Research Letter | Health Policy

US Food and Drug Administration Review Time of Supplemental New Indication Approvals of Drugs and Biologics, 2017 to 2019

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Introduction

In October 2022, the US Food and Drug Administration (FDA) announced the Split Real-Time Application Review (STAR) pilot program under the Prescription Drug User Fee Authorization Act VII. Like its predecessor, the Real-Time Oncology Review (RTOR) program for oncology drugs, STAR is designed to shorten regulatory review of supplemental new indication approvals of drugs and biologics that treat serious conditions with an unmet need. The STAR program allows the FDA to begin reviewing Part 1 submissions (containing all components of the efficacy supplement except for final clinical study reports and integrated summaries of effectiveness and safety) as received, in a split fashion, with Part 2 submissions (containing the aforementioned items) submitted roughly 2 months later.

Preliminary evidence suggests that supplemental new indication applications were reviewed 3 months faster within RTOR compared with those only designated for priority review. However, baseline regulatory review times for STAR for nononcology indications are not established. Accordingly, we characterized the FDA regulatory review time of supplemental new indication approvals of drugs and biologics approved between 2017 and 2019.

Methods

From a previously collected sample of all new supplemental indication approvals of drugs and biologics between January 1, 2017, and December 31, 2019, we identified submission and approval dates from approval letters obtained from the Drugs@FDA database. We used previously described methods to determine whether supplemental new indications were approved under other special regulatory programs and their therapeutic area. Regulatory review times were rounded to the nearest month and described using medians and IQRs. Institutional review board approval and

Table. Regulatory Review Time for US Food and Drug Administration Supplemental New Indication Approvals of Drugs and Biologics Between 2017 and 2019

<table>
<thead>
<tr>
<th>Stratification category</th>
<th>No. of approvals (%) (N = 146)</th>
<th>Median regulatory review time (IQR), moa</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>99 (67.8)</td>
<td>6 (6-10)</td>
<td>.20</td>
</tr>
<tr>
<td>Biologic</td>
<td>47 (32.2)</td>
<td>6 (6-10)</td>
<td></td>
</tr>
<tr>
<td>Special regulatory program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>72 (49.3)</td>
<td>10 (6-10)</td>
<td>.0119</td>
</tr>
<tr>
<td>Any</td>
<td>74 (50.7)</td>
<td>6 (5-6)</td>
<td></td>
</tr>
<tr>
<td>Accelerated approval</td>
<td>20 (13.7)</td>
<td>6 (6-6)</td>
<td>.0118</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>35 (24.0)</td>
<td>6 (4-6)</td>
<td></td>
</tr>
<tr>
<td>Non-RTOR priority review</td>
<td>49 (33.6)</td>
<td>6 (5-6)</td>
<td>.0074</td>
</tr>
<tr>
<td>RTOR</td>
<td>12 (8.2)</td>
<td>3 (2-4.5)</td>
<td>.0118</td>
</tr>
<tr>
<td>Therapeutic area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncology</td>
<td>78 (53.4)</td>
<td>6 (5-6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nononcology</td>
<td>68 (46.6)</td>
<td>10 (6-10)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: RTOR, Real-Time Oncology Review.

a Overall median regulatory review time was 6 (IQR, 6-10) months.

b Represents comparison between time to approval for approvals under any special regulatory program vs none.

c Represents comparison between time to approval for RTOR and non-RTOR priority review approvals.
informed consent were not required because this cross-sectional study was based on publicly available information and involved no patient records, in accordance with 45 CFR §46. The study followed the STROBE reporting guideline. All analyses were performed using JMP Pro, version 16.0.0 (SAS Institute). Data analysis was performed between October 28 and November 11, 2022.

Results

From 2017 to 2019, the FDA approved 107 therapeutics for 146 supplemental new indications, including 99 small molecule drugs (67.8%) and 47 biologics (32.2%) (Table). Of these, 78 (53.4%) were oncology therapeutics and 74 (50.7%) received at least 1 special regulatory review designation, including 50 (64.1%) designated for priority review and 12 (8.2%) reviewed under RTOR. Of the 50 designated for priority review, 12 (24.0%) were also approved under RTOR.

The median regulatory review time was 6 (IQR, 6-10) months, with no difference between drugs and biologics (6 [IQR 6-10] months for both; \( P = .20 \)) (Table). However, the median regulatory review time was significantly shorter for oncology therapeutics that received at least 1 special regulatory review designation (6 [IQR, 5-6] months) compared with nononcology therapeutics (10 [6-10] months; \( P < .001 \)) and for oncology therapeutics reviewed under RTOR (3 [2-4.5] months) compared with non-RTOR approvals designated for priority review (6 [5-6] months; \( P < .001 \)).

Discussion

In this cross-sectional study of 146 supplemental new indications approved by the FDA between 2017 and 2019, the median regulatory review time was 6 months. Consistent with prior studies, the shortest review times were for supplemental new indication approvals reviewed under RTOR, which were roughly half the duration of non-RTOR oncology approvals designated for priority review.\(^3\)

Limitations of this study include its 3-year sample and not accounting for approvals in other countries, which the FDA may have considered in its evaluations.

These findings inform efforts to launch STAR and suggest that the program may shorten regulatory review times for supplemental new indication approvals. However, the administrative burden required to meet shorter deadlines deserves consideration, particularly since physicians can prescribe approved products off label and FDA approval may not affect insurance coverage. In addition, shorter regulatory review times may be associated with unintended risks, as shorter regulatory review has been associated with an increased risk of FDA safety actions after approval for new drugs.\(^5,6\) The STAR program should ensure that the FDA has adequate resources to staff more rapid review of supplemental new indication applications.

ARTICLE INFORMATION

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Author Contributions: Ms Dhodapkar and Dr Ramachandran had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Dhodapkar.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Dhodapkar.

Supervision: Ross, Ramachandran.

Conflict of Interest Disclosures: Ms Dhodapkar reported receiving a Ruth Jackson Orthopaedic Society Annual Meeting Medical Student Scholarship outside the submitted work. Ms Dhodapkar also reported serving as the associate editor of visual abstracts for the North American Spine Society Journal. Dr Ross reported receiving grants from the US Food and Drug Administration (FDA), Johnson & Johnson, the Medical Devices Innovation Consortium, the Agency for Healthcare Research and Quality, and the National Heart, Lung, and Blood Institute outside the submitted work. Dr Ross also reported serving as an expert witness at the request of the relator’s attorneys, the Greene Law Firm, in a qui tam suit alleging violations of the False Claims Act and Anti-Kickback Statute against Biogen, Inc that was settled in September 2022. Dr Ramachandran reported receiving grants from the Laura and John Arnold Foundation, the Stavros Niarchos Foundation, and the FDA during the conduct of the study and consulting fees outside the submitted work from the ReAct-Action on Antibiotic Resistance Strategic Policy Program at Johns Hopkins Bloomberg School of Public Health, which is funded by the Swedish International Development Cooperation Agency. Dr Ramachandran also reported serving as unpaid chair of the FDA Task Force of Doctors for America and as board president of Universities Allied for Essential Medicines North America.

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Data Sharing Statement: See the Supplement.

REFERENCES

SUPPLEMENT.
Data Sharing Statement