Accelerated approval of drugs: ethics versus efficacy

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Abstract

Objective

To analyse the post-marketing status of molecules approved through the expedited review process in the last quintile

Methods

This observational study was carried out between January 2016 and June 2016. The details of the time taken to approve drugs were collected from the official website of the United States Food and Drug Administration (FDA). The average time taken to review drugs and take a decision following the review was ascertained from the FDA's annual release of novel drugs from 2011 to 2015. Information on adverse drug reactions noted after approval was gathered from the FDA Drug Safety Communication and FDA Adverse Event Reporting System (FAERS).

Results

In the last five years, 166 products were approved by expedited review. Of these, 45 (27.1%) did not meet the stringent criteria framed for expedited review. Reports of serious adverse event alerts were submitted for 79 (47.5%) of the 166 molecules. Fourteen (8.4%) drugs were associated with inducing severe autoimmune disorders. It can be observed that a lower average time of review is positively correlated with a greater number of adverse events ($p<0.05$). Thirty-seven (45.7%) of the molecules failed to be of any benefit in the treatment scenario.

Conclusion

Drug approval by accelerated review should be stringent. Beneficence and non-maleficence are applicable to the global population, and should apply equally to subjects involved in trials. Approving drugs on the basis of trivial evidence is non-scientific and absolutely unethical, since it can lead to clinical failure and produce serious adverse events.

Introduction

Fast-track designation of an investigational drug for expedited review may be aimed at meeting an unmet medical need. To deal with such needs, the United States Food and Drug Administration (FDA) introduced several measures, which are collectively known as expedited drug review, and an approval process. Meeting an *unmet medical need* is defined as providing a therapy where none exists, or providing a therapy which may be potentially superior to the existing therapy. The latter is applicable when the emerging therapy is intended to reduce an adverse effect of an already existing drug molecule. Through these fast-track review processes, a drug can be granted approval after a Phase 2 trial and the mean time taken to reach a decision is 180 days (1). The FDA's Expedited drug review process is supported by priority review and accelerated approval, fast-track approval and first of its kind drugs under the Prescription Drug User Fee Act (PDUFA) , for making new drugs available as soon as possible. The programme enables the FDA to approve a molecule on the basis of an interim analysis of a surrogate marker, making use of frequent review procedures and even giving guidance to the drug investigator (2).

Accelerated approval has several critics who feel that it undermines safety, and that approving a drug on the basis of trivial information is non-scientific and hence, unethical. In 2008, Olson et al concluded in their analysis that a drug approved by expedited review produces more adverse effects than a molecule that has been subjected to the standard drug review process.

This statement was supported in 2015 by the most recent evidence presented by Aaron S Kesselheim et al in the *BMJ*. Having analysed the trends in expedited drug approval between 1987 and 2014, the authors concluded that the process did not adhere to the guidelines and approved insignificant molecules that had barely any efficacy, but were associated with significant adverse effects (3).

It must be noted that this does not concern just one process or a single molecule: it is something which has a global impact. Once a drug is approved and authorised for marketing, it is prescribed for and consumed by millions and millions of individuals.

Expedited trials are often conducted as major global trials, in which other countries, including India, contribute significantly. Hence, our population is often tested with molecules that pose a danger to their safety. Less than 10 molecules have been patented in India in the last five decades. India, which harbours a plethora of non-communicable diseases, is one of the major consumers of pharmaceutical products and when the FDA approves a molecule without clear superior benefits, it puts the population at even greater risk.

This study assesses the drugs approved by expedited review in the last quintile and their current status.

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Methods

This analysis was conducted by the Department of Pharmacology, Saveetha Medical College, between January and June 2016. The details of the time taken to approve drugs were collected from the official website of the US FDA. Information on the mode of approval of drugs, including the number of phases conducted, and the average time taken for the review and for the decision to be taken after the review was collected from the FDA's annual release of novel drugs from 2011 to 2015. The justifications for expedited reviews of molecules were also analysed, using the United States Guidance for Industry Programs for Serious Conditions for expedited drug review process. Analysis was then carried out on the US FDA Adverse Event Reporting System (FAERS). Data were retrieved on the reported adverse effects, the nature of the drug and the mode of approval of the drug to analyse whether standard review or expedited review had been conducted. The information collected was entered on Microsoft Excel and descriptive statistics were employed to describe the frequencies. A non-parametric test, the Kendall rank correlation test, was employed to infer the significance of the association between the time taken for review in the last quintile and the number of adverse effects noted

Results

In the last five years, 166 products were approved by expedited review. Forty-five (27.1%) drugs did not meet the stringent criteria framed for expedited review. As shown in Table 1, the average time of review varied from about 11.2 months to 6.4 months from 2011 to 2015. Serious adverse event alerts were submitted in the case of 79 (47.5%) of the 166 molecules. Fourteen (8.4%) drugs induced severe autoimmune disorders among the recipients. A lower average time of review was positively correlated with a greater number of adverse events ($p<0.05$). Thirty-seven (45.7%) molecules proved to be of no benefit in the real treatment scenario. Of the 166 molecules, 48 (28.9%) were drugs/biologics used for cancer and precancerous conditions. Among the drugs or biologics that were granted approval, only 22 (45.3%) showed any clinical benefits against cancer. Seven (14.5%) drugs were proven to induce second tumours among the recipients. Statistical significance was calculated using two-way proportional analysis between the numbers of molecules showing efficacy in the trial versus the clinical scenario ($p<0.05$), and similarly, between a lower time of evaluation and a greater number of adverse events reported in the category of anti-cancer drugs or biologics ($p<0.01$) (Tables 1 and 2, respectively).

The drugs approved by expedited review and their serious adverse effects are listed in Table 3 (6).

Discussion

Why accelerated approval of new drugs is risky

The principle of "*Primum non nocere*" (First, do no harm) is integral to therapeutics. It may be meaningful to increase the number of new drugs when strict criteria have been framed for the purpose and these criteria are followed. However, in the recent scenario, accelerated approval has proved to be controversial. Drug approval is a process that involves risks – first, for the people who participate in the trials and second, for the many who will be taking the drugs once they are granted approval. The historical disasters involving drugs such as Elixir Sulfanilamide and modern COX-2 inhibitors are well known. Both were approved following fast-track designation, and the latter caused an increase in cardiovascular events (4).

Is the condition being addressed rare or serious?

Diabetes is a widespread disease, and five classes of oral anti-diabetic agents that are well-established and evidence-based are available. These drugs are subsidised in many countries. Despite the fact that these agents have good efficacy, the US FDA approved seven molecules of dipeptidylpeptidase IV inhibitors and sodium glucose lumen transport inhibitors between 2011 and 2014. All these molecules are now proven to cause serious adverse reactions. In this case, there was no question of justifying an unmet need, and the FDA has not explained why these molecules did not undergo regular scrutiny and were, instead, given accelerated approval.

Table 1
Comparison of effects of expedited review anti-cancer drugs in trial vs their efficacy in post-marketing period

Total no of new chemical anti-cancer drugs approved	No of molecules approved as having superior efficacy during trial	No of molecules approved as non-inferior in clinical trial	No of molecules that failed to be of superior efficacy after marketing
48	**34 (70.3%)**	**14 (20.7)**	**37 (77.08%)**

Table 2
Average time taken for evaluation of expedited drug review between 2011 and 2015

Year	Average time of evaluation	No of adverse effects reported
2011	11.2 months	09
2012	9 months	13
2013	8.7 months	20
2014	8.2 months	15
2015	6.4 months	22

Table 3
Expedited drug review products for which potential adverse effects alerts were reported during 2011–2015

Drug / biologics	Category	Adverse event reported
Dabigatran	Anticoagulant	Haemorrhage with fatal outcome
Linagliptin, Saxagliptin, Alogliptin	Oral hypoglycaemic agents	Renal failure, mouth ulceration
Dapagliflozin, Canagliflozin Empagliflozin	Oral hypoglycaemic agents	Precipitation of ketoacidosis, urosepsis, stroke
Lacosamide	Antiepileptic	Neutropenia
Sofosbuvir, Simeprevir	Anti-hepatitis C	Cardiac arrhythmia
Dasabuvir, Telaprevir Ombitasvir, Paritaprevir	Anti-hepatitis C	Hepatic failure, Hypersensitivity
Pazopanib	Anti- cancer agent	Interstitial lung disease
Vemurafenib	Anti-cancer agent	Cutaneous cancer
Ponatinib	Anti-cancer agent	Veno-occlusive disease, withdrawn from market
Ofatumumab	Anti-cancer agent	Hepatitis B reactivation
Everolimus	Immunosuppressant	
Dimethyl fumarate	Immunosuppressant	Progressive multifocal leukoencephalopathy
Natalizumab	Immunosuppressant	
Brentuximab vedotin	Immunosuppressant	
Fingolimod	Immunomodulator	Haemophagocytic syndrome
Dronedarone	Anti-arrhythmic	Pulmonary toxicity
Pomalidomide	Immunomodulator	Hepatotoxicity
Pegloticase	Recombinant urate oxidase	Anaphylaxis and infusion reactions
Peginesatide	Erythropoietin stimulator	Fatal allergic reaction, withdrawn from market
Adalimumab, Golimumab, Etanercept	TNF-alpha blockers	Drug-induced sarcoidosis Reactivation of tuberculosis

Dabigatran, which was claimed to be superior to the conventional oral anticoagulant, warfarin, failed miserably in the clinical setting within a year. Drugs for non-communicable diseases are consumed by millions of patients worldwide and, hence, what is required is strict analysis in the pre-marketing phase rather than accelerated approval (5, 6).

Is there a significant improvement in clinical outcomes?

Biologics used in cancer and autoimmune diseases may be given accelerated approval, provided the benefits are clearly demonstrated and proven to address a real unmet need. Currently, regimens for almost all cancers are available and the maximum life expectancy is known (7).

Adding new biologics in the terminal stages of cancer is merely like using an extra drug without conferring any benefit in terms of the patient's quality of life and survival. These molecules were rapidly approved on the basis of a few trials or surrogate markers within a span of six months. Not only do these molecules increase the costs incurred by the patient and the pill burden, they produce an even greater number of adverse effects. In the *Journal of the American Medical Association (JAMA)*, October 2016 (8), Hwang et al discuss the factors responsible for the clinical failure of drugs and how the drug approval process is among the key determinants of failure or success.

Ponatinib, a drug approved for chronic myeloid leukaemia, was withdrawn due to its association with fatal veno-occlusive disease. This drug was approved within six months, on the basis of a single historical control, phase 2 trial by the US FDA. Vemurafenib, which was approved with much expectation for terminal-stage melanoma, increases survival for only four months longer than the current regimen, and induces severe cutaneous second tumors among patients. Similarly, immunomodulators are complex molecules that interact with many biological signalling pathways and induce new autoimmune conditions, and even tumors. Fatal hepatosplenic lymphoma and drug-induced sarcoidosis are a few examples (8, 9,10).

In the *Journal of Social Science and Medicine*, April 2015, Davis C discussed in detail the concept of pharmaceuticalisation and aggressive marketing, which, according to the author, failed to show end-of-life care benefits in patients with cancer (11). This is corroborated by our discussion and findings.

How did the drug fare after approval?

Anti-hepatitis C drugs fulfilled unmet criteria as there was no specific drug available till 2011, when three molecules, including sofosbuvir, were introduced. These molecules produced significant adverse effects. In July 2015, the FDA approved two more molecules, which led to severe and fatal liver injury within 3–4 months of exposure. This is clearly

unsafe, and it is totally unethical that these drugs were approved within six months on the basis of a reduction in the surrogate marker namely, viral load, and that proper safety analysis was not conducted before marketing authorisation was granted (10).

How can this problem be minimised?

Since the 1980s, accelerated approval has been granted to classical molecules, including many anti-HIV drugs, such as lamivudine, and anti-cancer drugs, such as platinum analogues. In the last quintile, a number of molecules given accelerated approval have turned out to do more harm than yield the expected benefits. The FDA and other global regulatory authorities should sincerely consider this matter and reduce the number of molecules selected for expedited review. Further, the review must take into account all parameters rather than a single parameter. The practice of granting approval on the basis of a reduction in surrogate markers or the statistical significance of end points must be reconsidered (10 -13).

Conclusion

The accelerated approval programme should be restricted to a few drugs intended to be used for serious and rare disorders, according to the guidelines framed. Careful study of drugs and the collection of adequate evidence can optimise the benefits of molecules for which accelerated approval is sought and can minimise the harm to the general population. The details submitted by sponsor pharmaceutical companies must be reviewed with greater vigilance. While assessing new molecules, not only must their efficacy be cross-checked with safety concerns, but ethical factors must also be considered before approval is granted. Adding a molecule that is merely termed "non-inferior" to the existing molecules may not fetch the expected benefits (14, 15, 16,17).

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