The Impact of FDA Priority, Accelerated, and Fast-Track Reviews on Approval Times and Postapproval Regulatory Activity

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Abstract

Objective: To assess the recent post-approval history of drugs approved by the Food and Drug Administration (FDA) using traditional or accelerated processes and to evaluate relevant differences between the two methods to determine if the results can inform new drug development paradigms.
Methods: Drugs granted FDA approval via standard, priority, accelerated or fast-track processes between the period of 2005-2008 were compared for: approval method, time from new drug application (NDA) submission to approval, type of risk evaluation and mitigation strategies (REMS), post-market commitment types, safety advisories and changes in indications. Accelerated approvals were compared with standards.
Results: 99 drugs were approved in the specified time period with 15 classified as accelerated. Accelerated products were: approved faster vs regular processes; had higher rate of added/expanded indications; had slightly more safety updates, which were added at similar times; and had similar REMS requirements. Accelerated approval agents were also found to belong to a relatively limited number of therapeutic classes compared with standards.
Conclusion: There were no material differences observed in the post-approval history of products undergoing standard or accelerated review by the FDA. Faster approval of accelerated drugs typically with more limited clinical experience does not appear to affect their post-approval regulatory activity in a manner different from standard approvals, and appears to be appropriate for initial indications of limited use. Extension of the accelerated approval process to the broader cohort of all drug submissions could therefore be considered as an option for a new drug development and approval paradigm.

Introduction

Initiated in 1992, the US FDA's Accelerated Approval process was designed to speed up approval of new agents for life-threatening diseases by using surrogate endpoints to assess safety and efficacy. Although originally designed to improve therapeutic options for HIV patients, accelerated approval was later adapted to antineoplastics. The process remains popular, with several new drugs approved via accelerated routes every year.

However, the characteristics that contributed to the success of the accelerated approval paradigm have become targets for its critique. Concerns over safety and efficacy of the agents approved based on surrogate endpoints were raised by the media and scientific community. In addition, some experts contend that accelerated approval does not result in faster review times, which defeats the purpose of the process.[1] Several large reviews comparing new molecular entities (NMEs) approved through standard and accelerated processes have been completed. Most note faster approval times and comparable safety/efficacy profile for agents approved through accelerated paradigm.[2-4] All agree on the importance of post-approval confirmatory studies and the use of well-validated surrogate endpoints.

The focus of our study was thus two-fold; to discover and characterize the relevant differences in the two approval methods; to determine whether the differences seen with the accelerated paradigm contributes value based on the speed of drug approval, level of safety, and continuing studies of the newly approved agent. These findings could inform new approaches to accelerated drug development paradigms.

Background

Accelerated approval process: designed to speed up commercial availability of agents for serious or life-threatening diseases by allowing sponsors to submit clinical trials based on surrogate endpoints, provided that the clinical studies confirming efficacy are either already underway or are planned to be carried out soon after the medicine's approval.[5]

Fast-track process: designed to facilitate the development and expedite the review of drugs to treat serious diseases **and** fill an unmet medical need, addressing a broad range of serious diseases. Most are eligible to receive a *Priority Review*. Fast-track designation is initiated by the sponsor at any time during development. FDA decides within sixty days whether the drug fills an unmet medical need in a serious disease. Early and frequent communication between the FDA and the sponsor is encouraged to ensure that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients.

Whether this process could adequately characterize efficacy and especially safety concerns was among the major discussion points for the opponents of accelerated approval. News stories examining the regulatory actions against midodrine (Amatine) and gefitinib (Iressa) focused on the limited amount of pre-approval research and the inability or unwillingness of the sponsors to complete confirmatory post-approval studies, citing these as major limitations. Some studies noted the need for more comprehensive post-approval research and better methods of enforcing completion of confirmatory studies.

A recent study on medicines that went through the Conditional Approval process (a European version of Accelerated Approval) between 1999 and 2009 noted that rates of added warnings were no higher for conditional versus standard approval agents, demonstrating that this accelerated approval process resulted in faster access to medicines that are of comparable safety to their standard counterparts.[3]

For the agents approved through the accelerated process between 1992 and 2010, mean approval time was significantly shorter than for their standard counterparts.[4] Therefore, we investigated the timing of approval and the post-approval characteristics of these review processes.

Methods

A listing of approved products with their dossier submission and approval dates was obtained from CIRS (London, England). Detailed data regarding the approval and post-approval history for each product were obtained from the FDA website and MedWatch websites, and other publicly available resources.

The period 2005 to 2008 was chosen to ensure that the products approved during this timeframe spent sufficient time on the market for relevant analyses. We focused on NME agents because we believed that inclusion of previously approved substances receiving new indications would bias the results against the accelerated approval, due to greater availability of safety and efficacy data for these agents.

Products that underwent standard and accelerated approval processes were evaluated for the following parameters, selected because they appeared to best address the inherent questions of the accelerated approval debate:

- Time to approval: calculated starting from NDA submission
- Time to new indication (defined as addition of new therapeutic targets, dosage forms, or packaging, excluding formulation changes) and post-marketing commitment information: used to evaluate the possible life cycle management benefits of the two approval paradigms
- Time to first post-approval safety update or Black Box warning: used to evaluate whether drugs approved through the accelerated process were of comparable safety to their standard approval counterparts
- Number and types of post-marketing commitments (PCMs): were split into "clinical", "non-clinical", and "other" categories and analyzed based on the number and overall balance of commitments. "Other" commitments included those that were redacted, did not fit either clinical or non-clinical definition, or fit both definitions at the same time

Drugs were also compared by intended therapeutic use, using the anatomical therapeutic chemical (ATC) classification system. Given the small sample set, comparisons were done by direct comparison of mean values and standard deviations.

Results

Figure 1. Agents analyzed by approval paradigm

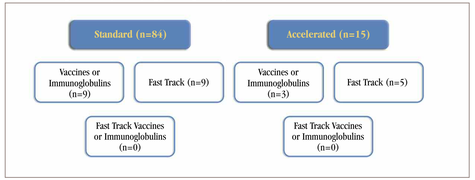

Figure 2. Comparison of time to approval

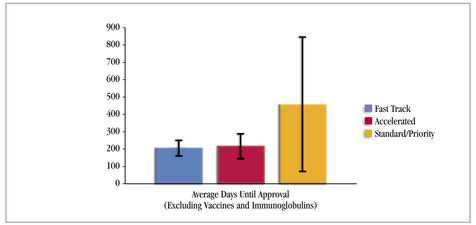

Table 1. Incidence of indications added or removed

	No. of Products With at Least 1 Indication Added (%) [total no. of new indications]	Mean Time to 1st New Indication from Approval Date (Days)	
		All Products	Vaccines or Immunoglobulins
Standard Review (n=84)	17 (20%) [24]	916	980
Accelerated Review (n=15)	7 (47%) [10]	1030	1510

Of the fast-track designated agents, 3 of 9 standard approval agents and 2 of 5 accelerated agents had at least one indication added, with the respective times to indication of 644 and 1217 days.

No indications were removed for any products in the subset we examined.

Number and types of REMS and post-marketing commitments (PMCs)

Three accelerated approval and 19 standard approval agents (20% and 23%, respectively) had some type of REMS requirements applied. Therapeutic areas for which REMS were required were not similar among the two approval paradigms. Antineoplastic agents had the most (2 out of 3) REMS requirements among the accelerated approval agents, while immunologic (8), CNS (4), and anti-diabetes (3) agents predominated among standard approval substances.

All accelerated approval agents and 73 of 84 (87%) standard approval agents had at least one post-marketing commitment at the time of approval. Accelerated approval agents also had a higher average number of total commitments per agent (9.4 for accelerated and 4.7 for standard). When analyzed by type, clinical post-marketing commitments were much more common for accelerated vs standard approval agents (7.3 vs 2.6 commitments/agent, respectively). Definition of clinical post-marketing commitments for the purposes of our study includes requirements to conduct randomized clinical trials, as well as to submit interim and conclusive safety and efficacy data from ongoing studies. Non-clinical and other types of post-marketing commitments did not significantly differ between the paradigms.

Treatment areas

Accelerated approvals were primarily in the areas of vaccines and immunoglobulins (3), systemic antiviral agents (5), and antineoplastic agents (5).

Standard approval agents represented a wider diversity of therapeutic areas (more than a dozen), with most indications in the immunomodulating agents, CNS therapies, anti-infective agents and hormonal therapies.

Time to First Black Box or Safety Update

Black Box warnings and Safety Updates added after the initial approval, or later redacted, were compared; those present at approval were not counted as these were weighed risks or class effects and were considered prior to granting initial approval.

Table 2. Safety Signals by Approval Type

	Standard (n=84)		Fast Track (n=14)		Accelerated (n=15)	
Agents with at least 1 Black Box or Safety Update (%)	53	63%	12	86%	15	100%
Agents with at least 1 added Black Box (%)	18	21%	7	50%	10	67%
Agents with at least 1 added Safety Update (%)	51	61%	11	79%	13	87%
Agents with at least 1 added Black Box and Safety Update (%)	16	19%	6	43%	8	53%
Agents with more than 1 added Safety Update (%)	14	17%	3	21%	5	33%
Average time to 1st added change (SD)	975 days	SD=478 days	1274 days	SD=452 days	1153 days	SD=495 days

53 (63%) of 84 standard approval agents had at least one added Black Box warning or Safety Update (18 (21%) Black Box warning, 51 (61%) Safety Update, 16 (19%) both a Black Box warning and a safety update). 14 products (17%) had more than one safety update. Average time to update was 975 days (SD=478 days). Average time to update for vaccine/immunoglobulin indications was 698 days (SD=442 days). Fast-Track designated agents had 3 Black Box warnings and 5 Safety Updates; a total of 7 agents had either form of warning, with 11 total warnings.

All of the accelerated approval agents had at least one Black Box or Safety Update, with 10 agents (67%) having a Black Box warning and 13 (87%) having a Safety Update; 5 (34%) of these had more than one safety update added. Average time to warning was 1153 days (SD=495 days). Fast-Track and orphan designation agents had higher rates of safety updates and longer time to update compared to non-fast track agents.

10 of 15 (67%) of accelerated drugs fell into the therapeutic areas of antineoplastic (L01) or antiviral (J05) agents. Given the prevalence, a direct comparison to other agents in these 2 classes would offer a clearer picture of the real divergence between safety signals and approval method.

Table 3. Antineoplastic and Antiviral Safety Signals by Approval Type

	Standard (n=11)		Fast Track (n=7)		Accelerated (n=10)	
Agents with at least 1 Black Box or Safety Update (%)	7	64%	6	86%	10	100%
Agents with at least 1 added Black Box (%)	4	36%	3	43%	6	60%
Agents with at least 1 added Safety Update (%)	7	64%	6	86%	10	100%
Agents with at least 1 added Black Box and Safety Update (%)	4	36%	3	43%	6	60%
Agents with more than 1 added Safety Update (%)	4	36%	3	43%	4	40%
Average time to 1st added change (SD)	979 days	SD=429 days	1266 days	SD=464 days	1031 days	SD=472 days
Agents with indications added (%)	4	36%	5	71%	9	90%
Agents with REMs (Average)	–	–	–	–	2	0.2
Agents with PMCs (Average per agent)	62	5.6	51	7.3	120	12

Conclusions

- Our results indicate no material differences in the post-approval history of products undergoing standard or accelerated review by the FDA.
- Products reviewed through accelerated routes were approved almost twice as fast as standard review, and had similar level of safety signals, supporting the main purpose of the accelerated approval procedure (to bring safe and effective agents to market faster).
- Label safety changes were more common among accelerated products. A longer time until first safety signal offsets the higher percentage of total updates in the accelerated paradigm. Higher percentage of safety signals in accelerated process is expected of agents under continued investigation. Also, the safety profiles of accelerated agents may be more closely assessed post-approval, which could drive the number of safety updates added.
- Time to safety update was longest for vaccines and immunoglobulins and slightly longer for accelerated than standard agents. This could be a class effect (for vaccines/immunoglobulins), or be related to the approval paradigm. The small sample size does not allow us to draw conclusions about the factors influencing time to safety update.
- No indications were removed for any products; however, a greater proportion of products undergoing accelerated approval had an indication added post-approval. Time to the first new indication was slightly longer for the accelerated approvals. A higher percentage of new indications in an accelerated paradigm could indicate its usefulness as a life cycle management approach to drug development.
- Both accelerated and standard approvals had a similar percentage of REMS, though they fell into different therapeutic categories. Accelerated agents have most REMS in antineoplastics; standard—in CNS, immunosuppressants/immunostimulants and DM agents. We believe the use of REMS in accelerated approval does not reflect a safety issue, but depends on therapeutic area of the indication more than on the approval paradigm.
- Post-marketing commitments were higher overall for accelerated approvals. Among subsets, clinical commitments were more common in accelerated products. This concurs with the requirements of the accelerated approval process.
- Accelerated approvals appeared to focus on therapeutic areas that have a history of using surrogate endpoints for critical diseases. Standard approvals represented a more diverse mix of therapeutic areas.
- The accelerated approval procedure could therefore be considered as an option for a new drug development and approval paradigm. Expansion of an accelerated process to more therapeutic areas will require the refinement of post-approval monitoring processes, and may require development of new well-validated surrogate endpoints in those therapeutic areas.

References

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