

## FROM THE ANALYST'S COUCH

## The Fast Track Effect

Fredric J. Cohen

The US FDA's Fast Track programme was designed to expedite drug development and approvals to address important unmet medical needs. There is now evidence, as delineated recently by the Tufts Center for Drug Development, that in this regard the programme has been a tremendous success, trimming total development time by nearly three years<sup>1</sup>. On the other hand, there is no language in the Fast Track provision to suggest that the FDA considers the likelihood of a programme's success when determining its suitability for Fast Track designation. However, many investors seem to believe that this is the case.

The Food and Drug Modernization Act of 1997 (FDAMA) codified existing FDA procedures and policies for facilitating drug development and expediting the approval of drugs that address serious or life-threatening unmet medical needs. A drug development programme (that is, a drug plus one specific indication) can be designated as Fast Track anytime after submission of an Investigational New Drug Application

(IND), although sponsors potentially receive more benefits the earlier in development the designation is made.

As was anticipated when FDAMA was first proposed, investors and traders seem to react to news of a Fast Track designation by bidding stocks higher. Of potentially greater interest to long-term investors are the motivations underlying short-term stock movements. There are several possibilities for the 'Fast Track effect', one of which is that some investors regard the designation as an endorsement of a drug programme by the FDA.

#### Special treatment

Several FDA procedures that are potentially available to all programmes are routinely made available to Fast Track programmes. These procedures include meetings, written correspondence, accelerated approval, rolling submission, priority review and dispute resolution. FDA meetings typically occur pre-IND, after Phase 1 and 2 trials, and before a New Drug Application (NDA) or Biologics License Application (BLA) submission. Fast Track provides for receipt and potentially review of an NDA/BLA in parts. For NDA/BLA filings granted priority review, the FDA sets a target date of six months (rather than ten) to reach a decision [AU:OK?] on the filing. At the FDA's Center for Drug Evaluation and Research (CDER), priority review is reserved for products that "provide a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease", whereas the Center for Biologics Evaluation and Research (CBER) requires that drugs also address serious or life-threatening diseases. Finally, dispute resolution provides an opportunity for decision appeals at the Division level and a level beyond if needed.

#### Does Fast Track predict approval?

The Fast Track programme began in March 1998. Between 1 January 1998 and 1 January 2004, 190 New Molecular Entity (NME) NDAs (163 non-Fast Track and 27 Fast Track) were submitted to CDER for marketing approval. A total of 130 (80%) non-Fast Track NME NDAs have so far been approved. Of the 26 Fast Track NME NDAs submitted,

Credit

21 (78%) have been approved (FIG. 1) [AU: Correct place to cite?]. Therefore, it seems that the approval rates for Fast Track and non-Fast Track NMEs that reached the stage of NDA filing during this period are comparable. What about those programmes that never advanced to an NDA filing? This is difficult to ascertain precisely without following a cohort of programmes from their IND filing through to their eventual NDA filing or demise. More experience with Fast Track is needed to answer the question definitively. However, because the IND filing rate has been relatively stable since the latter half of the 1990s, we can use the ratio of IND filings to NDA filings to approximate the development attrition rate of a group of programmes starting at about the same life cycle stage. From 1998 through 2003, CDER received 2,641 commercial INDs, and 702 NDAs, or 3.8 INDs for each NDA. As mentioned above, during the same period, CDER granted 157 fast track requests and had received NDAs from 24 programmes, or 6.5 designated programmes for each NDA. Viewed this way, Fast Track designation seems to be associated with higher attrition before NDA filing. This observation, if corroborated by additional data, could mean that Fast Track programmes destined to fail will fail earlier in development with the help of more frequent FDA-sponsor interactions.

#### Conclusions

Fast Track designation might be a signal to some investors that a drug programme has been 'blessed' by the FDA. They might then equate this blessing with a higher likelihood of approval. But drug approval data do not support this contention. Fast Track moves drugs along faster, perhaps even helping doomed drugs fail earlier in their life cycle, but it does not seem to herald eventual approval. Nevertheless, on the basis of data described here, there is no doubt that Fast Track announcements correlate with very short-term stock price appreciation, and that lesser-valued companies benefit relatively more. Small companies should use care when promoting the value of a Fast Track designation to avoid creating unrealistic investor expectations, which could be bad for the company in the long run. ▶

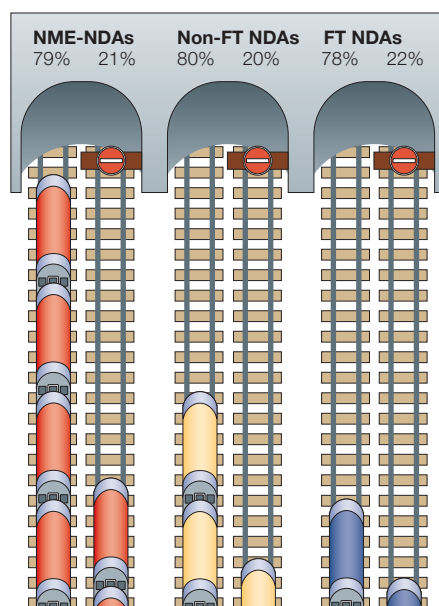


Figure 1 | Fate of NME NDAs by Fast Track status 1998-2003. Each pair of trains represents an NME NDA type. Approved NDAs are shown on the left; NDAs not approved on the right. Length of train represents number of NDAs. NDA, New Drug Application; NME, New Molecular Entity.

THE FAST TRACK EFFECT | MARKET INDICATORS

Publicly traded US pharmaceutical companies that announce the Fast Track status of their programmes witness acute increases in their stock valuations. This acute bump in valuation is referred to as the 'Fast Track effect' (FIG. 2). Although stocks of the relatively small companies (FIG. 3) that have recently made a Fast Track announcement do appreciate acutely (often with just a single-day spike), they actually performed somewhat better, on average, in the period leading up to their announcements than afterwards, suggesting that optimal returns come from identifying promising development programmes early. TABLE 1 highlights recent Fast Track NDAs.

*Fredric J. Cohen, M.D., is President and Senior Analyst at independent healthcare research and consulting firm Crownstone, 3331 Street Road, Suite 140, Bensalem, Pennsylvania, USA. e-mail: fred@crowstonegroup.com*

doi:10.1038/nrd1349

1. FDA's Fast Track Initiative Cut Total Drug Development Time by Three Years, According to Tufts CSDD. Tuft's Center for the Study of Drug Development website [online] (cited 17.03.2004) <http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=34> (2003).
2. All data on drug submission and approvals can be found on the FDA's web site at <http://www.fda.gov>.

**Online links**

**FURTHER INFORMATION**

Rules, regulations, policies and procedures in detail: FDA Guidance Document for Fast Track Products: <http://www.fda.gov/cder/guidance/2112fnl.pdf>  
**Section 112 of the Food and Drug Modernization Act of 1997:** <http://www.fda.gov/cder/guidance/105-115.htm#SEC.%20112>  
**Access to this interactive links box is free online.**

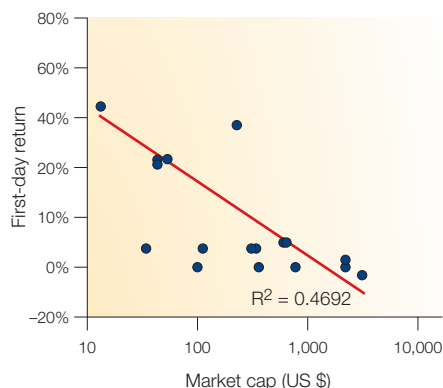


Figure 3 | **Relationship between Fast Track effect and market capitalization.** Data shown are from companies in FIG. 2, excluding two large outliers (Intrabiotics: one-day return 111%; and Genentech: market cap ~38B); market cap as of close prior to Fast Track announcement. An  $R^2$  of 0.47 indicates that roughly 47% of the variation in one-day price appreciation can be explained by the market cap of the company alone. There was a strong relationship between market cap and the Fast Track effect, with greater price appreciation among lesser valued companies. All companies are micro- or small-cap. Source: Crownstone Research.

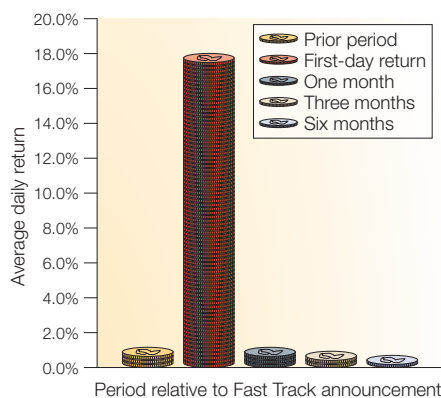


Figure 2 | **The Fast Track effect.** Shown is the acute effect of Fast Track announcement on stock price among US-based companies: APHT, CELG (2), DNA, DNDN, GNTA, HGSI, IBPI, ILXO, INGN, MLNM, OXGN, PARS, PCYC, SNUS, SPPI, SUPG, TELK, TLRK, TNOX, VXGN. Prior period is from open 27 January 27 2003 to close on the last trading day prior to announcement. First-day return is from close prior to announcement to close after it. The one-, three- and six-month periods are from close prior to announcement to respective closes after. Average daily return in the prior period was  $0.684\% \pm 1.40\%$  versus average first-day return of  $19.0\% \pm 29.4\%$  ( $p = 0.008$ ). There was no difference between prior period average daily return and one-, three- or six-month returns. Source: Crownstone Research.

Table 1 | **Fast Track NME NDAs until 31 December 2003\***

Drug name	Sponsor	Approval date	Indication
Efavirenz (Sustiva)	Dupont	17.9.1998	HIV
Abacavir sulphate (Ziagen tablets/oral solution)	Glaxo Wellcome	17.12.1998	HIV
Amprenavir (Agenerase capsules/oral solution)	Glaxo Wellcome	15.4.1999	HIV
Docetaxel (Taxotere)	Aventis	23.12.1999	Locally advanced or metastatic NSCLC
Lopinavir (Kaletra oral solution/capsule)	Abbott Labs	15.9.2000	HIV
Arsenic Trioxide (Trisenox)	Cell Therapeutics	25.9.2000	Acute promyelocytic leukaemia
Caspofungin acetate (Cancidas) [AU: OK?]	Merck	26.1.2001	<i>Aspergillus</i> infections
Imatinib mesylate (Gleevec capsule)	Novartis	10.5.2001	Chronic myeloid leukaemia
Tenofovir disoproxil fumarate (Viread)	Gilead	26.10.2001	Treatment of HIV
Nitisinone (Orfadin)	R and R Registration	18.1.2002	Hereditary tyrosinaemia type I
Oxaliplatin (Eloxatin)	Sanofi- Synthelabo	9.8.2002	Colorectal cancer
Anastrozole (Arimidex)	AstraZeneca	5.9.2002	Adjuvant treatment of early breast cancer in post-menopausal women
Enfuvirtide (Fuzeon)	Hoffmann LaRoche	13.3.2003	HIV
Pegvisomant (Somavert)	Pharmacia & Upjohn	25.3.2003	Acromegaly
Gefitinib (Iressa)	AstraZeneca	5.5.2003	NSCLC
Bortezomib (Velcade)	Millennium	13.5.2003	Relapsed/refractory multiple myeloma
Emtricitabine (Emtriva)	Gilead	2.7.2003	HIV
Miglustat (Zavesca)	Actelion	31.7.2003	Type I Gaucher disease
Prasterone, DHEA (Prestara)	Genelabs	Not applicable	Corticosteroid-induced bone loss in women treated for SLE
Oblimersen (Genasense)	Genta	Not applicable	Combination with dacarbazine for advanced melanoma
Ista (Vitraxe)	Ista	Not applicable	Vitreous haemorrhage
Azacitidine (Vidaza)	Pharmion	Not applicable	Myelodysplastic syndrome
G17DT (Gastrimmune)	Aphton	Not applicable	Advanced pancreatic cancer
Exisulind (Aptosyn)	Cell Pathways	Not applicable	Familial adenomatous polyposis coli

\*Sources: FDA and Crownstone Research. Ziagen, Agenerase, and Kaletra were each counted twice owing to approval of separate NDAs for each formulation. DHEA, dehydroepiandrosteron [AU: OK?]; HIV, human immunodeficiency virus; NSCLC, non-small-cell lung cancer; SLE, systemic lupus erythmatosus [AU: OK?].