PINK SHEET
CITELINE REGULATORY

25 Jun 2019 | **Partnered Content**

# Mapping The FDA Approval Path: 20 Years Of Precedent With RxTROSPECT

*Thought Leadership In Association With RxTROSPECT*

by

The pace of innovation in oncology, with aggressive drug development, new approaches such as immunotherapies, increasing patient segmentation and multiple drug targets even within a single cancer type demands equally creative responses from regulators. The US Food and Drug Administration (FDA) has expedited cancer-drug development through mechanisms and incentives such as the accelerated approval program, the breakthrough therapy designation and the Orphan Drug Act. Associated initiatives such as adaptive study endpoints, reliance on earlier evidence supplemented by real-world data and less complex trial designs have helped to ease the pathway for cutting-edge cancer therapies.

The pace of innovation in oncology, with aggressive drug development, new approaches such as immunotherapies, increasing patient segmentation and multiple drug targets even within a single cancer type demands equally creative responses from regulators. The US Food and Drug Administration (FDA) has expedited cancer-drug development through mechanisms and incentives such as the accelerated approval program, the breakthrough therapy designation and the Orphan Drug Act. Associated initiatives such as adaptive study endpoints, reliance on earlier evidence supplemented by real-world data and less complex trial designs have helped to ease the pathway for cutting-edge cancer therapies.

These flexibilities are of considerable benefit to drug developers. However, they create challenges in gauging regulatory requirements and plotting the optimal approval pathway for pipeline oncology products. The speed and volume of change are daunting, and there is also little detailed, actionable information available on FDA precedents for key parameters such as surrogate endpoints, acceptable patient numbers for cancer studies or pragmatic regulatory

concessions such as streamlined trial designs.

For example, the shift to personalized medicine has seen many cancer-drug candidates positioned for rare-disease indications. In this setting, where unmet needs may be acute, patient availability for trials limited, indications more diverse and comparative therapies non-existent the FDA may be more inclined to relax its approval criteria by permitting single-arm studies or accepting less stringent endpoints such as overall response rates (ORRs).

For orphan drugs, it is "tremendously challenging to recruit for these large comparative studies, particularly in the ultra-orphan space," comments Mark Rutter, head of strategic partnerships at Chicago-based RxTROSPECT Oncology. "It just becomes a question of feasibility." Moreover, some rare diseases are typically so debilitating to patients that "any type of clinical response can have a huge benefit on their quality of life," he observes.

"If you look back at the approvals for multiple myeloma, the acceptable endpoints 15 years ago tended to be time to progression and ORR, then with the next generation of proteasome inhibitors and imids [immunomodulating agents], as unmet need evolved, you were looking at progression-free survival with supporting overall survival," Rutter notes. "Then suddenly you get these remarkable agents like daratumumab and others in the later lines, which are incredibly efficacious and well tolerated, and the FDA needed to approve them on a surrogate endpoint, that is, ORR. So these things can just evolve so quickly."

## *A Clear Picture Of Approval Requirements*

For companies planning development strategies and/or looking to substantiate investor interest, having a clear picture of when and how these concessions may apply is invaluable in mapping out an approval pathway, raising or allocating funds and informing future discussions with the FDA on regulatory requirements for cancer drugs. RxTROSPECT has been gathering, analyzing and customizing information on FDA approval trends in oncology since the turn of the millennium. It has built a substantial database (including some 12,000–13,000 data points) of regulatory precedents for cancer drugs, enriched with analytics and extracted into easily searchable terms structured around some 35 key parameters, such as patient numbers, study designs or trial endpoints.

The RxTROSPECT data fall into three main areas:

- All the relevant drug names and approved oncology indications to date including the regulatory designations at approval, for example, fast track, breakthrough, orphan, priority

review, accelerated/regular approval, etc.

- Key characteristics of the pivotal study(s) used for registration including the phase, whether the trials were single-arm or comparative, the primary registrational endpoint(s), the number of patients recruited for each trial, etc.

- A summary of the risk-benefit equation for each approval, in line with product labeling and including information on clinical-trial designs (e.g., umbrella, adaptive). This extends to whether real-world data were used as a component of the approval package, as was the case with Pfizer's Ibrance (palbociclib) for male breast cancer.

Search results from the RxTROSPECT tool are presented as user-friendly dashboards, with data and charts that can be downloaded into PowerPoint presentations in a matter of seconds. Instead of sifting through 1,000-page review documents for clues to FDA thinking in a fast-evolving regulatory landscape, tool users can zero in on exactly what steps they should take to optimize their regulatory strategy and de-risk R&D decision-making.

## *Single-Arm Studies In Oncology*

As one illustration of how regulatory requirements have adjusted to the needs and circumstances of oncology-drug development, RxTROSPECT's online tool shows that of 120 new cancer indications approved by the FDA on the basis of a single-arm study, 98 carried an orphan-disease designation (ODD) and 39 a breakthrough-therapy designation (BTD). Exhibit 1 gives a comparative overview of approval times and patient numbers for single-arm cancer-indication studies with or without orphan-drug status.

*Exhibit 1. FDA single-arm approvals for oncology indications, orphan versus non-orphan*

*Click here to explore this interactive content online*