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Association of expedited review programmes with postmarketing safety events of new drugs approved by the US food and drug administration between 2007 and 2017

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ABSTRACT

Objective To explore the associations between the risks of postmarketing safety events of new drugs and the four expedited programmes of priority review, accelerated approval, fast track and breakthrough therapy established by the US Food and Drug Administration (FDA); and to investigate whether multiple uses of expedited programmes, and the combinations of expedited programmes with orphan designation, were relevant to different safety profiles.

Design Cohort study.

Setting USA.

Participants All new drugs approved by the FDA between 1 January 2007 and 31 December 2017, followed up until 10 April 2021.

Outcome measures Safety events included safety-related withdrawal, new boxed warning, drug safety communication, postapproval risk evaluation mitigation strategy and safety-related labelling changes. The duration from marketing approval to the occurrence of a safety event was measured.

Method Cox models were performed to determine the factors related to the time-to-safety event.

Results The FDA approved 338 new drugs between 2007 and 2017, among which 53.6% (181) were under expedited review and 32.2% (109) received two or more expedited programmes. It took median time of 1.75 years (IQR 1.10–2.93) and 2.31 years (IQR 1.33–4.21), respectively, for new drugs to be observed of their first event and first serious event. The raised risk for first safety event was found to associate with breakthrough therapy (adjusted HR 1.83; 95% CI 1.21 to 2.77; p=0.004), and with the combination of accelerated approval with orphan designation (adjusted HR 2.84; 95% CI 1.12 to 7.23; p=0.028). Triple or more use of expedited programmes correlated with higher risk for first serious event (adjusted HR 4.16; 95% CI 1.69 to 10.22; p=0.002).

Conclusions The increased risks of the breakthrough therapies, accelerated orphan drugs and triple or more use of expedited programmes indicated the necessity for intensive postmarketing risk surveillance.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We extended the identification of postmarketing safety events that enabled analysis for risks of all events and of serious events.
⇒ The timeline of sample allowed exploration about the latest programme of breakthrough therapy.
⇒ The relatively short follow-up might be inadequate to shape the complete picture for the safety risks of orphan drugs.

INTRODUCTION

Expedited drug review programmes are first established by the US Food and Drug Administration (FDA) to deliver innovative therapies faster to patients, through which the development and approval of drugs can be facilitated and less time-consuming. To date, the FDA has designed four expedited programmes to help earlier access to novel treatments that are for serious conditions and are likely superior over known medications: priority review (started in 1992) which commits to shorter review duration, fast track (1987) and breakthrough therapy (2012) which promote the development process, and accelerated approval (1992) which allows for conditional approval under surrogate or intermediate clinical endpoints (more detailed introduction for the four expedited programme was provided in online supplemental table 1).[1] Following the USA, countries worldwide have implemented analogous expedited regulatory pathways for novel therapeutics, including China. Since 2015 the China drug agency has successively initiated programmes of priority review, conditional approval and breakthrough therapy.[2] Timely availability of drugs with substantial clinical interests benefits the patients, which is however companioned with larger uncertainties and concerns of increased safety risks. This trade-off between speed and safety is a conundrum facing drug agencies.[3] To

address it, the very beginning is to understand how expedited programmes affect the postmarketing performance of new drugs with regard to both efficacy and safety, which are hard to accurately predict based on premarketing evidence.

In terms of efficacy, researchers have found that new drugs experiencing expedited programmes are more likely to be rated as highly therapeutic valuable than non-expedited drugs.[4] While as for the safety aspect, prior studies focusing on postmarketing safety outcomes and their factors conclude that the worse safety outcomes are associated with certain expedited programmes,[5–10] such as priority review and accelerated approval. The safety risks of expedited programmes have been identified to some extent. Nevertheless, with over 20% of expedited applications receiving two or more expedited programmes,[11] investigations on whether the multiple use of expedited programmes would introduce incremental safety risks are still of dearth. Besides, as growing orphan drugs are developed,[1] the interaction effects of orphan drug designation and expedited programmes await to be discussed as well.

The leading measures of safety include withdrawal due to safety issues and additional boxed warning, but which are relatively limited to depict the risk profile. Adverse drug events are also employed, but it is sometimes hard to determine the relevance of the spontaneously reported cases and the drug use.[12 13] Building on previous works, we design a wider coverage for safety events to characterise the postmarketing safety profile for a new drug: the safety-driven withdrawal, new boxed warning, drug safety communication, postapproval risk evaluation mitigation strategy (REMS) and safety-related labelling changes (SrLCs). Drug safety communication established by FDA since 2010 is the public bulletins of drug safety information pertinent to serious risk. REMS is a drug risk management programme designated by FDA when specific serious risk is of great concern.[14] SrLCs are the postmarketing changes occurring in the seven sections of drug labelling which are related to drug use safety. The broader identification of safety events is supposed to provide new meaningful knowledge.

Based on new drugs approved by the FDA, our study uses postmarketing safety events as the proxy for drug safety risks, and explores their association with expedited review programmes. We improve on the existing literature by including the latest programme of breakthrough therapy, extending identification of safety events, and examining whether multiple uses of the expedited programmes as well as their underlying interactions with orphan drug designation are associated with postmarketing safety events.

METHODS

Data

Using the Drugs@FDA database,[15] we collected all the new drugs (new molecule entities and biologics) approved by the US FDA between 1 January 2007 and 31 December 2017. The new drugs were classified into new drug application (NDA) and biologics licence application (BLA) according to their application number provided by Drugs@FDA. The qualifications for the four expedited programmes of priority review, accelerated approval, fast track and breakthrough therapy, were determined by the annual review reports through searching on the website of FDA. The orphan designation was identified using Drugs@FDA. Review duration of each drug was days from the submission date to the final approval date, and was determined through drug approval letter disclosed in Drugs@FDA. The WHO' s Anatomic Therapeutic Classification (ATC) system was used to identify the therapeutic area of each drug.[16] As for a few drugs not listed in WHO ATC system, we assigned the primary area according to their initial approved indications which were abstracted from approval letters.

Safety events

Safety outcomes were defined as the five categories of postmarketing events as aforesaid, and online supplemental table 2 summarises the definitions and sources for these safety events. Withdrawal, new boxed warning,[6] drug safety communication[6 17] and REMS[14] were regarded as serious events. SrLCs covered a wide range of label changes with various degree of severity, and they were therefore regarded as more general events. All safety events were collected up to 10 April 2021. Disclosure of drug withdrawal was from documents of the Federal Register, and only withdrawal related to safety issues was included. New boxed warning was defined as the following postmarketing changes in drug labelling: (1) new added section of boxed warning; (2) major revisions on existing boxed warnings that added new distinguishing conditions requiring close attention and (3) substantive modification on, addition to, or detailing of existing boxed warnings that would exert further restriction on drug utilisation. Changes to boxed warnings only referring to new initiation of REMS were excluded to prevent duplicated counts. The Drug SrLC Database,[18] and the MedWatch Medical Product Safety Information Archive,[19] provided revisions in the boxed warning section as well as other sections related to safety concerns. Additional REMS following marketing approval could be deemed as an action to serious safety issues, while an initial REMS at approval often implied noticed safety risks and was regarded as a control variable in our study. FDA offered the REMS Products data which were used to determine all the drugs involved in REMS programmes.[20] Drug safety communications only referred to new boxed warning or additional REMS were excluded, and communications concerning name confusion or other non-drug-driven cautions were not counted too. Drug safety communication could be obtained on its webpage.[21] As to SrLCs which usually incorporated several changes in different labelling sections at one time, the SrLCs only contained new boxed warning were excluded. SrLCs could be obtained through its database and the MedWatch archive as stated above.

Table 1 Descriptive characteristics of new drugs approved by FDA between 2007 and 2017 (n=338)

Variables	No (%)
Drug class	
NDA	260 (76.9)
BLA	78 (23.1)
ATC category	
A Alimentary tract and metabolism	42 (12.4)
B Blood and blood forming organs	16 (4.7)
C Cardiovascular system	22 (6.5)
D Dermatologicals	10 (3.0)
G Genitourinary system and sex hormones	9 (2.7)
H Systemic hormonal preparations, excluding sex hormones. and insulins	8 (2.4)
J Anti-infectives for systemic use	38 (11.2)
L Antineoplastic and immunomodulating agents	106 (31.4)
M Musculoskeletal system	11 (3.3)
N Nervous system	31 (9.2)
P Antiparasitic products, insecticides and repellents	5 (1.5)
R Respiratory system	14 (4.1)
S Sensory organs	6 (1.8)
V Various	20 (5.9)
Orphan designation (n=125)	
Non-expedited review	24 (19.2)
Expedited review	101 (80.8)
REMS at approval	51 (15.1)
Review duration, median (IQR), days	303.50 (222-370)
Priority review (n=162)	
With orphan designation	91 (56.2)
Without orphan designation	71 (43.7)
Fast track (n=92)	
With orphan designation	52 (56.5)
Without orphan designation	40 (43.5)
Breakthrough therapy (n=44)	
With orphan designation	28 (63.6)
Without orphan designation	16 (36.4)
Accelerated approval (n=42)	
With orphan designation	34 (81.0)
Without orphan designation	8 (19.0)
Non-expedited review	157 (46.4)
No. of expedited programmes	181 (53.6)
1 (n=72)	
Priority review only	55 (76.4)
Fast track only	14 (19.4)
Accelerated approval only	3 (4.2)
Breakthrough therapy only	0
2 (n=65)	
PR and FT	45 (69.2)
PR and BT	10 (15.4)
PR and AA	9 (13.9)
FT and AA	1 (1.5)
3 (n=38)	
PR and FT and BT	15 (39.5)
PR and BT and AA	12 (31.6)
PR and FT and AA	10 (26.3)
AA and BT and FT	1 (2.6)
4 (n=6)	
AA and BT and FT and PR	6 (100.0)
Follow-up, median (IQR), years	7.74 (5.48–10.45)

AA, accelerated approval; ATC, Anatomical Therapeutic Chemical classification; BLA, biologics license application; BT, breakthrough therapy; FT, fast track; NDA, new drug application; PR, priority review; REMS, risk evaluation and mitigation strategy.

Statistical analysis

The elapsed time from approval to a safety event constituted the time-to-event outcome. To provide more perspectives on safety risks, the outcomes fell into the overall pattern and the serious pattern: time-to-first event took account of all kinds of events, while time-to-first serious event focused on the severe outcomes. Medians were used for the descriptive analysis. Kaplan-Meier estimate with log-rank test was used to compare the survival differences between groups with and without a specified programme of the four expedited programmes.

In the multivariate analysis, we first examined the associations between multiple uses of expedited programmes and postmarketing safety issues, with the times to first event and the times to first serious event modelled by Cox proportional-hazards regression. The number of granted expedited programmes would be the main factor of interest. Other characteristics of the ATC category, drug class, review duration, orphan designation and approved year were also included as potential confounders. Next, the relationship between the two time-to-event outcomes and each expedited programme was assessed, in which the factors of interest were whether drugs received the specified expedited programme. Given its potential distinguishing effect, orphan designation was deemed as a distinct pathway instead of an expedited review programme. The interactions of orphan designation with the utilisation of expedited programmes were therefore examined. The significance level was set to be 0.05 for two-tailed tests. Stata V.15 (StataCorp LP) and R V.4.0.2 (Surminer package) were used to conduct the analysis.

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

Features of the study drugs

Basic characteristics were summarised in the table 1. A total of 338 medicines were approved by the US FDA between 2007 and 2017, among which NDAs were the majority (260 (76.9%)). The new drugs covered all therapeutic areas depicted by the ATC system, with antineoplastics making up nearly one-third (106 (31.4%)). Over half of new drugs (181 (53.6%)) were granted one or more expedited programmes: the most common programme was priority review (162 (47.9%)), followed by fast track (92 (27.2%)), while breakthrough therapy (44 (13.0%)) and accelerated approval (42 (12.4%)) were less used. More than one-third of new drugs (125 (37.0%)) were designated as orphan, among which 101 (80.8%) were expedited reviewed. Fifty-one (15.1%) new drugs were required to initiate a REMS at the time of approval. The new drugs experienced a median review duration of 303.50 days (IQR 222–370). Table 1 presents the distribution of the expedited programmes. Seventy-two new drugs received only one expedited programme, of which priority review constituted 76.4%. Multiple uses of these programmes were frequent, with 60.2% of the expedited drugs qualifying for more than one programme. Breakthrough therapy was always combined with other review programmes. Fast track jointed with priority review predominated in the double use. In addition, multiple uses tended to increase over time, for example, during 2007-2011 triple or more use accounted for only 1.7% (2 out of 118) among all drugs, while the share rose to 19.1% (42 out of 220) throughout 2012–2017. The median follow-up was 7.74 years (IQR 5.48–10.45).

Safety events

As of 10 April 2021, 315 (93.2%) of the study drugs incurred 1794 postmarketing safety events, leaving 23 drugs free of any safety concern yet (table 2). Eighty-two drugs (24.3%) were subject to 126 serious events. Most first safety events were SrLCs (292 (92.7%)). New boxed warnings were the most common first serious events (42 (51.2%)), followed by drug safety communications (36 (43.9%)). The new drugs took a median time of 1.75 years (IQR 1.10–2.93) to their first safety event, and a median time of 2.31 years (IQR 1.33–4.21) to their first serious event.

Table 2 Safety events of the study drugs

Safety event	No (%)	Time to event, median (IQR), years
All events		
SrLC	1669 (93.0)	4.26 (2.59–6.70)
Added REMS	8 (0.4)	5.45 (2.17–10.70)
New boxed warning	64 (3.6)	3.26 (1.65–5.64)
Drug safety communication	50 (2.8)	2.41 (1.58–4.02)
Withdrawal	3 (0.2)	3.81*
Total	1794(100)	4.14 (2.47–6.61)
First event		
SrLC	292 (92.7)	1.80 (1.12–3.00)
New boxed warning	11 (3.5)	1.56 (1.17–3.84)
Drug safety communication	11 (3.5)	1.32 (0.59–1.66)
Withdrawal	1 (0.3)	3.35*
Total	315(100)	1.75 (1.10–2.93)
First serious event		
Added REMS	2 (2.4)	2.59*
New boxed warning	42 (51.2)	2.78 (1.34–5.12)
Drug safety communication	36 (43.9)	2.09 (1.31–4.24)
Withdrawal	2 (2.4)	3.58*
Total	82(100)†	2.31 (1.33–4.21)
No event	23	4.87 (3.61–6.50)‡

*IQR was not calculated due to the very low samples.
†The percentages did not add to 100% due to rounding.
‡The time to end of follow-up was measured for drugs with no event.
REMS, risk evaluation and mitigation strategy; SrLC, safety-related label change.

Factors associated with safety events

The results of the Kaplan-Meier analyses suggested the expedited programmes, except priority review, were significantly associated with more frequent safety events (figure 1), notwithstanding such associations were not statistically significant for serious events (online supplemental figure 1).

Table 3 presents the HRs associated with multiple uses and other factors on safety events. In the model which accounted for the time-to-first event, single use of expedited programmes correlated inversely to the chance of safety events (adjusted HR 0.63, 95% CI 0.45 to 0.89; p=0.009), while triple or more use had marginally significant higher risk (adjusted HR 1.58, 95% CI 0.99 to 2.53; p=0.055). For the serious pattern, it was shown that new drugs granted at least three programmes were more susceptive to serious safety events (adjusted HR 4.16, 95% CI 1.69 to 10.22; p=0.002). With the recognition of interactions, the results of multiple uses did not vary

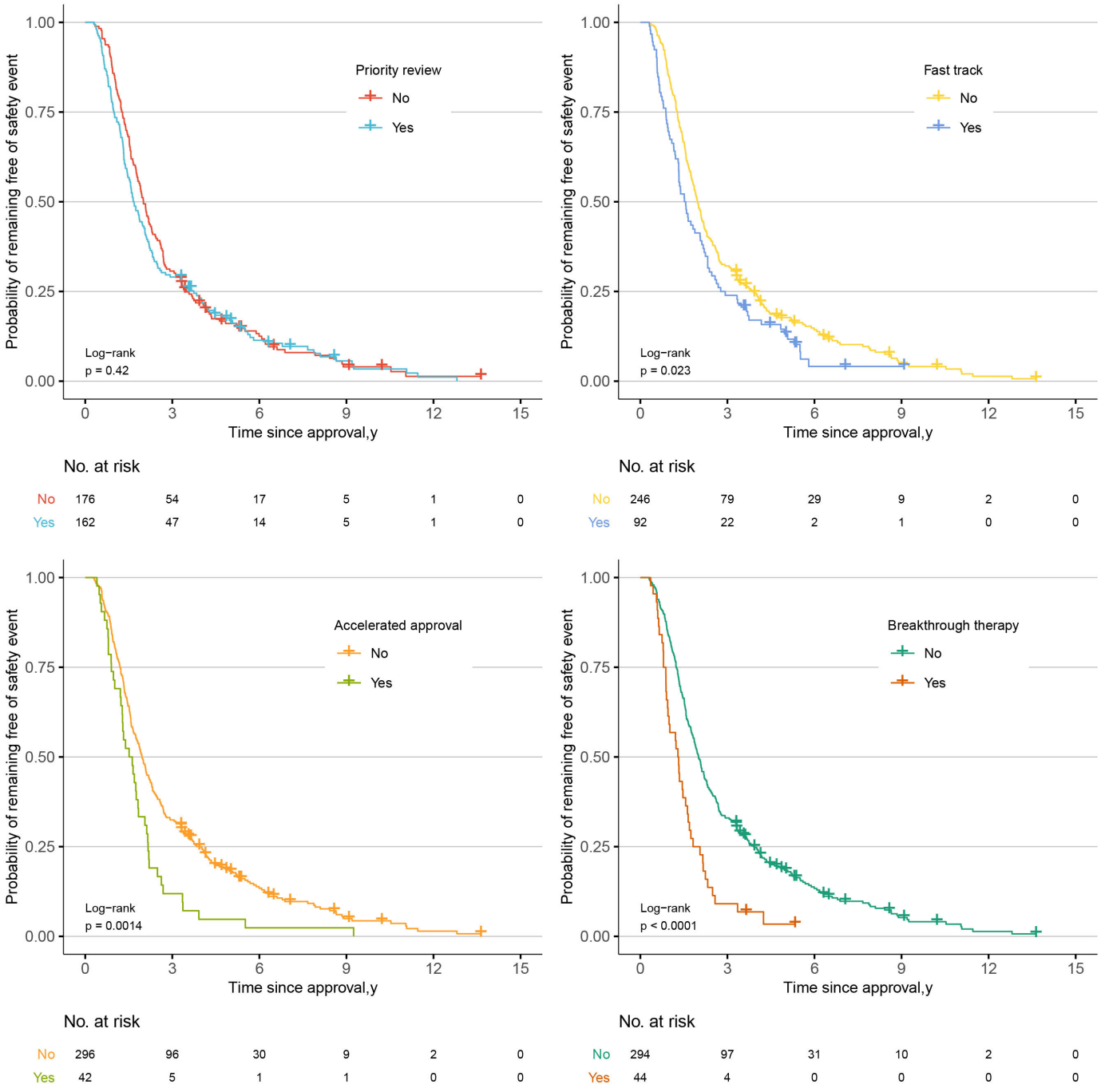

Figure 1 Kaplan-Meier curves of new drugs subject to safety events, in terms of the four expedited programmes. Each curve indicated whether the new drugs received the specified expedited programme, irrespective of the receipts of other programmes. Differences between every two curves regarding the specified programme were compared with log-rank test. The pluses on the plots denoted the censored observations.

across orphan and non-orphan drugs. Throughout both the models, REMS at approval was a strong predictor for a higher probability of safety events. The sufficient sample size for only use of priority review supported to estimate its independent association with postmarketing safety events (online supplemental table 3). It was found that, as compared with non-expedited review, only use of priority review was associated with lower risk for first event (adjusted HR 0.60, 95% CI 0.41 to 0.87; p=0.007), but with insignificant higher risk for first serious event (adjusted HR 1.37, 95% CI 0.67 to 2.81; p=0.382). Similarly, as the most common double use, the risk of priority review jointed with fast track could be assessed separately, whereas no detectable differences between their combination and non-expedited review were observed (online supplemental table 4). The small sample size precluded further collapse of the combinations, and thus the analysis for every combination was not considered.

Table 4 presents the HRs of each expedited programme and its interaction with orphan designation. In the model

Table 3 The associations between multiple uses of the expedited programmes and risks of safety events based on Cox models

	First event		First serious event	
Variables	**Adjusted HR (95% CI)**	**P value‡**	**Adjusted HR (95% CI)**	**P value**
Drug class				
NDA	1 (Reference)		1 (Reference)	
BLA	0.84 (0.63 to 1.13)	0.247	0.65 (0.34 to 1.24)	0.194
ATC category				
A	1 (Reference)		1 (Reference)	
B	0.93 (0.50 to 1.72)	0.809	1.28 (0.45 to 3.71)	0.643
C	1.31 (0.76 to 2.27)	0.332	1.26 (0.46 to 3.45)	0.650
D	0.70 (0.33 to 1.46)	0.341	0.45 (0.06 to 3.61)	0.454
G	1.17 (0.55 to 2.50)	0.684	0.62 (0.13 to 2.94)	0.548
H	0.50 (0.22 to 1.14)	0.100	NA*	
J	1.05 (0.64 to 1.73)	0.836	1.76 (0.73 to 4.23)	0.208
L	1.48 (1.00 to 2.19)	**0.049**	0.85 (0.38 to 1.94)	0.705
M	0.77 (0.38 to 1.56)	0.465	1.03 (0.27 to 3.98)	0.964
N	1.35 (0.82 to 2.22)	0.236	0.97 (0.38 to 2.44)	0.940
P	0.19 (0.06 to 0.63)	**0.006**	NA*	
R	0.85 (0.45 to 1.63)	0.631	NA*	
S	1.77 (0.69 to 4.58)	0.238	NA*	
V	0.58 (0.32 to 1.05)	0.075	NA*	
REMS at approval				
No	1 (Reference)		1 (Reference)	
Yes	1.73 (1.23 to 2.44)	**0.002**	3.29 (1.84 to 5.88)	**<0.001**
Approved year	1.06 (1.01 to 1.10)	**0.008**	1.05 (0.96 to 1.14)	0.301
Review duration, days	1.00 (0.9994 to 1.0001)	0.208	1.00 (0.9998 to 1.0006)	0.243
Orphan drug				
No	1 (Reference)		1 (Reference)	
Yes	0.85 (0.64 to 1.14)	0.270	0.43 (0.24 to 0.79)	**0.006**
No. of expedited programmes				
0	1 (Reference)		1 (Reference)	
1	0.63 (0.45 to 0.89)	**0.009**	1.08 (0.53 to 2.20)	0.220
2	1.09 (0.74 to 1.60)	0.673	1.72 (0.82 to 3.59)	0.151
≥3	1.58 (0.99 to 2.53)	0.055	4.16 (1.69 to 10.22)	**0.002**
Interaction between no. of expedited programmes and orphan designation				
0×non-orphan†	1 (Reference)		1 (Reference)	
0×orphan†	0.89 (0.54 to 1.47)	0.674	0.65 (0.24 to 1.77)	0.404
1×non-orphan†	0.65 (0.43 to 0.99)	**0.046**	0.80 (0.33 to 1.95)	0.624
2×non-orphan†	0.95 (0.59 to 1.53)	0.827	2.30 (1.03 to 5.13)	**0.042**
≥3×non-orphan†	2.27 (1.18 to 4.37)	**0.014**	6.07 (2.11 to 17.44)	**0.001**
1×orphan†	0.90 (0.45 to 1.81)	0.767	1.52 (0.35 to 6.49)	0.575
2×orphan†	1.26 (0.60 to 2.65)	0.535	0.27 (0.05 to 1.40)	0.118
≥3×orphan†	0.61 (0.26 to 1.41)	0.244	0.38 (0.09 to 1.63)	0.194

Continued

Table 3 Continued

Variables	First event		First serious event	
	Adjusted HR (95% CI)	P value‡	Adjusted HR (95% CI)	P value

*The absence of the coefficients of H, P, R, S and V under the ATC categories in columns (3) and (4) resulted from the very few observations in these groups that failed to estimate their coefficients.
† × denoted the interaction between orphan drug characteristic and characteristics of no. of expedited programmes.
‡Bold values in the table are P values lower than 0.05.
ATC, Anatomical Therapeutic Chemical; BLA, biologics license application; NA, not applicable; NDA, new drug application; REMS, risk evaluation and mitigation strategy.

Table 4 The associations between the expedited programmes and risks of safety events based on Cox models

Variables	First event*		First serious event*	
	Adjusted HR (95% CI)	P value††	Adjusted HR (95% CI)	P value
Orphan drug				
No	1 (Reference)		1 (Reference)	
Yes	0.79 (0.59 to 1.04)	0.097	0.43 (0.24 to 0.78)	**0.028**
Accelerated approval†				
No	1 (Reference)		1 (Reference)	
Yes	1.33 (0.89 to 1.97)	0.164	1.18 (0.55 to 2.51)	0.674
Priority review‡				
No	1 (Reference)		1 (Reference)	
Yes	0.84 (0.63 to 1.11)	0.215	1.59 (0.91 to 2.80)	0.106
Fast track§				
No	1 (Reference)		1 (Reference)	
Yes	1.16 (0.86 to 1.56)	0.328	1.51 (0.83 to 2.75)	0.177
Breakthrough therapy¶				
No	1 (Reference)		1 (Reference)	
Yes	1.83 (1.21 to 2.77)	**0.004**	1.73 (0.77 to 3.86)	0.181
Interactions of each programme and orphan designation				
Non-expedited×non-orphan**	1 (Reference)		1 (Reference)	
Non-expedited×orphan**	0.78 (0.50 to 1.20)	0.258	0.66 (0.27 to 1.62)	0.362
AA†×non-orphan**	0.59 (0.26 to 1.33)	0.205	0.17 (0.02 to 1.33)	0.092
AA†×orphan**	2.84 (1.12 to 7.23)	**0.028**	23.92 (2.44 to 234.45)	**0.006**
PR‡×non-orphan**	0.87 (0.59 to 1.28)	0.491	1.86 (0.96 to 3.62)	0.068
PR‡×orphan**	0.91 (0.51 to 1.61)	0.742	0.53 (0.17 to 1.68)	0.279
FT§×non-orphan**	0.91 (0.59 to 1.40)	0.680	1.45 (0.69 to 3.05)	0.333
FT§×orphan**	1.49 (0.84 to 2.63)	0.171	0.75 (0.25 to 2.26)	0.612
BT¶×non-orphan**	4.09 (2.13 to 7.84)	**<0.001**	4.35 (1.69 to 11.24)	**0.002**
BT¶×orphan**	0.31 (0.14 to 0.68)	**0.004**	0.11 (0.02 to 0.51)	**0.005**

*Adjusted for drug class, ATC classification, REMS at approval, approved year and review duration.
†A new drug receiving accelerated approval would be identified as 'yes' and 'no' otherwise, regardless its qualifications for other expedited programmes. Hence, the new drug with accelerated approval, or without it, might receive other programmes at the same time.
‡Once a new drug received priority review it would be identified as 'yes', regardless its qualifications for other expedited programmes.
§Once a new drug received fast track it would be identified as 'yes', regardless its qualifications for other expedited programmes.
¶Once a new drug received breakthrough therapy it would be identified as 'yes', regardless its qualifications for other expedited programmes.
** × denoted the interaction between expedited programme characteristics and orphan drug characteristic.
††Bold values in the table are P values lower than 0.05.
AA, accelerated approval; ATC, Anatomical Therapeutic Chemical; BT, breakthrough therapy; FT, fast track; PR, priority review; REMS, risk evaluation mitigation strategy.

checking the associations of each programme with the times to first event, breakthrough therapy associated to significant raised risk (adjusted HR 1.83, 95% CI 1.21 to 2.77; p=0.004). As to the interactions of expedited programmes with orphan designation, the bond of accelerated approval and orphan drug seemed to increase the risk for safety events (adjusted HR 2.84, 95% CI 1.12 to 7.23; p=0.028), while the risk of orphan breakthrough therapies appeared to decline (adjusted HR 0.31, 95% CI 0.14 to 0.68; p=0.004). For the serious pattern, it was revealed that the expedited programmes correlated to elevated but insignificant serious risk, whereas orphan drugs seemed less likely to encounter serious events (adjusted HR 0.43, 95% CI 0.24 to 0.78; p=0.005). The interaction of accelerated approval with orphan drug was related to escalated risk for serious safety event (adjusted HR 23.92, 95% CI 2.44 to 234.45; p=0.006), while the interaction of breakthrough therapy with orphan drug was associated with reduced risk for severe issues (adjusted HR 0.11, 95% CI 0.02 to 0.51; p=0.005).

Sensitivity analysis

To test the robustness of our results for serious safety events, the time-to-most serious event of the study drugs was modelled. The identification of most serious event was supplied in Supplementary, with other model specifications resembling the aforementioned models. New boxed warning predominated in the most serious events (online supplemental table 5). It was shown that the four programmes did not affect the risk for most serious issues, while orphan drugs with accelerated approval were associated with remarkable risk (adjusted HR 20.65, 95% CI 2.11 to 202.18; p=0.009). Triple or more use expanded the likelihood of experiencing serious events (adjusted HR 3.65, 95% CI 1.51 to 8.84; p=0.004). Results for most serious event were congruent with those for first serious event (online supplemental table 6).

DISCUSSION

The expedited programmes have been found to be beneficial by improving accessibility of new drugs with high therapeutic value, but to render larger safety risks at the same time. Our evidence furtherly reveals the increased chance of postmarketing safety events for triple or more use of expedited programmes. Theoretically, there are three major mechanisms through which different expedited programmes enlarge the uncertainty of new drugs in respect of safety and make them to be more unsafe: first, the shortened review duration makes it difficult for scrutiny of the provided evidence and the following deliberate decision[22]; second the expedited premarketing development may leave out some research or lead to less comprehensive evidence package; at last, surrogate endpoints may fail to predict the actual risk–benefit balance.[23 24] The combined use of expedited programmes which work in various fashions is assumed to pose additive risks, while our findings were still unable to support the assumption that the likelihood of safety events would arise as the number of expedited programmes increased. The HR of single use of the programmes was less than one significantly, and through further analysis the single use of priority review was observed to relate to an alleviated risk for first safety event. Priority review was determined based on the assessment of the FDA without formal requests from sponsors.[11] Accordingly, it was plausible that the selected applications only granted with priority review had sounder evidence packages which facilitated both the review process and better postmarketing performance on safety. As to the multiple use of expedited programmes, triple or more use showed greater risk for serious events, while the results of double use appeared to be insignificant. Triple or more use meant the candidates had their preapproval clinical phases interfered by at least two programmes, and thus, the evidence generated might be less complete. Moreover, it should be noted that the double use in our sample almost always contained priority review. Given the above, it was presumptive that when solely used or combined with abbreviated review duration, each programme could play a limited role in compromising the thoroughness of the resultant evidence; whereas the further expedited development process should be of concern. The effects of the double use between the other three programmes except for priority review are open to investigate due to no available observations in our sample. It is noteworthy that we found programmes influencing the evidence generation more likely to affect the risks for postmarketing safety events, while initiatives acting on the review process were less impactful. Future research is expected to determine the incremental effect of each programme.

This work also examined the associations of each expedited programme and the orphan drug pathway with postmarketing safety outcomes as prior studies used to perform, and first attempted to capture the potential interactions between expedited programmes and orphan designation. It was presented that drugs designated as orphan tended to have decreased risk for serious events. One explanation is that orphan drugs approved for rare conditions would be less utilised and therefore a relatively short period might not be enough to shape their complete picture for serious safety risk. Concerning the four expedited programmes, we found that the raised risk for safety events was associated with breakthrough therapy which had not been studied before. Breakthrough therapy offered all features of fast track along with intensive guide on trial design from the FDA, which was therefore expected to be more productive than fast track. Under breakthrough therapy the trials could be well tailored to the requirements of the agency, yet they might be likewise less-rounded, since unrequired data or outcomes might not be in the sponsor's plans. Besides, data from trials without randomisation and control groups were wide used in breakthrough therapy,[25] which might weaken the evidence; and the small size of enrolments that characterised most drugs through breakthrough therapy[25]

would make it harder to assemble safety information. We furtherly found that the orphan drugs with accelerated approval seemed to have poorer risk profiles. Pursuant to regulations,[26] the broader flexibility in applying standards for life-threatening illnesses, especially for rare conditions,[27] served the accelerated orphan drugs that were incapable of large RCTs, which also caused greater uncertainties. Strict surveillance is underlined for breakthrough therapies and accelerated orphan drugs. The seeming decreased risks of interactions of orphan drug with breakthrough therapy should be interpreted cautiously, as non-orphan breakthrough therapies had quite larger HRs which indicated again the negative association between breakthrough therapy and safety events. Breakthrough therapy designation was applied after 2012, and orphan drugs might experience longer time to be detected of safety signals, which would jointly lead to that breakthrough orphans have some safety outcomes not yet arisen or observed in the follow-up period, rather than become safer.

With more programmes received, the drugs tended to be riskier, and at the meantime, the multiple uses were common and seemingly increasing from 2007 to 2017. When expedited programmes are jointly used, intensive postmarketing surveillance and rapid response actions are entailed for these subjected medical innovations to manage safety risks and facilitate their rational use. Beside the passive vigilance of spontaneous reporting system which tends to under-report,[28] more efforts are required: active vigilance of the sentinel initiatives can serve as supplementary to understand the drug's safety profile, particularly for drugs licensed through less evident risk–benefit assessments.

This study only reflected the safety profile of new drugs, and did not attempt to give any suggestion to current employment of expedited programmes since the effects of these programmes on the effectiveness of new drugs were not involved. To assess the overall implications of expedited programmes, the efficacy profile of new drugs should be taken into account together. Some loss of safety can be justifiable for the end-of-life period and ultrarare conditions where health gain is often valued higher, and the expected patient health improvement from earlier availability of promising new drugs can outweigh its increased safety risks in some cases.

Limitations

Limitations of this study were inevitable. The results did not reflect causal effects. When estimating the coefficients of each expedited programme, their references were set to be drugs without specific programme but which might receive other programmes. Thus, the employed references might be in higher-risk situations than non-expedited drugs, and the results might be underestimated.

Besides, the used safety outcomes were still not exhaustive, more information related to safety can be included to form further evaluations. Our follow-up for safety events was relatively short and thus might be insufficient to observe safety signals for breakthrough therapies which were only created after 2012 or for drugs with small utilisation. The wide CIs in some of our results indicated the potential of outliers, which might stem from the small number of drugs affected by serious events. In our sample only 24.3% of all drugs encountered serious events, and the influence of outliers could be therefore sizeable. Expanded sample and prolonged follow-up are promising solutions to above limitations, as well as the imperative to capture independent effects of each programme and each of their combinations. Lastly, some covariates were not included, for example, factors associated with premarket meetings, other characteristics in review windows, along with the safety-related postmarketing requirements and their fulfilment. They might make a difference regarding the safety of a new drug, but we did not control their potential confounding effects.

CONCLUSION

With extended outcomes of safety events, our study revealed that breakthrough therapy correlated with enlarged risk for postmarketing safety events, and new drugs with multiple expedited programmes were more prone to serious events. The joint of accelerated approval and orphan designation was associated to notable increase risks for safety concerns as well. Close monitoring and comprehensive risk management plans are important to ensure the safe and rational use of expedited new drugs. Further studies are needed in order for the mixed utilisation of expedited programmes to better strike the speed-safety balance of new drugs.

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