

# Expedited drug review process: Fast, but flawed

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“I don’t believe medical discoveries are doing much to advance human life. As, fast as we find ways to extend it we are inventing ways to shorten it.”

-Christiaan Barnard.

Many drugs that are relatively new to the market their way out as fast as they entered it.

Is expediting drug discovery really solving the unmet needs of society?

## WHAT IS “FAST TRACK” AND WHY WAS IT INTRODUCED?

The United States Food and Drug Administration (US-FDA) defines Fast Track as a process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need. Filling an unmet medical need is further defined as providing a therapy where none exists or providing a therapy which may be potentially superior to existing therapy. This was introduced to curtail the duration in drug regulation and approval process, and to facilitate the discovery and marketing of drugs targeted for serious or rare diseases and to accelerate the approval of molecules showing superior efficacy than the existing one. Fast-track approach was introduced in 1988; a sponsor can apply for fast-track drug approval process along with investigational new drug application. The FDA conveys the decision within sixty calendar days to the sponsor about fast-track consideration. When a drug is accredited with the fast-track process, it enables investigators to work along with FDA to conduct the trial and to submit the relevant data. The FDA can approve the drug under fast-track designation after reviewing a single phase 2 study.<sup>[1]</sup>

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## FAST-TRACK STATISTICS AND OTHER EXPEDITED DRUG REVIEW PROCESS

In 1992, the FDA introduced two more drug review processes, namely, “Priority Review” by which a drug review process will be completed within 6 months against the 10 months of the standard review schedule and “Accelerated Approval” of a drug or biologics based on its efficacy shown by surrogate markers. Most of the drugs considered under fast-track process may also be considered under priority review and accelerated approval. According to FDA archival, efavirenz, the anti-HIV drug was the first accepted fast-track product on September 17, 1998. Until now, 147 drugs or biologics have been approved as fast-track products. The approval trend has shown steady increase since 1998 as depicted in Table 1. The number of products utilizing the expedited review processes is about 543. These products undergo scrutiny by the Centre for Drug Evaluation and Research or Centre for Biologics Evaluation and Research before obtaining marketing authorization.<sup>[2]</sup>

## EXPERIENCE FROM THE PAST

Careful interpretation of the preclinical and clinical studies performed for a drug is very crucial. The best example is the thalidomide tragedy in Europe. The drug was not marketed in the USA only because a single drug controller with the US-FDA, Dr. Frances Kelsey, raised concerns regarding the insufficient safety data and risk of peripheral neuropathy. This decision prevented children with phocomelia due to thalidomide being born in the United States. Later, experimental findings provided the scientific basis for the revival of thalidomide based on its immunomodulatory effects and ability to inhibit angiogenesis. In 2006, FDA approved thalidomide for erythema nodosum leprosum and multiple myeloma.

Although fast-track processing of drugs facilitates earlier access of drugs that are urgently needed by society, it also may undermine safety. From 1988 to 2010, some of the fast-track products have gone unpredicted and withdrawn

which is mentioned in Table 2. Increased cardiovascular events from selective cox-2 inhibitors valdecoxib and rofecoxib, rapacuronium-induced bronchospasm, alosetron-induced ischemic colitis, hepatotoxicity from cerivastatin, and troglitazone were grievous. Lack of efficacy is also exemplified from some fast-track products such as drotrecogin alfa, mibefradil, moxalactam, and cefonicid.<sup>[3]</sup>

## CURRENT SCENARIO

### Is it too fast and furious?

There are critics that FDA is liberal and approve the molecules in an accelerated way based on trivial information submitted by marketing authorities. The critic is evidenced by the annual report of FDA approval of 35 new chemical entities in 2011; the review was completed in an average of 8.2 months will make us frown surprisingly. Despite the critics, FDA approved 41 novel compounds in 2014 (15 fast-track products) and 45 novel compounds (14 fast-track products) in 2015.<sup>[4]</sup>

Dabigatran, an oral direct thrombin inhibitor developed by Boehringer Ingelheim, was projected as superior as conventional warfarin and awarded fast-track process. The FDA reviewed and approved the molecules within 6 months on October 19, 2010. FDA justified for producing fast-track status stating dabigatran is safe and hence monitoring can be omitted, unlike warfarin. This justification is nullified by postmarketing surveillance, which revealed increased gastrointestinal bleeding by dabigatran and safety alert announced by May 13, 2014.<sup>[5]</sup> The same pharmaceutical Boehringer Ingelheim is now

marketing Idarucizumab as an antidote for dabigatran-induced bleeding in 2015. Dabigatran and its antidote are neither cost-effective nor safer than warfarin and its antidote, Vitamin K. Developing and marketing a new molecule out of weak hypothesis and then inventing an antidote by the same pharmaceutical company within 4 years support the pitfalls of inadequate review time and process by FDA.

Ezogabine, a potassium channel blocker, was approved under expedited program for partial seizure has shown severe retinal damage and loss of vision in postmarketing evaluation.<sup>[6]</sup> Similarly, chronic myeloid leukemia is treated by imatinib and two more molecules, namely, dasatinib and nilotinib in imatinib resistance cases with very high success rate. For the same indication, ponatinib was granted fast-track status and was approved by the FDA on December 2012. Widespread exposure of ponatinib unmasked its propensity to cause fatal veno-occlusive disease and it was withdrawn in the span of 11 months in October 2013. It is totally unconvincing to expose patients to a dangerous molecule arose out of reluctant interpretation of a single Phase II trial.<sup>[7]</sup>

### Is it going on right track?

Most of the drugs for hepatitis C underwent a fast-track process and were approved based on viral load reduction. These molecules produced severe acute liver injury among recipients. Ombitasvir, paritaprevir, and dasabuvir were approved on December 19, 2014, and on January 15, 2016, FDA issued warning of severe hepatic decompensation. Other approved anti-hepatitis C drugs simeprevir and sofosbuvir are also proven to be hepatotoxic. This is justifiable on medical grounds since no specific anti-hepatitis C drugs are available, yet assessing these drugs with greater number of patients might have predicted the toxicity. For diabetes mellitus, two group of drugs, namely, dipeptidyl peptidase-IV (DPP-IV) inhibitors saxagliptin (2009), linagliptin (2011), alogliptin (2013), and sodium glucose co-transporter 2 (SGLT2) inhibitors canagliflozin (2013), dapagliflozin (2014), and empagliflozin (2014) were granted fast-track approval and subsequently marketed worldwide. DPP-IV inhibitors were implicated in severe mouth ulcers, renal impairment, and angioedema. SGLT2 inhibitors are known to precipitate ketoacidosis and urosepsis. Presently, the risk-benefit assessment of almost all DPP-IV inhibitors and SGLT2 inhibitors is being reworked.<sup>[8-11]</sup>

### Is it leading to unpredictable journey?

Pharmacological effects of cytokine analogues and immunomodulators are complex and underexplored. Assessing the effects of biologics through fast-track processing seems incongruous. All the tumor necrosis factor-alpha (TNF- $\alpha$ ) blockers introduced for several autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease (IBD), and relapsing multiple sclerosis produce serious adverse effects. TNF- $\alpha$  analogs have been shown to induce

**Table 1: Fast-track designation products statistics since inception**

Years	Number of drugs approved under fast-track process (n=147) (%)
1998-2000	010 (6.8)
2001-2003	013 (8.8)
2004-2006	028 (19.0)
2007-2009	029 (19.7)
2010-2012	026 (17.6)
2013-2015	041 (27.89)

**Table 2: Fast-track designation products withdrawn from the market**

Drug/biologics	Category	Reason for withdrawn
Valdecoxib, rofecoxib	Selective cox-2 inhibitor	Increased cardiovascular events
Rapacuronium	Skeletal muscle relaxant	Bronchospasm and death
Troglitazone	Oral hypoglycemic	Hepatotoxicity
Cerivastatin	Hypolipidemic	Hepatotoxicity
Drotrecogin alfa	Anti-inflammatory	Lack of efficacy
Mibefradil	Anti-anginal drug	Lack of efficacy
Cefonicid, Moxalactam	Cephalosporins	Lack of efficacy

**Table 3: Fast-track designation products received potential adverse effects alert during 2011-2015**

Drug/biologics	Category	Adverse event reported
Ponatinib	Tyrosine kinase inhibitor	Veno-occlusive disease, withdrawn from market
Dabigatran	Factor Xa inhibitor	Bleeding events including hemorrhage with fatal outcome
Cangrelor, anagrelide vorapaxar	Antiplatelet	Increased bleeding Failed to exhibit superior efficacy
Linagliptin, saxagliptin, alogliptin	Dipeptidyl peptidase IV inhibitor	Renal failure, mouth ulceration
Dapagliflozin, canagliflozin empagliflozin	Sodium glucose lumen transport 2 inhibitors	Precipitation of ketoacidosis Urosepsis, stroke
Lacosamide	Sodium channel blocker	Neutropenia Toxic epidermal necrolysis
Roflumilast	Phosphodiesterase 3 inhibitor	Gynecomastia
Lomitapide	Hypolipidemic	Severe diarrhea
Sofosbuvir, simeprevir	Anti-hepatitis C	Cardiac arrhythmia, bradycardia
Pazopanib	Tyrosine kinase inhibitor	Interstitial lung disease
Dasabuvir, telaprevir, ombitasvir, paritaprevir	Anti-hepatitis C	Hepatic failure, hypersensitivity
Vemurafenib	Tyrosine kinase inhibitor	Serious skin reactions including drug reaction with eosinophilia and systemic symptoms Hepatitis B reactivation
Ofatumumab	Anti-CD 20	
Everolimus	mTOR inhibitor	
Dimethyl fumarate	Anti-integrin	Progressive multifocal leukoencephalopathy
Natalizumab	Anti-integrin	
Brentuximab vedotin	Anti-CD 30	
Fingolimod	Immunomodulator	Hemophagocytic syndrome
Dronedarone	Antiarrhythmic	Pulmonary toxicity
Ezogabine	Antiepileptic	Vision loss
Pomalidomide	Immunomodulator	Hepatotoxicity
Pegloticase	Recombinant urate oxidase	Anaphylaxis and infusion reactions
Methylalaltrexone	Opioid antagonist	GI perforation
Asenapine	Atypical antipsychotic	Severe hypersensitivity reaction
Peginesatide	Erythropoietin stimulator	Severe hypersensitivity, withdrawn from market
Infliximab, adalimumab, golimumab, cetuximab, etanercept	TNF-alpha blockers	Optic neuritis Drug-induced sarcoidosis Reactivation of tuberculosis
Rabeprazole, dextansoprazole	Proton pump inhibitor	Hypomagnesemia, renal failure
Olmesartan	Angiotensin receptor antagonist	Drug-induced enteropathy
Sorafenib, sunitinib	Tyrosine kinase inhibitor	Hepatic and renal failure
Vanecilline	Nicotine receptor antagonist	Suicidal ideation, seizures
Tolvaptan	Vasopressin antagonist	Hypersensitivity
Dalfampridine	Potassium channel blocker	Seizures, arrhythmias
Ado-trastuzumab	HER2/neu antibody	Cardiotoxicity, pancreatitis Neonatal pulmonary hypoplasia
Efavirenz	Anti-HIV	Birth defects involving the face
Bevacizumabs	Anti-VEGF	Osteonecrosis of jaw, Hypertension Colon perforation

VEGF=Vascular endothelial growth factor, mTOR=Mammalian target of rapamycin, HER2=Human epidermal growth factor receptor 2, TNF=Tumor necrosis factor, GI=Gastrointestinal

sarcoidosis and found to induce hepatosplenic lymphoma.<sup>[12]</sup> Anti-integrin molecule natalizumab used in IBD has been implicated in the development of fatal progressive multifocal leukoencephalopathy and fingolimod produces a rare disorder called hemophagocytic syndrome.<sup>[13,14]</sup> There is enough evidence to alert us that biologics should have longer review time to predict their complex biological effects. Expedited approval may cure an autoimmune disorder and incite another one.

### Is it leading to a blind end?

Anticancer drugs and biologics are being approved based on its effect on surrogate markers of a particular cancer. In reality, the significance in terms of regression or preventing the progression is inconspicuous,<sup>[15,16]</sup> and hence, adding a new drug or biologics may not actually benefit the patients. The classical example is vemurafenib, approved for advanced melanoma on the basis of increased survival of patients on vemurafenib versus dacarbazine. The median survival

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increased by about 3.5 months only between the two groups which may gain statistical significance, but not in terms of quality of life. Adding to unclear benefits, vemurafenib has a potential to induce squamous cell carcinoma among receivers.<sup>[17-20]</sup>

### Is it an effective track or deceptive?

Fast-track processing gave an edge in the 1990s to combat HIV, AIDS, and certain malignancies. Some of the drugs that were developed as fast products such as lamivudine, imatinib, erlotinib, oxaliplatin, and levofloxacin are used extensively even today. At present, fast-track processing should be restricted only to instances when the need for the drug is very crucial. The manner in which these drugs are proven as “non-inferior” to the standard treatment also needs to be modified. New, noninferior molecules may have adverse effects and are usually costlier.<sup>[19,20]</sup> In the last 5 years, nearly 57% fast-track molecules received a black box warning. Summary of all significant adverse events alerts is shown in Table 3.<sup>[21]</sup> The most recent issue which prompted this editorial is the fast-track antiplatelet product called cangrelor, which was approved as an adjunct in percutaneous intervention. This drug has shown no additional benefits in trials comparing cangrelor and clopidogrel except for increased bleeding during the procedure.<sup>[22,23]</sup>

## CONCLUSION

Fast-track processing will be more effective: (1) When the developing molecule is really expected to treat a disease with no cure. (2) When there is an existing therapy, a new drug or biologic of novel mechanism can be approved by fast-track process. However, the other members of the same group should be considered for fast-track approval only after sufficient postmarketing surveillance supporting the efficacy and safety of the new compound. (3) Approval based only on surrogate markers should be reconsidered. (4) In malignancies with very poor prognosis, the statistical significance of an increase in survival from a fast-track process must be matched with clinical benefits. (5) Regulatory authorities should be more vigilant about undue or fallacious evidence-based information by pharmaceuticals.<sup>[24-27]</sup>

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