SOCIETY FOR TRANSLATIONAL ONCOLOGY®
The Oncologist IS THE SOCIETY'S OFFICIAL JOURNAL

2017 Society for Translational Oncology Fellows' Forum

# Oncology Drug Development: A Regulatory Perspective

Faculty Presenter
**Tatiana Prowell, MD,** Breast Cancer Scientific Lead, FDA Office of Hematology & Oncology Products; Assistant Professor of Oncology, Johns Hopkins Kimmel Comprehensive Cancer Center, U.S. Food & Drug Administration, Silver Spring, MD, USA

## Scholars' Summaries

*Authored by **Robyn M. Scherber, MD, MPH**, Oregon Health and Sciences University, Portland, OR, USA*

In her presentation at the 2017 Society for Translational Oncology Fellows' Forum, Dr. Tatiana Prowell discussed the regulatory considerations of oncology drug approval in the United States (US). Dr. Prowell is a Scientific Liaison at the Federal Drug Administration (FDA) as well as a breast cancer physician.

*The History of Drug Laws in the US*

In the history of the US, regulation of drugs in the US is a relatively new development. In 1906, the US enacted the Food and Drug Act, which was the first law of its kind to provide the FDA with the power to enforce regulations against misbranded and adulterated foods and drugs. However, these requirements were only enforced if the drug had been discovered.

In 1938, the Federal Food, Drug and Cosmetic (FD&C Act) was written and passed by Congress. This act introduced the review of a new drug by the FDA prior to its availability to patients. However, in 1957 the "experiential" administration of thalidomide, given to 1000 patients, was submitted to the FDA. Ultimately this drug was not approved due to phocomelia; this story highlights the importance of testing in the development of new drugs.

The 1962 Kefauver-Harris Drug Amendment to the FD&C act required that drugs must be safe and effective. The drug approval must be based on substantial evidence consisting of well-controlled trials and conducted by experts with sufficient training and experience.

Due to the work of patient advocacy groups, namely in HIV and malignancy, accelerated approval regulations were enacted in 1992. The approval was conditioned on a "surrogate endpoint reasonably likely to predict clinical benefit." A new drug must be better than "available therapy", and post marketing trials were required to confirm benefit of the drug. Approximately 15% of drugs with accelerated approval will not go on to get full approval.

In 1997, the FDA modernization act was created to expedite drug development for life-threatening diseases. This act created the fast track and priority review categories in FDA drug approval. Since then, there have been a few more laws which have impacted drug approval in the US, but we have for the most part a developed and thorough system of drug approval, particularly for oncology drugs.

*Challenges in Drug Development*

Oncology drug development brings with it many challenges. Given that drugs are being developed for life-threatening diseases, tension between patient access and time frame is inevitable. Drug approvals are often based on small populations with short exposure times. Severe toxicities may be deemed acceptable to achieve even modest effectiveness. Indications for treatment are extremely broad, ranging from prevention to treatment of incurable rapidly progressive disease. Registration trials may poorly predict real-world experiences with an oncology drug. Once the drug is marketed, patients previously routinely treated, such as those with poor performance status, end-organ dysfunction, cytopenias, or CNS involvement, may be excluded.

*Elements to FDA Drug Approval*

Ultimately, drug approval is given based on two critical elements: 1) substantial evidence of efficacy with acceptable safety in well-conducted studies with adequate controls, and 2) the ability to generate product labeling that outlines the patient population and provides sufficient information to allow for safe and efficacious use.

In the FDA, there are a few designations for drug development that are important for understanding the oncology drug approval process.

A. Fast track: granted early in clinical development. This can be based on clinical responses in a specific indication. Ultimately this entitles a company to a rolling new drug application (NDA) submission.
B. Priority review: determined after the complete NDA submission. Priority review is granted if there is no existing therapy or the drug appears to have significant improvement compared to marketed products. This designation expedites the goal date for regulatory action by 4 months (i.e., 10 months standard approval, 6 months accelerated approval).
C. Accelerated approval: based on an endpoint other than a direct measure of clinical benefit or validated surrogate. It is not based in borderline evidence in an established endpoint or a failed trial. This designation is contingent on further post-marketing studies to validate an established endpoint.

The challenge of accelerated approval usually regards the secondary testing that must occur to ensure that established response endpoints are met. This can include the difficulties of enrolling patients into a clinical trial in which the drug is already widely available. A mitigating strategy would be to initiate the confirmatory study and enroll patients prior to receiving accelerated approval.

*The Importance of Clinical Benefit As an Endpoint*

So what is clinical benefit? There is a US regulatory definition of clinical benefit as “how a patient feels as a direct measure based on epidemiologic, therapeutic, pathophysiologic, or other evidence.” Although overall survival is a critical endpoint demonstrating clinical benefit, it is often not feasible, as it requires larger sample sizes and longer studies. There are instances in which progression free survival is not impressive, but significant improvements are seen in overall survival. An example of this is the study of nivolumab in metastatic renal cell carcinoma.

Response may indicate direct clinical benefit in some circumstances. In this instance, there are key considerations that are evaluated, including 1) magnitude of response, 2) nature of response, 3) association of response with symptoms, 4) depth of response (i.e., waterfall plot), and 5) durability and persistence of response. If these surrogate endpoints are impressive and result in significant improvements in duration or quality of life, even single arm trials may be granted full approval.

Progression free survival (PFS) is the time from randomization to disease progression or death from any cause. An alternative endpoint is time to progression (TTP), which is defined by the time from randomization to disease progression or death from disease progression. Due to difficulties with determining the cause of death, the FDA generally prefers PFS over TTP. The challenges of PFS include missing assessments, insufficient assessments, non-measurable disease (bone metastases, fluid collections), inadvertent unblinding, discordance between investigator and independent radiologic review, and uncertainty about the clinical benefit of PFS alone, particularly if PFS is small.

*Patient-reported Outcomes (PRO)*

Clinicians often underreport symptoms, and therefore the use of PRO measures have been employed to directly assess clinical benefit. In the Basch et. al. trial of self-reported symptom monitoring presented at ASCO 2017, not only were ED visits and QOL improved with patient reported symptom monitoring, overall survival improved from 26.0 to 31.2 months (P=0.03). Challenges regarding PRO measures can include issues with reliability, language translation, detection of changes over time that are meaningful and relevant to treatment, and appropriate recall time frame. The FDA is trying to incorporate PRO measures into future trials.

*Conclusions*

In conclusion, the FDA is a regulatory agency that incrementally became responsible for the monitoring and regulation of drugs in the US. In regards to oncology drugs, there are multiple designations in the approval process that may indicate expedited time to review or approval that may require additional data compared to full approval. Determining clinical benefit endpoints can be challenging during the evaluation of oncology drugs. PRO instruments can be helpful and effective in monitoring direct patient benefit of drugs and are being included in new clinical trials.

---

*Authored by **Clinton Yam, MD**, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA*

Until 1906, there was little regulatory oversight in the commercialization of medicines and adulterated foods, resulting in several harmful consequences to the public. Through this highly interactive and exceptionally engaging lecture, Dr. Tatiana Prowell took us through the history of the Food and Drug Administration (FDA), the modern day challenges of oncology drug development and regulatory decision-making, the drug review and approval process from a regulatory perspective, and common errors to avoid in the development of oncology drugs for regulatory approval.

Although the Food and Drug Act of 1906 gave the FDA authority to enforce laws forbidding misbranded and adulterated food and drugs, the FDA did not have a role in pre-market evaluation of drugs. This led

to nationwide medical catastrophes like the Elixir Sulfanilamide Disaster of 1937. In response, the 1938 Federal Food, Drug and Cosmetic Act (FD&C) mandated pre-market safety testing of drugs for the first time in the world. The FD&C Act was amended in 1962, introducing modern standards of regulatory evidence of efficacy, in addition to safety, to support drug approval. However, this invariably led to delays in getting new and effective drugs to patients. Thus, in 1992, Accelerated Approval Regulations were introduced to facilitate approval of new drugs for life-threatening diseases such as AIDS and cancer. Since then, several other amendments were introduced to increase the efficiency of drug development from a regulatory standpoint.

Because cancer is a life-threatening illness, there is a constant tension between providing patient access and adequately studying the new drug. Multiple avenues for expedited development and review exist for new oncology drugs, and differences between Fast Track Designation, Priority Review, Accelerated Approval, and Breakthrough Therapy Designation were thoroughly clarified. In parallel, the importance of appropriate selection of endpoints for clinical trials in oncology and getting the FDA involved early was highlighted through several examples of successful regulatory experiences. Importantly, the appropriate integration of patient-reported outcomes as an endpoint in clinical trials and measure of clinical benefit was highlighted, giving us the opportunity to understand many of the practical considerations involved.

Multiple pitfalls exist in oncology drug development. As a result of our efforts to bring new drugs to patients as efficiently as possible, drug approvals are often based on small populations of patients in clinical trials with relatively short exposures. Thus, real-world experiences with an oncology drug may differ from reported observations in clinical trials. In addition, several common errors in developing oncology drugs for approval were discussed, including lack of dose optimization, failure to isolate the effect of the new drug, and biomarker misadventures.

In summary, the FDA assesses clinical benefit of a drug in terms of the net benefit/risk ratio, and this outstanding lecture underscored the fact that, while many regulatory challenges exist in oncology drug development, everything we do as physicians is first and foremost for the good of patients; as long as we keep that as our compass always, we can hope to change the lives of many through the work that we do.

---

*Authored by **Xin Gao, MD**, Beth Israel Deaconess Medical Center, Boston, MA, USA*

There are several considerations which are specific for drug development in oncology. Most importantly, oncology drugs are developed for life-threatening diseases, and there may be a natural tension between providing patients early access to the drugs and having adequate data on the safety and efficacy of such drugs. As a result, oncology drug approvals are often based on small populations of patients with relatively short exposures to the drugs and limited longer-term safety data. Furthermore, severe toxicities may be deemed more acceptable in oncology drugs in order to achieve modest gains in efficacy. Large registration trials may not readily predict real-world experiences as clinical trials often

exclude patients based on marginal performance status, end-organ dysfunction, diminished marrow reserve, or brain metastases.

The Food and Drug Administration (FDA) has developed several mechanisms to expedite drug development and review which are particularly relevant in oncology. These exclude (i) fast track designation, (ii) priority review, (iii) accelerated approval, and (iv) break-through therapy designation. First, fast track designation may be granted to a drug early in its clinical development and entitles the company to a rolling New Drug Application (NDA) or Biologic License Application (BLA) submission. Second, priority review is a designation granted to companies after the NDA or BLA submission for products thought to represent a significant improvement compared to marketed products or if no satisfactory alternative therapy exists. Priority review typically expedites the goal date for regulatory action to 6 months from the standard 10-month review process. Third, accelerated approval is an FDA approval based upon a surrogate endpoint that is reasonably likely to predict clinical benefit and requires validation of an established clinical benefit via a subsequent confirmatory trial. Accelerated approval is particularly relevant for oncology drugs as the mechanism is meant to expedite the availability of drugs for serious or life-threatening diseases for which few or no good alternative therapies exist. Finally, the breakthrough therapy designation may be granted for drugs intended to treat a serious or life-threatening disease and has preliminary clinical evidence indicating potential substantial improvement over existing therapies on at least one clinically significant endpoint. The breakthrough therapy designation is of greatest value early in drug development as it allows the company to receive early input from subject matter experts from all disciplines in review divisions and “real-time” response to development strategy.

Despite the complexities of the drug development and regulatory process, FDA regulators view clinical benefit in terms of whether the net benefit-risk ratio of a drug is favorable. In other words, would cancer patients be better off having widespread access to this drug or not? This question may be more salient in oncology, where the stakes are higher due to the acuity and life-threatening nature of the disease. Whether we are involved in direct patient care, clinical investigation, drug development, or regulatory affairs, it is imperative that oncologists bear in mind that the good of the patient should be first and foremost and let this be the guiding compass in everything that we do.