

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 **Roberto A. Leon-Ferre, MD**, Mayo Clinic College of Medicine, Rochester, MN, USA

Dr. Tatiana Prowell provided us with a fantastic overview of the FDA review process, including an extremely helpful clarification of the categories for expedited development and review. She also provided a historical perspective on the public cases that led to the establishment of some of the FDA rules and regulations. Some of the key points exposed by Dr. Prowell included:

- For drug approval, 2 key elements must be present: 1) there must be substantial evidence of efficacy with acceptable safety in adequate and well-controlled studies, and 2) Data available must provide the ability to generate product labeling.
- There are 4 expedited development and review designations by the FDA, and the implications of obtaining one of these designations may not be immediately obvious to the public (including treating physicians):
 - Fast track: it is a designation granted early in clinical development. This is a really low bar to meet, and most oncology drugs receive this designation. Basically, it has to be shown that there is evidence of clinical response (even one) for a specific indication and that there is an acceptable development plan. The drug company benefits from the good marketing this generates, but practically speaking, it is not a very important designation.
 - Priority review: allows a drug to be reviewed in 6 months (compared to 10 months in standard review). This designation is granted if the drug represents a significant improvement compared to available products and there is no satisfactory alternative.
 - Accelerated approval: it is a form of conditional/provisional approval, based upon an endpoint other than a direct measure of clinical benefit or validated surrogate. Direct measure of clinical benefit or validated surrogate must be confirmed later; if not, drug is taken off the market.
 - Breakthrough therapy: granted for a drug and an indication that treats a life-threatening disease and has preliminary clinical evidence indicating potential substantial improvement over existing therapies on at least one clinically significant endpoint. Usually given to drugs that the FDA thinks are going to be transformative.
- Dr. Prowell then defined the main endpoints for trials, along with their advantages and disadvantages: Overall survival, progression free survival, time to progression, overall response rate.
- She then illustrated with real cases some of the common errors in drug development, for example: using the maximum tolerated dose in inappropriate circumstances, testing a hypothesis not relevant for the United States' population, and flaws in design that do not allow isolation of the effect of the drug of interest.

Authored by **Toru Mukohara, MD, DMedSci**, Kobe University Hospital, Kobe, Japan

Dr. Tatiana Prowell started her talk by introducing the history of drug regulation law and the Food and Drug Administration (FDA), which included a disastrous story of Elixir Sulfanilamide in the 1930s, reminding us of the purpose of the FDA and drug regulation. Subsequently, Dr. Prowell explained the 4 categories of expedited approval: fast track designation, priority review, accelerated approval, and breakthrough therapy designation. Dr. Prowell mentioned that currently oncology drugs obtain fast track designation almost routinely because only a tiny sign of clinical response in a specific indication and an

acceptable development plan are required for the designation. She emphasized the importance of precise understanding on that, because media or even medical professionals often mistakenly believe that the designation indicates high demand authorized by FDA. She explained that priority review, which takes about 6 months vs. ~10 months for standard review, is adopted when either the drug represents a significant improvement compared to marketed drugs or no alternative exists. She then explained that accelerated approval is no more than an approval based on surrogate endpoints and always requires confirmatory trials with endpoints measuring direct clinical benefit such as overall survival or disease free survival. While accelerated approval has the advantage of providing potentially efficacious drugs to society more rapidly than regular approval, it could cause difficulty in implementing a confirmatory trial, because patients and investigators could be afraid of being assigned to the control group in the trial. Ensuring crossover in confirmation trials or implementing confirmatory trials in countries where the investigational drugs are not available may potentially solve the issue. Lastly, the breakthrough therapy designation is granted for drugs intended to treat specific serious diseases, such as cancers, with evidence of potentially substantial improvement. This path enables drug companies to have early and frequent contact with the FDA but does not guarantee an approval. The last few minutes of her talk were spent in discussion surrounding endpoints. In particular, the challenging nature of adopting patient-reported outcomes (PROs) as clinical trial endpoints was emphasized, though they are direct measures of clinical benefit. By referring to a ruxolitinib trial in which PRO was successfully employed as an endpoint of registry trial, the following aspects were suggested to be conditions for it: enrolling symptomatic patients, early engagement with FDA, development of simple RPO tools with limited items, development of electronic device for on-time RPO reports, showing a plausible relationship between objective tumor response and RPO score, and statistical consideration to prove superiority of the new drugs.

*Authored by **Chirayu G. Patel, MD, MPH**, Vanderbilt University Medical Center, Nashville, TN, USA*

Dr. Tatiana Prowell presented an overview of the history of the FDA, explained challenges in oncology drug development, clarified the differences between 4 ‘fast-sounding’ concepts, and discussed endpoints for approval in oncology. The history of the FDA portrays the agency as evolving in response to public health disasters. Concepts such as clinicaltrials.gov (est. 1997) and the FDA mandate of post-marketing requirements (est. 2010) are surprisingly recent developments.

Major challenges in oncology drug development include:

- These drugs are being developed for life-threatening diseases
- Diseases may involve small populations which inherently restrict study size
- Drugs may lead to severe toxicities which may be deemed acceptable to achieve modest gains in efficacy, and
- The range of indications span prevention to incurable, metastatic disease.

Dr. Prowell explained the counterintuitive differences between 4 major concepts and their overarching importance:

1. **Fast track:** this designation is routinely granted early in the drug development process, with any type of clinical response, provided that the company has a plan for development. This is not particularly difficult to obtain and does not constitute an approval but is meant to facilitate drug development process to get drugs to patients faster.
2. **Priority review:** this designation shortens the FDA review process from 10 months (standard) to 6 months.
3. **Accelerated approval:** this is regulatory approval that is based on qualities other than a direct measure of clinical benefit (defined as ‘feels, function, or survival’) or a validated surrogate. Regular approval occurs when there is direct evidence of clinical benefit or improvement in an established surrogate for clinical benefit. Accelerated approval is sometimes, but not always, faster than regular approval – the definition is based on endpoints, not time to approval. Over time, with a confirmatory trial or an increase in follow-up in a well-designed initial trial that provides evidence of clinical benefit or validated surrogate of clinical benefit, a drug approved under accelerated process can pass regular approval. An important challenge is that randomized controlled trials are difficult to conduct following accelerated approval, with loss of equipoise.
4. **Breakthrough therapy designation:** this very important category is reserved for drugs meant for severe, life-threatening diseases which show preliminary clinical evidence for substantial improvement over existing therapies. This designation is specific to the drug, indication, and line of therapy.

In the remainder of her talk, Dr. Prowell discussed the various endpoints in oncology, which depend on natural history, prevalence, and treatment setting (i.e. prevention, adjuvant, neoadjuvant, etc.). While overall survival is the ‘gold standard,’ in certain diseases, such as prostate cancer and breast cancer, progression-free survival corresponds to a real benefit in

overall survival but takes less time to show a difference given the long natural history of these cancers. Caution must be employed, however, as sometimes progression-free survival may not show a difference early in trial, but overall survival does, as in the example of nivolumab in renal cell cancer. Patient-reported outcomes were also discussed, with a tendency of oncologists to underestimate patient symptoms. A case study of ruxolitinib in decreasing spleen size and relationship to quality of life demonstrated these points.

Authored by **Daniel S. Shin, MD**, University of California, Los Angeles, CA, USA

I learned the historical and current FDA perspective of new drug development with regard to clinical trial design and execution, which I have never learned previously from clinical fellowship training. It helped me to better understand the different regulatory pathways for drug approval and how should we utilize our resources in each step of a clinical trial in order to maximize the benefit for patients. Moreover, we have to carefully evaluate our endpoints of the studies to determine whether they appropriately capture the characteristics of disease, and we need to initiate the dialogue with FDA to lead the study in the right direction.

Authored by **Victoria Wang, MD, PhD**, University of California – San Francisco (UCSF) San Francisco, CA, USA

Dr. Tatiana Prowell presented a highly informative talk on FDA regulation of drug development, a topic to which fellows often don't get much exposure during training. She discussed a brief history of the FDA and a number of public health disasters which helped to shape the FDA regulatory policies today (sulfanilamide and thalidomide). Dr. Prowell then provided an overview of the FDA regulatory pathways leading to the approval for new therapies and the role that ODEC plays during this process. Definition of various terms, which are often associated with drug development, including fast track, priority versus standard review, regular versus accelerated approval, and breakthrough therapy, were explained in detail. Surprisingly, accelerated approval often provides less certainty about the efficacy of the drug and requires a confirmatory post-marketing trial. She also explained what constitutes clinical benefit and endpoints commonly used in clinical trial design to measure clinical benefit (OS, PFS versus TTP, and PRO). An elegant phase III study leading to the approval of ruxolitinib in myelofibrosis was conducted based on PRO and RR in splenic size. It is imperative that PRO be simple to use, in order to maximize data collection, and linked to RR mechanistically. Several real world examples of clinical trial design, including loss of equipoise and failure to isolate the clinic effect of the drug, were discussed. She concluded the presentation with a poignant example of how to request expanded access or compassionate use of a drug not yet approved for patients.

Authored by **Y. Shrike Zhang, PhD**, Harvard Medical School Cambridge, MA, USA

Dr. Tatiana Prowell's lecture from the FDA perspective was just amazing and allowed me to understand the drug development process from a totally different standpoint. I was able to learn so much that I did not know anything about before. For example, I learned the history of drug laws incurred by the occurrence of many tragic incidences when no enforcements were in effect years ago; I learned about the different drug review/approval categories such as fast track, priority review, accelerated approval, and breakthrough designation; I learned common errors in development of oncology drugs for regulatory approval and ways to mitigate the errors; and I learned how to obtain objective, correctly structured patient-reported outcomes. This lecture greatly improved my understanding of the drug approval procedure and will enable me to avoid mistakes if, by any chance, I would ever develop my own drug or any related products in the area that need regulatory approvals.