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# LETTERS TO THE EDITOR

## Premarket safety population size associated with approval of expedited program drugs and orphan drugs

Safety populations consist of patients used to assess premarket drug risks and are valuable for detecting commonly occurring adverse drug effects, deciding drug approvals, and planning postapproval studies. For expedited programs and orphan drugs, which address unmet medical needs of rare diseases that affect fewer than 200,000 individuals in the United States, the safety populations are often limited in size [1−4]. Whether safety population size affects marketing approval of these drugs remains unclear. This study informs on whether a large safety population, defined as 1,500 or more subjects, helps predict approval of these drugs.

### 1. Method

The observational study included drug applications under expedited programs or orphan drugs that the FDA's Center for Drug Evaluation and Research (CDER) reviewed for approval from 1 October 2007 to 19 August 2014. Approved and nonapproved fast track and orphan drugs, from FDA's regulatory science databases, were analyzed for factors associated with drug approval.

Multivariable logistic regression models were used to assess the relationship of safety population size and drug approval, while adjusting for confounders. Potential confounders were safety population size adequacy, drug product type (biologic or drug), drug designation group (combined fast track and orphan, fast track only, or orphan only), chronic drug use, priority review status, FDA CDER Office, and treatment indication category. Efficacy was not a covariate because all the drugs were expected to show efficacy for FDA to review the drug applications. Reasons for nonapproval were explored in additional analyses of regulatory correspondences. Statistical analyses were conducted using JMP, version 11 (SAS Institute). A two-sided $P$ value less than 0.05 was considered significant. The study did not involve human subjects.

### 2. Results

Of 100 fast track and orphan drugs, 86 were approved and 14 nonapproved, Figure 1. Baseline characteristics showed approved drugs having a higher rate of drugs under chronic use and priority reviews, in Supplementary Data Table. Approved drugs had a median safety population size of 1,096 (IQR, 597-2,120) subjects, and nonapproved 721 (IQR, 280-1,154) subjects. Notably, 34% (29/86) of approved drugs and 14% (2/14) of the nonapproved had large safety populations.

On adjusting for variables shown in Table 1, large safety population was associated with increased odds of drug approval over nonapproval (adjusted OR, 10.75; 95% CI, 1.52−133.43). Similarly, adequately sized safety populations, FDA reviews deemed sufficient, were associated with increased odds of drug approval (adjusted OR, 4.4; 95% CI, 1.04−20.72). Additional analyses showed efficacy issues predominated as reasons for nonapprovals.

### 3. Discussion

Having a large safety population was associated with drug approval. Only a third of the approved drugs presented large safety populations. Safety populations likely reflect disease prevalence, which in some cases may not allow for large safety populations. Regulatory guidelines for determining safety population size adequacy for these drugs are limited. The study's findings may provide support for sponsors discussing early with regulatory bodies regarding what constitutes adequate safety populations [4,5]. In addition, efficacy issues detected during regulatory review cannot be ignored as key reasons for drug nonapproval. Study limitations include sample size, unaccounted confounders, and expedited programs, including the recently introduced breakthrough therapy designation.

### CRediT authorship contribution statement

**Kachi Illoh:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

Disclaimer: This article reflects the views of the author and should not be construed to represent FDA's views or policies.

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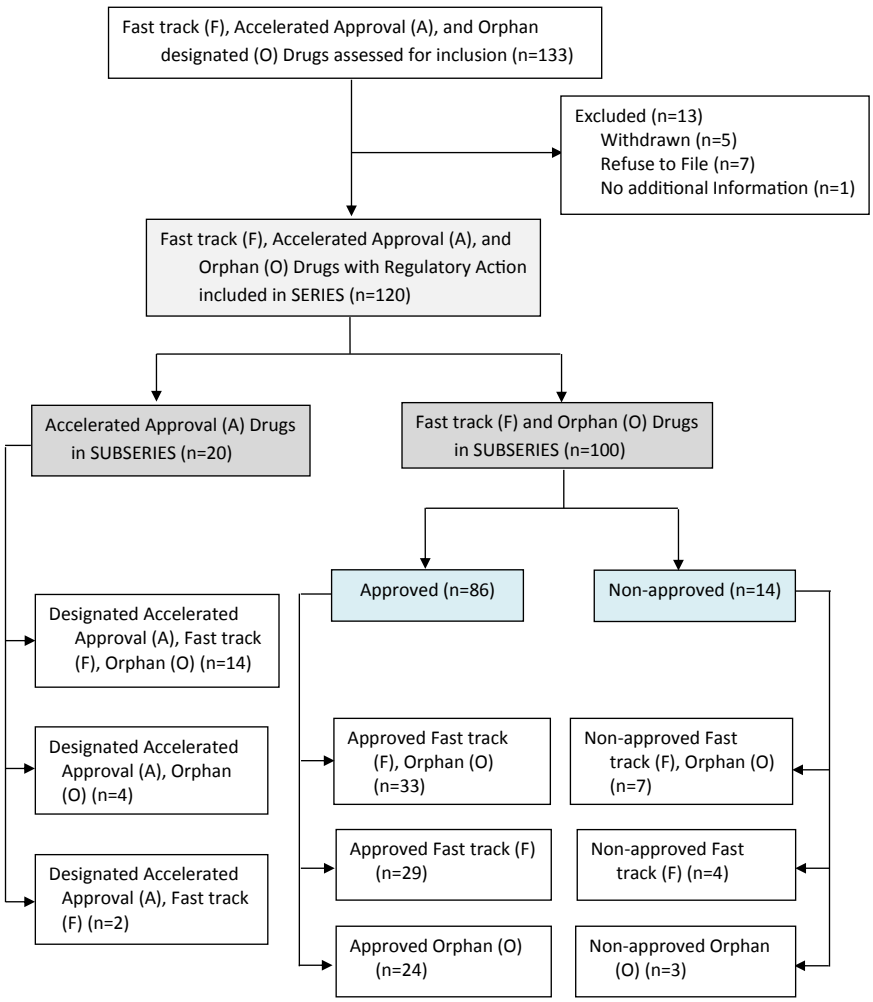


**Figure 1.** Flowchart of expedited program and orphan drugs with marketing approval decision between October 2007 and August 2014, entire series and subseries. (This report excludes description of the Accelerated Approval subseries).

**Table 1**
Association between drug characteristics and approval of fast track and orphan drugs

| Variable | Approval, *N* (%) (*n* = 86) | Nonapproval, *N* (%) (*n* = 14) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| Safety population size | | | | |
| Small to medium (<1,500) | 57 (66.3) | 12 (85.7) | 1 (Reference) | 1 (Reference) |
| Large (≥1,500 subjects) | 29 (33.7) | 2 (14.3) | 3.05 (0.77–20.46) | 10.75 (1.52–133.43) |
| Safety population size adequacy | | | | |
| Inadequate or unclear | 19 (22.1) | 7 (50.0) | 1 (Reference) | 1 (Reference) |
| Adequate | 67 (77.9) | 7 (50.0) | 3.53 (1.08–11.56) | 4.40 (1.04–20.72) |
| Drug program combination | | | | |
| Fast track and orphan | 33 (38.4) | 7 (50.0) | 1 (Reference) | 1 (Reference) |
| Fast track only | 29 (33.7) | 4 (28.6) | 1.54 (0.42–6.37) | 1.03 (0.18–6.72) |
| Orphan only | 24 (27.9) | 3 (21.4) | 1.70 (0.43–8.49) | 2.82 (0.55–18.24) |
| Chronic drug use (at least 3 mo) | | | | |
| No | 20 (23.3) | 7 (50.0) | 1 (Reference) | 1 (Reference) |
| Yes | 66 (76.7) | 7 (50.0) | 3.30 (1.02–10.77) | 7.37 (1.57–45.26) |
| Priority review status | | | | |
| Standard | 28 (32.6) | 11 (78.6) | 1 (Reference) | 1 (Reference) |
| Priority | 58 (67.4) | 3 (21.4) | 7.60 (2.17–35.58) | 13.15 (2.90–87.40) |

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## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2019.04.021.

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