach we took to assess the value of fast track designation was to ask industry itself.

METHODS

In spring 2000, Tufts Center for the Study of Drug Development (CSDD) conducted a survey of sponsors of drug and biological products that had been identified as having received fast track designations during 1998 to 1999. Because FDA was not making designation awards public, a sampling frame was constructed from public information sources including weekly trade newsletters, industry journals, press releases, and industry Web sites. We identified 32 such products. We have estimated that this number represents about half of the total designations granted during 1998 to 1999. From product or company descriptions accompanying the announcement of the fast track designation, we initially categorized 20 of the designated treatments as products of the biotechnology industry and 12 as products of the pharmaceutical industry.

The two-page survey was faxed to potential responders with a brief introduction explaining the purpose of the survey and its confidentiality, and alerting them that it could be sent to them electronically, if preferred. Of the 32 potential respondents, 23 answered the survey for a response rate of 72%.

Although initial care was taken to select potential respondents who had been identified in several sources as recipients of fast track designations, several questions served to further ensure that survey responders (at least) were members of the group of interest. Survey participants were initially asked to confirm that their product (specified by trade and generic name as well as by indication) had, in fact, received a fast track designation from FDA under section 112 of the FDA Modernization Act of 1997. They were also asked to provide the date the designation re-

quest was made as well as the date it was granted.

Other survey questions related to the details of the product's development program such as: which FDA center and review division/office the request was sent to; what phase of development the product was in at the time of the request and at the time of the survey response; age range of the indication(s); and, how many person-hours were required to prepare the fast track designation request.

Further questions were directed at evaluating industry's level of involvement by inquiring about which programs had been applied for and how many meetings had been held with FDA. Another set of questions attempted to ascertain how responsive FDA had been in its implementation of the program by asking survey participants to detail what written correspondence and other documentation deliverables had been received by sponsors as a result of meetings with FDA.

Still another set of questions asked survey participants to rate each of the fast track programs and operational factors on a scale of 1 to 5, where 1 = most benefit, 2 = some benefit, 3 = little benefit, 4 = no benefit, and 5 = not applicable. Finally, survey participants were asked to assess the extent to which the development of their product had benefited from fast track designation.

RESULTS

From company and product descriptions we had initially categorized nearly two-thirds of the 32 potential survey respondents as members of the biotechnology industry. While this may still be substantially correct, survey results from the 23 actual survey respondents showed that 65% of the designation requests went to CDER and only 35% went to CBER. Of the designation requests going to CDER review divisions: four went to Anti-Viral Drug Products; two to Anti-Infective Drug Products; four to Oncology Drug Products; two to Pulmonary Drug Products (including one that went to both Oncology and Pulmonary); and one each to Cardio-Renal Drug

Products, Anti-Inflammatory, Analgesic & Ophthalmologic Drug Products, Gastrointestinal and Coagulation Drug Products, and Neuropharmacological Drug Products. Of the requests going through CBER offices six went to Therapeutics Review & Research, one to Vaccines Review & Research, and one unknown (but presumably to therapeutics based on other information).

The phase of development during which respondents made their request for designation was close to evenly split as 55% were in Phase III or later and 45% were in Phase II or earlier. During the approximately one to two-year period from the time designation requests were made by sponsors (the first was in January 1998, the last was in September 1999) until the beginning of the survey in March 2000, 39% of respondents' products were still in the same phase of development. However, 61% of respondents' products had advanced in phase of development during the study period. In fact, five products were reported to be in the postmarketing period, and an additional four in the pre-NDA/BLA or NDA/BLA review phase, by the time they were surveyed. Another two respondents said they planned to file their NDA/BLA in 2000, another four in 2001, two more in 2002, and six did not provide a date.

As far as the number of person-hours required by sponsors to prepare the designation requests, 17 of 23 respondents provided numerical figures. Of these, 41% gave figures from 40 to 100 hours; another 35% stated that it was between 10 and 24 hours; and the remaining 24% put the figure between 1 and 5 hours. FDA had estimated that this process would require 40 to 80 hours per designation request (9). FDA based this estimate on its determination that a designation was required to identify the condition and need, provide a plausible basis for these assertions and plans for evaluation of the product's potential, and that submission documentation should not be voluminous (1).

The FDA guidance document states that FDA will respond to a request for fast track designation within 60 days of receipt of the request. The survey results indicated that

based on respondents' answers to questions related to the date of the request and the date the designation was granted, FDA fulfilled its obligation to sponsors 75% of the time. Because of possible discrepancies between FDA and sponsors as to which date constituted the actual date of the request (ie, date sent by sponsor or date stamped-in by FDA), any close calls were resolved in favor of the FDA. Regarding the 25% of designation requests requiring more than two months, the survey was not able to ascertain if these delays were due to deficiencies in the designation request, postponements due to dispute resolution, rejection and resubmission, or simply administrative processing delays.

As seen in Figure 3, the age range covered by the indications of survey respondents' products was almost evenly divided between adults with 20 indications and pediatric age groups with 21 indications. Since a single product may have indications for various age groups (categorized by the authors as: adult; adolescent; child; infant; and, neonate), these totals add up to more than the number of products with each product averaging nearly two age groups. In actuality, 12 products had only adult indications and 3 products had only pediatric indications, while 8 products covered both adult and pediatric age groups.

In addition, 13 sponsors were pursuing orphan designations for the same product/indication which had received the fast track designation. Of those 13 orphan designation requests, 5 were for products covering pediatric age groups.

Next, survey participants were queried about their use of particular fast track programs. Initially the focus was on FDA-sponsor conferences. These were described in the questionnaire as substantive preplanned "formal" meetings that are meant to have a significant impact on the development process, especially ones specified in the fast track guidance document: pre-IND conferences, end-of-Phase I (EOP 1) conferences, end-of-Phase II (EOP 2) conferences, pre-NDA/BLA conferences, and labeling conferences. The total number of FDA-sponsor conferences, or formal meetings, held at the critical

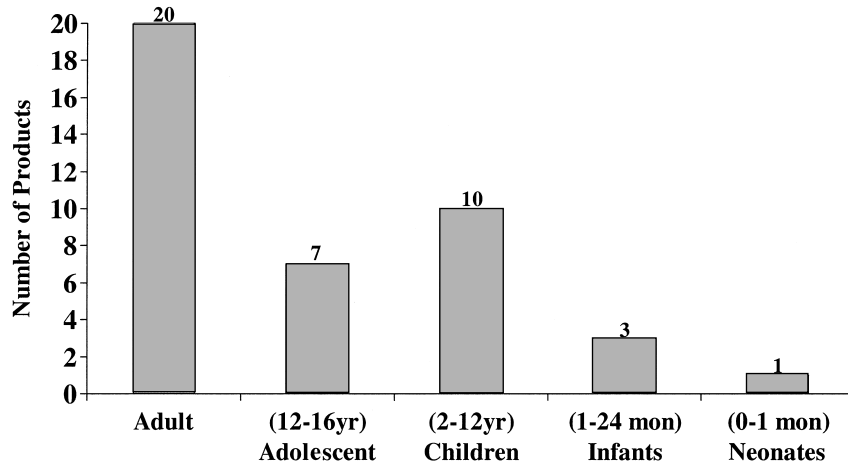


FIGURE 3. Age range of product indications.
 Source: Tufts Center for the Study of Drug Development 2000

development junctures recommended by FDA were as follows: 11 pre-IND meetings, 6 end-of-Phase I meetings, 16 end-of-Phase II meetings, 11 pre-NDA/BLA meetings, and 1 labeling meeting (Figure 4). In addition to these meetings at development junctures specifically mentioned in the guidance document, some sponsors held other formal meetings as well (ie, five meetings were categorized as “other” by survey respondents).

In addition to type of meeting, we also ascertained the number of formal meetings

per sponsor. The breakdown was as follows: six sponsors had one meeting; seven sponsors had two meetings; seven sponsors had three meetings, one sponsor had four meetings; and one sponsor had five meetings (Figure 5). Overall, at the point in the development of their product at which we surveyed them, the 23 respondents had held 50 formal meetings, with 16 respondents having conducted 2 or more formal meetings.

Another program benefit of fast track designation listed in the FDA guidance docu-

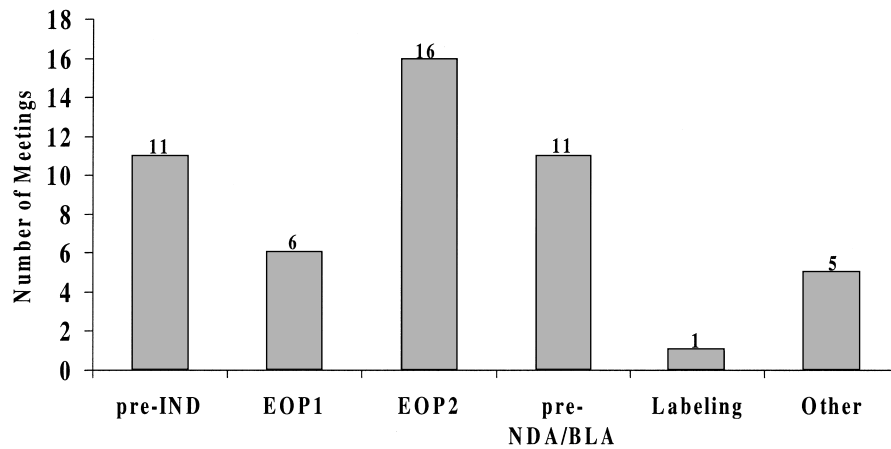
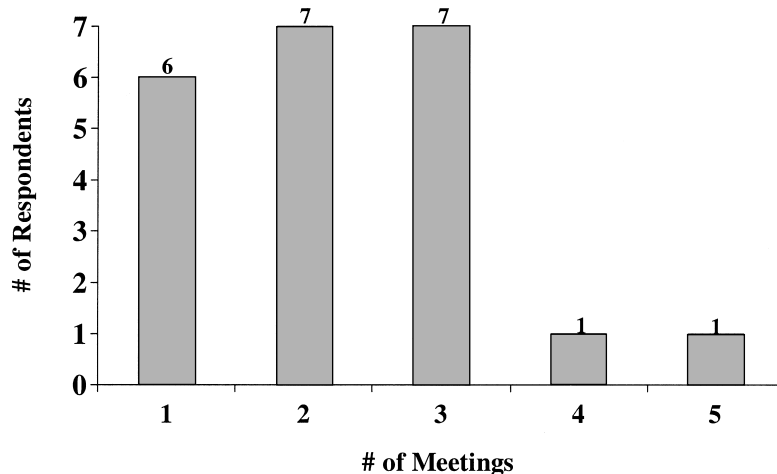


FIGURE 4. Number and type of formal meetings between FDA and survey respondents.
 Source: Tufts Center for the Study of Drug Development 2000



* One respondent reported no formal meetings

FIGURE 5. Use of formal meetings by survey respondents.
 Source: Tufts Center for the Study of Drug Development 2000

ment is written correspondence from FDA based on the outcome of the FDA-sponsor conferences as well as premeeting packages and other information provided to FDA by the sponsors. We queried survey participants about the responsiveness of FDA in providing timely comments (within 45 days) on principal trial design and adequacy of the Phase II/III development plans at the end of Phase I and/or end of Phase II. In addition, the guidance document notes that the outcome of the pre-NDA/BLA meeting should be agreement on a number of “critical issues” (1). One in particular which applied to all sponsors was agreement on the content and format of the NDA/BLA. This was selected by the authors to assess FDA responsiveness at pre-NDA/BLA meetings. Survey responses indicated that: 15 received timely comments on principal trial design; 2 received end-of-Phase I letters on adequacy of the development plan; 8 received end-of-Phase II letters on adequacy of the development plan; 11 achieved agreement on the content and format of their NDA/BLA; and 2 received none of these responses (Figure 6). Of these last two sponsors, one received fast track designation late in its development

process and had conducted only a pre-IND meeting, while the other sponsor was very early in its development process and had not had any meetings yet.

In addition to meetings, written correspondence, and dispute resolution, the other component of the fast track product designation program, according to FDA’s paradigm, is participation in fast track review programs. Participation by respondents in these review programs was as follows: 7 applications for accelerated approval, 11 applications for rolling submission, and 12 applications for priority review. In addition, 40% of respondents had participated in two or more of these review programs, 30% in just one review program, and 30% in none.

Next, respondents were asked to evaluate which programs they thought were responsible for the benefit derived from fast track designation. While 87% of respondents thought that FDA-sponsor conferences and the attendant written correspondence from FDA were responsible for most or some of the benefit (other choices were little benefit, no benefit, or not applicable), 52% responded that fast track designation itself was responsible for such benefit. Priority review, rolling

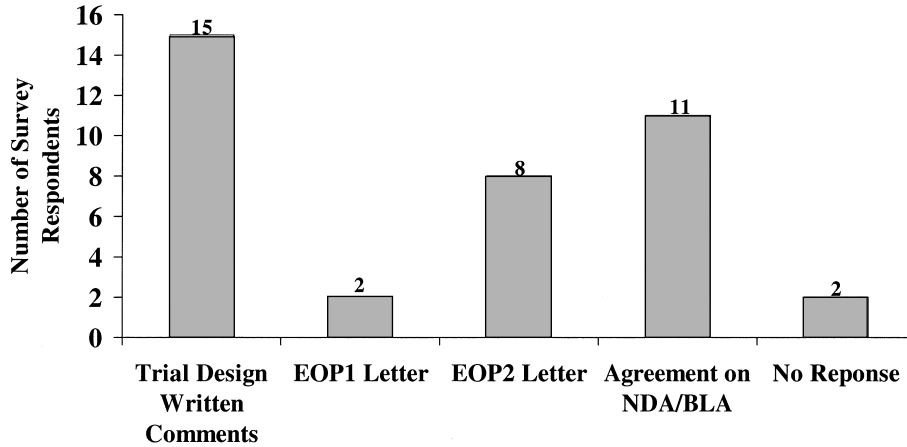


FIGURE 6. Number of survey respondents by type of written correspondence/agreement from formal meetings with FDA.
Source: Tufts Center for the Study of Drug Development 2000

submission, and accelerated approval were considered to provide most or some of the benefit from fast track designation 57%, 43%, and 39% of the time, respectively (Table 1).

Similarly, sponsors were asked to rate the operational factors responsible for any benefit from fast track designation (again, the five potential choices were most, some, little, or no benefit, and not applicable). In response to this question, 83% of sponsors identified increased interaction with FDA as the operational factor responsible for most or some of the benefit from fast track designation, while 61% said it was increased face-to-face contact with FDA. For 65%, most or some of the benefit was derived from positive publicity due to the designation announcement, and

for 57% it was attributable to the designation serving as an early indication of receiving priority review status. Additional operational factors, such as preparation for FDA-sponsor meetings, application of a flexible risk-benefit standard by FDA, and increased participation of patients, were considered to be responsible for most/some benefit only 39%, 26%, and 13% of the time, respectively (Table 2).

When survey participants were asked directly if the development of their product had benefited from participating in the fast track products designation program 39% of respondents said it was too early to tell; 9% said yes, to a large extent; 30% said yes, to

TABLE 1
Survey Respondents' Ratings of Program Effects

Meetings/correspondence	87%
Priority review	57%
Fast track designation	52%
Rolling submission	43%
Accelerated approval	39%

Source: Tufts Center for the Study of Drug Development 2000

TABLE 2
Survey Respondents' Ratings of Operational Factors

Interaction with FDA	83%
Publicity from designation	65%
Face-to-face contact	61%
Indication of priority review	57%
Preparation for meetings	39%
Flexible standard	26%
Participation of patients	13%

Source: Tufts Center for the Study of Drug Development 2000

some extent; 17% said yes, to a minimal extent; and 4% said no.

DISCUSSION

One of the primary goals of the fast track provision of FDAMA was to expand the scope of expedited review and approval programs beyond treatments for AIDS and cancer to any treatment for serious and life-threatening diseases (13). Before FDAMA, two-thirds of the fast-tracked products were treatments for AIDS/HIV and cancer, and only one-third were for all other diseases. Our review of the indications from the products in our survey sampling frame demonstrated a trend in the direction hoped for by Congress. Half of the indications were for AIDS/HIV and cancer, while the other half were for a variety of other diseases and conditions such as systemic lupus erythematosus, bypass surgery complications, hemolytic-uremic syndrome, sickle-cell anemia, Crohn's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, and pneumococcal lung disease.

Our study noted another signal that the scope of treatments for serious and life-threatening diseases is expanding under FDAMA. Biopharmaceutical development tends to be more focused on diseases and conditions with genetic and metabolic causes because they tend to be more amenable to macromolecular rather than small molecule processes. Thus, the fact that our survey results show that 35% of the respondents' products were reviewed by CBER suggests that a broader range of treatments for these diseases and conditions may soon be available.

The indication scope of the fast track program under FDAMA has expanded in another direction as well. Almost half of the surveyed products included pediatric groups among their indication age range. Fast track designation is also working synergistically with another program focused on meeting the needs of special populations as over half of the survey respondents were also pursuing designation of their products as an orphan drug, typically awarded for disease indica-

tions affecting subpopulations under 200000 patients.

Another goal of the legislation creating the new fast track designation was to build upon, and presumably improve, the existing FDA fast track programs (14). One way that this could occur would be through participation of sponsors early in the development process. Our survey results show a positive trend in that direction because close to half of survey respondents had requested designation during Phase II or earlier. This also belies some of the early criticism of fast track as benefitting only the late stages of development. Improving the program, of course, does not mean putting up additional roadblocks on the path to development and approval. Congress was mindful of this when it set a low threshold for eligibility with permissive criteria language such as "intended to treat" and "potential to address." FDA has conducted the program so far according to the spirit of the law. FDA requires that fast track designation requests contain a plausible demonstration of the products' potential and emphasizes that requests should not be voluminous (1). More than half of our survey respondents were able to prepare their requests in less than the time initially estimated by FDA. FDA has also been able to approve three-quarters of respondents' designation requests within two months.

Another way to assess whether fast track designation is an improvement upon the existing fast track programs is to gauge industry's response to the process. One finding that stands out from the survey results is that the interaction effects with FDA, which had been characterized early on as "soft benefits," seem to be important to industry after all. This interaction effect may be a significant improvement in the long run. As mentioned earlier, a study published by the Tufts CSDD of approved NCEs demonstrated that meetings were associated with decreased clinical development times. It also reported that pre-FDAMA fast track drug sponsors (Subpart E and accelerated approvals) had not taken advantage of the opportunity for increased interaction with FDA any more

than nonfast track sponsors despite the emphasis on increased sponsor-FDA consultation in the Subpart E regulations (8). When compared to this historical cohort, survey respondents had 1.5, 4, and 6 times as many meetings at critical clinical development junctures (pre-IND, Phase I, and Phase II). Even at the pre-NDA/BLA point there was almost parity despite the fact that only one-third of the products surveyed had reached the point of approaching FDA review (Figure 7).

Our survey indicates clearly that industry recognizes this consultation program as a benefit of fast track designation. Eighty-seven percent of respondents thought that meetings/written correspondence was the highest rated program, while 83% also said that interaction with FDA was the most highly rated operational factor. This benefit may become even more valuable in the near future as FDA's workload pressures continue to build, especially in the area of FDA-sponsor meetings. In 1999, CDER held 1200 meetings (15), and CBER had nearly 400 requests for Prescription Drug User Fee Act product meetings in fiscal year 1999 (12). Fast track designation may serve as a method

to prioritize sponsor access to FDA if demand for FDA consultations begins to exceed its capacity.

As far as the utility of the review programs within fast track designation, seven respondents were applying for accelerated approval. This is a large number since there were only 20 accelerated approvals in the six years before FDAMA (9). Also, one-half of the respondents were applying or planning to apply for rolling submission and/or priority review. This also indicates a high level of participation in these programs since only somewhat more than half of respondents were in the later phases of their development programs.

But as we have stated, these programs are by-and-large available outside of fast track designation. Is the designation itself considered valuable by industry and if so, why? Sixty-one percent of respondents reported fast track designation itself as being beneficial. Part of the answer may lie in the fact that 65% of respondents viewed positive publicity from the designation as very beneficial. Similarly, there were high ratings for the benefits attributed to FDA interaction (83%) and face-to-face contact (61%) as a result of designation.

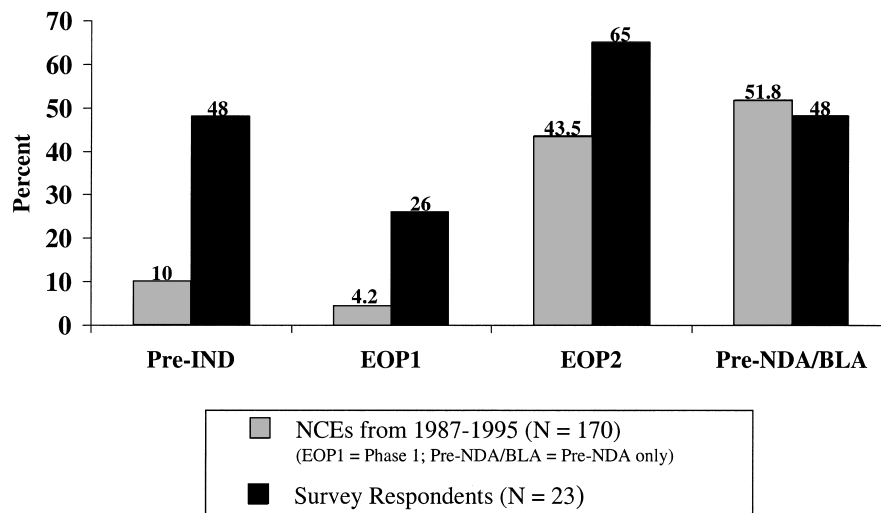


FIGURE 7. Survey respondents versus NCEs from 1987 to 1995 by percent of pre-IND, EOP1, EOP2, and pre-NDA/BLA meetings.
 Source: Tufts Center for the Study of Drug Development 2000

Another goal of the legislation was to expedite development and approval of treatments for serious and life-threatening diseases (13,14). This means faster drugs, but if fast track designation is to be an improvement, it also means better drugs. Thus, fast track designation must enhance speed without sacrificing safety. We know that the programs work. Fast track is fast! Of the 50 fastest approvals in the Tufts CSDD database of new drugs marketed from 1963 to 1999, 42 have occurred since 1988 when the first fast track program (Subpart E) became available. Of those 42 fastest approvals, 36% have had help from either Subpart E or accelerated approval programs.

Does faster mean riskier? A review of Tufts CSDD databases showed nine drug products withdrawn for safety reasons since late 1997: troglitazone, cisapride, grepafloxacin, bromfenac sodium, mibefradil, terfenadine, astemizole, fenfluramine, and dexfenfluramine. While six were approved after PDUFA went into effect, only one was a priority review drug, and none were accelerated approval or Subpart E drugs. Thus, only one of these nine drugs was the beneficiary of a program now associated with fast track designation.

Moreover, the benefits in the risk-benefit equation should not be overlooked! As fast track participation increases and implementation is effectively carried out, fast track drugs will benefit from shorter approval times. As public awareness of the program grows, recruitment for clinical trials will be enhanced, and clinical development time will decrease as well. Once the program is viewed as successful, it will be emulated by other countries, as was our orphan drug program, which will facilitate global registration of fast track drugs. These events, in turn, will attract investment and interest in the development of fast track drugs as well as increase the potential market at launch. The end result will be increased access to urgently needed drugs and hope to those who need it most.

Ultimately, a definitive answer to the question of whether fast track designation will be only as effective as the sum of its

parts or a significant improvement is not feasible so early in the designation program's history. On the one hand, preliminary answers to questions such as whether designation enhances speed of development or whether the development experience of designees is better than nondesignees utilizing only individual fast track programs may be available within the next year. Nearly half of survey respondents' products are likely to be approved by the end of 2000. On the other hand, it will be another few years before the safety and marketing history of designated products can be reliably evaluated. Yet, our survey results indicate that industry is cautiously optimistic about the program as about 40% viewed fast track designation favorably, 40% had a wait-and-see attitude, and less than 20% said the program had not benefited their product development.

There is good reason for such optimism. The signs are fairly favorable that FDAMA's fast track designation will go the pre-FDAMA fast track programs one better. In 1998 to 1999, five of the fast track designated products in our survey received marketing approval (including one supplemental approval) for the treatment of AIDS (two products), metastatic breast cancer, rheumatoid arthritis, and pneumococcal lung infection—diseases responsible for over 50000 deaths per year and tens of billions of dollars of health care expenditures. Four of those five fast track products would qualify for the 50 fastest approvals (11), and were available to patients on average almost 20 months sooner.

REFERENCES

1. Food and Drug Administration. *Guidance for Industry: Fast Track Drug Development Programs—designation, development, and application review*. Rockville, MD: Food & Drug Administration; September 1998.
2. Another view on industry response to fast track program. *US Regulatory Reporter*. 1998 Sep;15(3):1–2.
3. Drug industry has not yet embraced FDAMA's "Fast Track" program. *US Regulatory Reporter*. 1998 Aug; 15(2):1–3.
4. An interview with Director of the Division of Cardio-renal Drug Products Raymond Lipicky, M.D. *US Regulatory Reporter*. 1999 Oct;16(4):3–7.

5. PhRMA proposals for fast-track products. *Pharma Marketletter*. 1998 Apr 27;25(7):13.
6. Shulman SR, Brown JS. The Food and Drug Administration's early access and fast-track approval initiatives: how have they worked? *Food Drug Law J*. 1995;50(4):503–531.
7. Cocchetto DM, Jones DR. Faster access to drugs for serious or life-threatening illnesses through the use of the accelerated approval regulation in the United States. *Drug Inf J*. 1998;32(1):27–35.
8. DiMasi JA, Manocchia M. Initiatives to speed new drug development and regulatory review: the impact of FDA-sponsor conferences. *Drug Inf J*. 1997; 31(3):771–788.
9. Food and Drug Administration. *Supporting statement for guidance for industry: fast track drug development programs designation, development, and application review* (OMB No. 0910–0389). Rockville, MD: Food & Drug Administration; 1998.
10. Behrman RE. "Fast Track." Presented at the Drug Information Association Annual Meeting, June 29, 1999, Baltimore, MD.
11. Parexel. An analysis of the FDA's fast track initiative, March 2000. *Parexel's pharmaceutical R&D statistical sourcebook 2000*. Waltham, MA: Parexel; 2000: 232.
12. Risso ST. *Fast track and priority review from the FDA perspective*. <http://www.fda.gov/cber/gdlns/fsttrk.pdf>.
13. Senate Committee on Labor and Human Resources. *Food and Drug Administration Modernization and Accountability Act of 1997 Senate Report 107–43, to accompany S830*. 105th Congress 1st Session. Washington, DC: US Government Printing Office; 1997.
14. House Committee on Commerce. *Prescription Drug User Fee Reauthorization and Drug Regulatory Modernization Act of 1997. House Report 105–310, to accompany HR 1411*. 105th Congress 1st Session. Washington, DC: US Government Printing Office; 1997.
15. Lumpkin MM. The ABC's of interaction with the FDA. Presented at Postgraduate Course in Clinical Pharmacology, Drug Development, and Regulation, Boston, Tufts Center for the Study of Drug Development, February 18, 2000.

