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# Safety related label changes for new drugs after approval in the US through expedited regulatory pathways: retrospective cohort study

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## ABSTRACT

### OBJECTIVE

To determine if drugs approved through the Food and Drug Administration's expedited development and review pathways have different rates of safety related label changes after approval compared with drugs approved through standard non-expedited pathways.

### DESIGN

Retrospective cohort study.

### SETTING

FDA public records, January 1997 to April 2016.

### PARTICIPANTS

382 FDA approved drugs.

### MAIN OUTCOME MEASURES

The number of times a particular safety section of a label (boxed warning, contraindication, warning, precaution, or adverse reaction) was changed during a drug's time on the market. The relative rate of safety related label changes per year for expedited pathway and non-expedited pathway drugs was compared by forming matched pairs of drugs in the same therapeutic class that were approved within three years of each other.

### RESULTS

Among the 382 eligible new drugs, 135 (35%) were associated with an expedited development or review pathway, and matches were available for 96 (71%). The matched pairs were associated with a total of 1710 safety related label changes during the study period. Expedited pathway drugs were characterized by a rate of 0.94 safety related label changes for each drug per year, compared with 0.68 safety related label changes per year for non-expedited pathway drugs

(rate ratio 1.38, 95% confidence interval 1.25 to 1.52). Compared with non-expedited pathway drugs, expedited pathway drugs had a 48% higher rate of changes to boxed warnings and contraindications, the two most clinically important categories of safety warnings (1.48, 95% confidence interval 1.07 to 2.06). A qualitative review of changes to the boxed warning sections revealed that less than 5% (3/67) were changed to describe reduced risks for patients.

### CONCLUSIONS

Expedited development and regulatory review pathways can accelerate the availability of new drugs, but drugs approved through these pathways are associated with increased safety related label changes after approval, particularly for the types of changes representing the highest risk warnings. To inform appropriate policy interventions, additional research should explore the causal factors contributing to these different rates.

### Introduction

Before a new drug can be marketed in the US, the manufacturer must first conduct clinical trials that demonstrate substantial evidence of efficacy and adequate safety. Traditionally, these trials start with phase I exploratory studies in healthy volunteers and progress through phase II studies in small groups of patients and often larger phase III randomized trials intended to establish a drug's efficacy for a particular indication. The Food and Drug Administration reviews the data and approves the drug if its benefits outweigh the risks. Numerous exceptions to this standard pathway are open to drugs meeting unmet medical needs or for treating serious or life threatening conditions. For example, drugs qualifying for the "fast track" or "accelerated approval" pathways are allowed an abbreviated development process. In the former case the drugs may be approved after a single phase II trial<sup>1</sup> and in the latter case they are based on surrogate measures that are only "reasonably likely" to predict actual clinical benefit.<sup>2</sup> Drugs designated as "priority review" receive faster review by the FDA—within six months, compared with 10 months for the standard review pathway.<sup>1</sup>

Manufacturers' use of these expedited development and review pathways has expanded in recent years, and currently a majority of drugs qualify for at least one of them.<sup>3</sup> It is possible that expedited development or review can lead to FDA approval of products with increased risks from safety issues that may not be identified prior to marketing, although this may be reasonable for patients facing no other therapeutic options. The potentially different degrees

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Recent legislation in America opens the possibility for the expansion and increased use of FDA expedited drug development and review pathways designed to respond to public health priorities

Evidence on whether drugs approved through expedited regulatory pathways carry higher levels of safety risks that are unknown at the time of approval is conflicting

Some studies suggest that the review process does not impact the quality of the safety assessment, whereas others show a difference

## WHAT THIS STUDY ADDS

In this analysis concerning more than 15 years of comprehensive data, expedited pathway drugs had a 38% higher rate of safety related label changes than drugs approved through non-expedited pathways

As policymakers continue to expand expedited regulatory pathways, physicians and patients should be aware of the potential safety trade-offs involved in these pathways

of risk presented by products approved through these expedited pathways are unknown. Prior studies have found that faster regulatory review times are associated with a higher likelihood or number of serious safety issues,<sup>4 5 6 7 8</sup> although these data are controversial because other reviews have found no such association.<sup>9 10 11 12</sup>

In 2016, Congress passed the 21st Century Cures Act, which opens the possibility that more new drugs will qualify for the FDA's expedited development and review pathways—for example, the legislation instructs the FDA to use these pathways for so-called regenerative medicine products,<sup>13</sup> which is defined broadly to encompass human cell and tissue products. To help understand the potential trade-offs for products approved through faster timelines and different data requirements, we compared rates of post-approval changes to the safety sections of the drug labels among drugs approved through these expedited pathways with rates for drugs approved through the FDA's standard pathway.

## Methods

### Identifying a cohort of new drug approvals

Previously, we collected a list of all novel therapeutics (vaccines and diagnostics were excluded) approved between 1997 and 2014,<sup>14</sup> which we have used in other analyses.<sup>3</sup> Each drug was classified into one of 13 different therapeutic categories within the World Health Organization's Anatomic Therapeutic Classification (ATC) system based on its initial approved indication: allergy and pulmonology; cardiovascular disease and its risk factors, including diabetes mellitus, hyperlipidemia, and hypertension; dermatology; endocrinology; gastroenterology; genitourinary disease; hematology; infectious disease; musculoskeletal disease and immunomodulators; neuropsychiatry; oncology; ophthalmology; and all other therapeutic areas.<sup>15</sup> For the approximately 6% of drugs not listed in the WHO ATC database, the primary ATC class had been assigned by consensus when the database was originally organized.

Next, we determined whether and which expedited development and review pathway was associated with the initial approval of each drug: fast track, accelerated approval, or priority review. For the purposes of this study we excluded drugs that qualified for the Orphan Drug Act designation because the act does not formally change the FDA's review criteria and because we expected the small patient populations to limit the potential for observing post-approval safety issues. We also excluded another expedited pathway, the “breakthrough therapy” designation, because it was only recently created in 2012.

We used the approval date for the new drug application to mark the date a drug entered the market. To determine the duration a drug was on the market, we searched historical sources, including published articles as well as the federal register, to identify drugs from this cohort that were subsequently withdrawn for any reason. A discontinuation date was identified for drugs

with a discontinued marketing status in the Drugs@FDA online database.<sup>16</sup> A date was assigned for these drugs by searching for their name in the federal register and, if no relevant documents were available, conducting an internet search for press releases involving the drug name and the term “discontinue” or “withdrawal.”

### Collecting safety label changes for approved drugs

Labeling changes for prescription drugs are categorized and published by the FDA on a monthly basis. We noted all labeling changes that involved a revision or addition to at least one of the following safety related subsections of a label: boxed warning (also called a black box warning), contraindication, warning, precaution, and adverse reaction. From FDA MedWatch tables (available online) we retrieved labeling changes occurring between January 2008 and April 2016.<sup>17</sup> From the FDA's publicly archived files, we downloaded and extracted the 1997–2007 records.<sup>18</sup>

Data from all sources were entered into a master database of safety labeling changes, including the month, year, and affected label subsections for drugs between January 1997 and April 2016. To confirm the accuracy of the information in this database we identified a validation subset. For each safety label section (eg, boxed warning, contraindication), we randomly selected one drug approved through an expedited development or review pathway and one drug approved through the standard pathway. To confirm the date and sections modified we validated data for 51 label changes by finding the associated letter published in the approval history section of Drugs@FDA.<sup>15</sup>

### Statistical analysis

To create a balanced comparison between drugs associated with expedited development and review programs and those associated with the standard pathway, we used 1:1 matching. Matches were formed for pairs of drugs that had the same ATC classification and were approved within three years of each other. The ATC category was preferentially matched at the third level of detail (eg, A10B: oral blood glucose lowering drugs). If a match was not available, then it was assigned at the second level (eg, A10: drugs used in diabetes). At a minimum, all matches shared the first level designation (eg, A: alimentary tract and metabolism).

For each drug, we calculated the annual rates of safety label revisions by dividing the total number of revisions by the number of years that each drug was on the market. We compared rates between drugs qualifying for expedited development and review programs and those approved through the standard pathway by calculating rate ratios and 95% confidence intervals. We examined rates and rate ratios for the outcome of any safety revisions as well as separately for each type of revision (eg, boxed warning, contraindication).

### Qualitative assessment of changes

To determine if the changes described increased safety risks for patients, we conducted a qualitative analysis

of alterations to boxed warnings. The FDA issues publicly available letters to manufacturers regarding label changes.<sup>16</sup> If this letter did not specify the nature of a change, we compared the revised label on the revision date with the most recent archived label. We judged additions of new risks or increases in the severity of existing risks as encompassing increased risks to patients.

### Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

### Results

Table 1 summarizes the drugs that were included and the results of the matching process. Among the 382 eligible new drugs approved between 1997 and 2014, 135 (35%) were associated with one of the three expedited development or review programs of interest. Matches were available for 96 of the 135 expedited drugs (71%); 89 (93%) received priority review, 27 (28%) were approved through the fast track pathway,

and 11 (11%) were approved through the accelerated approval pathway (33 (34%) were approved through the fast track or the accelerated approval pathway, or both). Overall, 100% were matched at the first ATC level, 55% at the second, and 35% at the third. The most common first level ATC class was antineoplastic and immunomodulating agents (24%) followed by anti-infectives for systemic use (19%).

The matched pairs were associated with a total of 1710 safety label changes during the study period, including 67 changes to boxed warnings, 83 changes to contraindications, 438 changes to warnings, 644 changes to precautions, and 478 changes to adverse reactions. Expedited pathway drugs were characterized by a rate of 0.94 safety label changes for each drug per year, compared with 0.68 safety label changes per year for standard pathway drugs (rate ratio 1.38, 95% confidence interval 1.25 to 1.52, table 2). Compared with standard pathway drugs, expedited pathway drugs had a 48% higher rate of changes to boxed warnings and contraindications, the two most clinically important categories of safety warnings (95% confidence interval 1.07 to 2.06).

### Discussion

In this study of safety related label changes in FDA approved drugs in the past two decades, we found that drugs of comparable therapeutic class and approval

**Table 1 | Approved drugs (1997-2014) included in study and results of matching process**

Variables	All drugs (n=382)*			Matched pairs (n=192)†		
	Expedited drugs	Standard drugs	Total (%)	Expedited drugs	Standard drugs	Total (%)
<b>Therapeutic category</b>						
A Alimentary tract and metabolism	10	33	43 (11)	10	10	20 (10)
B Blood and blood forming organs	13	12	25 (7)	10	10	20 (10)
C Cardiovascular system	2	24	26 (7)	2	2	4 (2)
D Dermatologicals	2	16	18 (5)	2	2	4 (2)
G Genitourinary system and sex hormones	3	20	23 (6)	3	3	6 (3)
H Systemic hormonal preparations, excluding sex hormones and insulins	1	4	5 (1)	1	1	2 (1)
J Anti-infectives for systemic use	39	18	57 (15)	18	18	36 (19)
L Antineoplastic and immunomodulating agents	31	23	54 (14)	23	23	46 (24)
M Musculoskeletal system	2	9	11 (3)	2	2	4 (2)
N Nervous system	4	50	54 (14)	4	4	8 (4)
R Respiratory system	1	12	13 (3)	1	1	2 (1)
S Sensory organs	14	9	23 (6)	9	9	18 (9)
V Various	13	17	30 (8)	11	11	22 (11)
Total	135	247	382 (100)	96	96	192 (100)
<b>Approval period</b>						
1997-2001	45	95	140 (37)	39	41	80 (42)
2002-06	40	54	94 (25)	27	19	46 (24)
2007-11	21	59	80 (21)	14	24	38 (20)
2012-14	29	39	68 (18)	16	12	28 (15)
Total	135	247	382 (100)	96	96	192 (100)
<b>FDA program</b>						
Expedited:	135	-	135 (35)‡	96	-	96 (50)‡
Accelerated approval	21	-	21 (5)‡	11	-	11 (6)‡
Priority review	126	-	126 (33)‡	89	-	89 (46)‡
Fast track	48	-	48 (13)‡	27	-	27 (14)‡
Standard	-	247	247 (65)‡	-	96	96 (50)‡
Total	135	247	382 (100)	96	96	192 (100)

\*All New Molecular Entities approved between 1997 and 2014, excluding drugs with orphan designation.

†Matched refers to pairs of drugs sharing ATC therapeutic category and approval date within three years of each other

‡Expedited pathways are not mutually exclusive; a drug can be associated with multiple pathways.

**Table 2 | Rate of safety label changes**

Modified section of safety label	Rate (95% CI) of safety related label changes (per year on market)		
	Expedited drugs*	Standard drugs	Rate ratio (95% CI)
Any section†	0.94 (0.88 to 1.00)	0.68 (0.63 to 0.73)	1.38 (1.25 to 1.52)
Boxed warning	0.04 (0.03 to 0.05)	0.02 (0.02 to 0.04)	1.62 (0.98 to 2.65)
Contraindication	0.05 (0.03 to 0.06)	0.03 (0.02 to 0.05)	1.41 (0.91 to 2.19)
Warning	0.24 (0.21 to 0.27)	0.18 (0.15 to 0.21)	1.39 (0.90 to 2.15)
Precaution	0.35 (0.32 to 0.39)	0.26 (0.23 to 0.29)	1.38 (1.18 to 1.62)
Adverse reaction	0.26 (0.23 to 0.29)	0.19 (0.16 to 0.22)	1.38 (1.15 to 1.66)
Boxed warning or contraindication	0.08 (0.07 to 0.10)	0.06 (0.04 to 0.07)	1.48 (1.07 to 2.06)
Warning, precaution, or adverse reaction	0.85 (0.80 to 0.91)	0.62 (0.58 to 0.67)	1.37 (1.24 to 1.51)

\*Includes accelerated approval, priority review, and fast track. Stratifying by each type yielded virtually identical results.

†Includes boxed warning, contraindication, warning, precaution, and adverse reaction sections.

Our qualitative review of the boxed warning changes showed that less than 5% (3/67) involved alterations that reduced the risk language.

dates were subsequently associated with more such changes if they were approved through expedited pathways. The increased incidence of safety related labeling changes among these expedited pathway drugs was particularly elevated for boxed warnings and contraindications, which represent changes to the recommended labeling of the highest clinical importance.

The scope and outcomes used in this study distinguish it from other research on the association between the FDA's different review procedures and safety outcomes of approved drugs. Some earlier studies assessed safety by examining a binary outcome, such as whether a drug was withdrawn from the market<sup>4 11 19</sup> or whether any safety warning was added to the label.<sup>4 9</sup> By considering the total number, kind, and rate of label changes, we were able to assess the degree to which a drug's overall safety profile is accurately characterized at the time of approval. Other studies assessed post-approval safety by analyzing adverse drug reactions spontaneously reported to the FDA.<sup>6 7 8 10 20 21</sup> Though it is useful to consider experiences at patient level, this data source faces several limitations<sup>20</sup> and does not have the benefit of the FDA's comprehensive analysis before determining whether it merits updating a subsection of the drug's label. One study from Europe did not find statistically increased levels of safety issues for drugs approved through exceptional and conditional pathways,<sup>22</sup> but these findings could result from the distinct processes at the European Medicines Agency. Most prior investigations have focused on safety outcomes from drugs approved in the 1990s and 2000s, whereas our dataset was up to 2016.<sup>7</sup> A recent study that focused only on the boxed warning sections of the labels of novel therapeutics produced consistent results to our assessment of all safety related label sections.<sup>23</sup>

When a new drug is FDA approved through expedited development, less may be known about the drug's safety because these drugs are tested in fewer patients and patients are often followed for shorter periods than drugs approved through the standard pathway. With shortened review times it may be more difficult to identify signals of harm in the vast amounts of data contained in the approval packages. In the case of treatments for unmet medical needs or life

threatening conditions, the greater uncertainty in risk to patients posed by such products may be acceptable. However, previous studies have shown that the use of expedited development and review has been increasing significantly over the past two decades, with the trend largely attributable to a greater number of less innovative non-first-in-class drugs qualifying for these pathways.<sup>3</sup> Most recently, the "breakthrough therapy" designation was created in 2012 to provide the prospect of greater "regulatory efficiency" intended to further expedite drug development and regulatory review. In the first 2.5 years of experience, 80 investigational drugs qualified for breakthrough therapy status.<sup>24</sup> Our results identify one important risk to patient safety of expansion of expedited designations beyond the limited cases of unmet medical need or life threatening conditions.

The increase in safety label changes we identified points to the importance of active safety surveillance of all drugs after approval, and in particular drugs approved through expedited development or review pathways. The FDA receives voluntary reports about drug related adverse events, which can lead to safety labeling changes, but this system is also characterized by many limitations, including selective reporting.<sup>25</sup> Beginning in 2007 the FDA's electronic monitoring of electronic healthcare data and other sources through the Sentinel system has provided a critical mechanism for the FDA to conduct active observational studies to supplement the voluntary reporting system. Our data suggest that drugs approved through expedited development and review pathways should be prioritized among Sentinel investigations to help identify any emerging problems necessitating a safety related label change as early as possible.

One way to mitigate the risks identified in our study is to make patients or physicians aware of the increased incidence of subsequent safety related label revisions. Currently, drugs approved through the accelerated approval pathway generally include a line in their official labeling that the "clinical benefit... has not been established" because of the reliance on an incompletely validated surrogate measure. Our results suggest that there should also be formal requirements for manufacturers to alert patients about the higher rate of subsequent safety labeling changes arising from drugs approved through the accelerated approval, fast



track, or priority review pathways. Physicians should also ensure that they communicate the uncertainty about risks to patients when they prescribe these products to allow patients to make more informed decisions about their use of the drugs. However, many physicians do not understand the FDA review process or the existence of different FDA review pathways,<sup>26</sup> suggesting first the need for greater education of physicians about the US drug regulatory system. This can be accomplished during undergraduate medical education<sup>27</sup> as well as by developing online courses that can earn continuing medical education credits while staying free of industry sponsorship.

### Limitations of this study

Our study had some limitations. The matching process excluded 29% of the expedited drugs in our original sample, which reduced our study's power for some of the secondary outcomes but improved the internal validity by ensuring that the matched sample of standard drugs was more similar with respect to therapeutic category and year of approval. A relatively small proportion of expedited drugs were approved through accelerated approval and fast track pathways, limiting our ability to conduct analyses stratified by those pathways. We measured the occurrence of label modifications that were reported each month; if a label section received multiple additions on the same date (eg, two new drugs added to list of contraindicated co-prescriptions), or multiple changes within the same month, the analysis would only count this as one change event because of the structure of FDA's monthly historical archive data. This occurs rarely—in a randomly selected sampling of 30 drugs in our cohort with 231 label related actions in their histories, we found two cases in which label changes occurred to the same drug during different days in the same month (2/231, 0.9%).

Second, while the rate of safety changes is a useful metric to understand the relative magnitude of changes for a given drug over time, it does not provide a qualitative assessment of the clinical relevance of a particular change. For example, the addition of "risk of serious cardiovascular events" to the boxed warning of a label in which there was already some cardiovascular outcomes mentioned may have less clinical impact than the addition of new psychiatric side effects that were not previously included in that section of the label. Such qualitative analysis of the label changes is complicated by the fact that in some cases FDA only indicates that a change was made but then presents the whole label section, and in others it underlines or italicizes the text but does not indicate what was changed. Greater clarity from the FDA about the exact nature of each label change and the number of changes each month would be useful in resolving these issues. However, some degree of relative severity may still be inferred because of the implicit hierarchy among different sections of the label (eg, boxed warning, warning, and precaution). Our expectation is that a majority of safety label changes are made because a

drug's post-marketing evidence exposes new safety concerns. Of course label changes can also be made for other reasons. For example, as with the recent case of varenicline,<sup>28</sup> if post-marketing data show that a drug is safer than it was originally understood to be, a label modification could be made to down grade the level of risk. Our qualitative analysis of the high profile boxed warning section showed that such changes are rare (<5% of the time).

### Conclusion

We found an association between expedited development and review pathways and the likelihood of subsequent safety related labeling changes. The recent 21st Century Cures Act created additional pathways intended to expedite drug development, including designation of certain drug development tools and use of "real world" data to support approved indications.<sup>13</sup> When combined with the recent breakthrough therapy designation, these changes suggest that the number of drugs widely available to patients that had benefitted from expedited pathways will continue to increase. Further research is required to understand the underlying process factors contributing to the differential rates in safety changes that were observed in this analysis. Policymakers will likely need to ensure that these pathways are not overused, that there is sufficiently close post-approval monitoring of drugs approved through these pathways, and that patients and physicians are fully informed of the risks that accompany the widespread use of expedited development and regulatory review pathways in the approval of new drugs.

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**Ethical approval:** Not required.

**Data sharing:** All data are publicly available.

**Transparency:** The authors affirm that the manuscript is an honest, accurate, and transparent account of the study was reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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