Postmarket safety of orphan drugs: a longitudinal analysis of United States Food and Drug Administration database between 1999 and 2018

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Introduction

Limited by inherently small sample sizes, evidence for orphan drugs safety is scarce and inconsistent. Uncertainties surrounding the long-term safety of orphan drugs remain. This study aimed to evaluate the long-term safety of orphan drugs and to identify any approval factors associated with postmarket safety events.

Methods

Approved orphan drugs between 1999 and 2018 were identified from the United States Food and Drug Administration (FDA) database, along with their approval information and any safety-related label changes till 31 December 2019. All safety-related label changes were recorded as postmarket safety events (PMSE). Negative binomial regression was applied to assess associations between approval factors and the number of PMSEs within five years after approval. Withdrawal, suspension, and boxed warning were further categorised as severe postmarket safety events (SPSE). Time to first SPSE was described using Kaplan-Meier estimates. Cox Proportional-Hazards regression was used to assess the associations between approval factors and SPSE occurrence.

Table 1. Comparison of the four FDA expedited programs

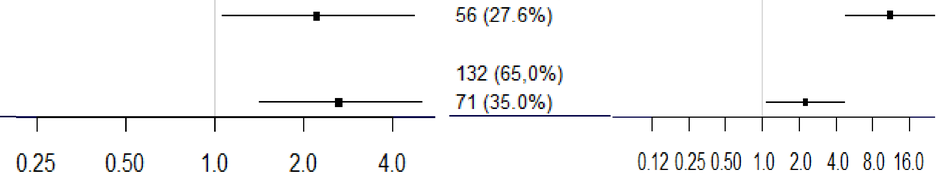
Expedited program	Type	Effect
Priority review	Designation	Reduces time of application review process from 10 months to 6 months of priority regulatory review
Breakthrough therapy	Designation	Expedites review of drugs that may show substantial improvement for patients with serious diseases over existing drugs
Fast track	Designation	Expedites drug development and review to treat serious conditions and fill unmet medical need
Accelerated approval	Approval pathway	Permits use of surrogate or intermediate clinical endpoint for filling an unmet medical need for serious conditions

Table 2. Characteristics of the novel orphan drugs approved by the FDA from 1999 to 2018

Characteristics	Number (%)
Novel orphan drugs	203
Follow-up years since approval [median (IQR)]	6.2 (2.8-11.6)
Therapeutic Area	
Antineoplastic and immunomodulating agents	95 (46.8)
Alimentary tract and metabolism	24 (11.8)
Nervous system	16 (7.9)
Blood and blood forming organs	13 (6.4)
Cardiovascular system	9 (4.4)
Systemic hormonal preparations, excl. sex hormones	9 (4.4)
Various	9 (4.4)
Anti-infective for systemic use	8 (3.9)
Musculo-skeletal system	7 (3.5)
Antiparasitic products, insecticides and repellents	6 (3.0)
Respiratory system	5 (2.5)
Sensory organs	1 (0.5)
Therapeutic radiopharmaceuticals	1 (0.5)
Approval status	
Priority Review	161 (79.3)
Accelerated Approvals	50 (24.6)
Breakthrough therapy	52 (25.6)
Approved with Boxed Warning	56 (27.6)
For Long-term Use	71 (35.0)
Near deadline approval	153 (75.4)
All postmarket safety events up to December 31, 2019	
Number of safety events	638
Withdrawal	1 (0.16)
Suspended marketing	1 (0.16)
Boxed warning	47 (7.63)
Contraindications	50 (8.12)
Drug Interactions	67 (10.88)
Warnings and Precautions	452 (73.38)
Adverse Reactions	435 (70.62)

Table 3. The relationship between approval factors with PMSEs and SPSEs

Characteristics	Approval factors and PMSEs occurrence: Proportion affected at 5 yrs, % (95% CIs)	Incidence Rate Ratio (95% CIs)	Approval factors and the number of SPSEs within 5 years: N (Proportion)	Hazard Ratio
Drug Class				
Biologics License Application	58.5 (45.1-70.7)		53 (26.1%)	
New Drug Application	40.0 (32.5-48.0)		150 (73.9%)	
Therapeutic area				
Not Antineoplastic Drugs	49.1 (39.8-58.4)		108 (53.2%)	
Antineoplastic Drugs	73.7 (64.0-81.5)		95 (46.8%)	
Priority Review vs. Standard Review				
Standard Review	61.9 (46.8-75.0)		42 (20.7%)	
Priority Review	60.2 (52.5-67.5)		161 (79.3%)	
Accelerated Approval vs. Not Accelerated Approval				
Not Accelerated	54.9 (47.0-62.6)		153 (75.4%)	
Accelerated	60.4 (46.3-73.0)		50 (24.6%)	
Breakthrough Therapy vs. Not Breakthrough Therapy				
Not Breakthrough	59.6 (51.6-67.1)		151 (74.4%)	
Breakthrough	63.5 (49.9-75.2)		52 (25.6%)	
Near regulatory deadline approval vs. Regular approval				
Regular	58.0 (44.2-70.6)		50 (24.6%)	
Near regulatory deadline	61.4 (53.5-68.8)		153 (75.4%)	
Approved with boxed warning vs. Approval without boxed warning				
No boxed warning	40.9 (33.4-49.0)		147 (72.4%)	
With boxed warning	50.0 (37.1-62.9)		56 (27.6%)	
For long term use vs. Not for long term use				
Not for long term use	50.8 (42.3-59.1)		132 (65.0%)	
For long term use	78.9 (68.0-86.8)		71 (35.0%)	



Results

1. 203 orphan drugs were approved by the FDA (84.2% approved through at least one expedited program, 27.6% approved with boxed warning).
2. During a median follow-up of 6.2 years since approval, 69.0% (n=140) of the orphan drugs had PMSE and 15.3% (n=31) had SPSE.
3. PMSEs were more frequent among orphan drugs approved for long-term use [incidence rate ratio (IRR)=2.62; 95% confidence interval (CI)=1.41-5.00] and those approved with boxed warnings (IRR=2.20, 95% CI=1.06-4.71).
4. Time to first SPSE was 4.4 [standard deviation (SD)=3.6] years. Approved with accelerated approval, approved for long-term use and approved with boxed warning were also associated with a higher risk of SPSE.

Conclusions

Amongst all FDA-approved orphan drugs, 15.3% were affected by SPSEs. Orphan drugs approved with accelerated approval, approved for long-term use, and approved with boxed warning have a higher risk of severe safety events. Long-term safety surveillance is imperative to ensure patient safety during the postmarketing phase.