

Oncology Drug Development: A Regulatory Perspective

Faculty Presenter

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The history of drug laws in the United States essentially begins with the Food and Drug Act of 1906, which resulted from the baseless "miracle cure" claims for inert and/or dangerous medicines and adulterated foods that were being marketed to unsuspecting citizens. This provided the United States Food and Drug Administration (FDA) with the authority to enforce laws that would forbid misbranded and adulterated foods and drugs; however, this was only effective if the violations (and violators) were actually discovered. There was no provision for pre-market evaluation of drugs in this act.¹ While this ruling had good intentions, it was not easy to enforce. For example, back in the 1930s, sulfanilamide was used in powder or tablet form for streptococcus infections in children, but there was a demand for a liquid formulation for this patient population. The SE Massengill company used diethylene glycol as a solvent for this formulation, which did not undergo safety testing in animals or humans. After 243 gallons of the liquid drug were shipped for use in the autumn of 1937, more than 100 deaths in children resulted. While FDA inspectors took action throughout the country and seized the drug, the company president claimed he "violated no law" and could not be prosecuted.² In response, the 1938 Federal Food, Drug and Cosmetic Act (FD&C) was issued. This new legislation mandated pre-market safety testing of drugs for the first time in the world, although there was no efficacy requirement in the initial act. This introduced the concept of pre-marketing drug approval by the FDA via the New Drug Application (NDA).³

Another tragedy brought drug safety to the attention of the American government in the late 1950s via the thalidomide disaster. Thalidomide was a sedative marketed by the Merrell company in Europe for treatment of pregnant women with morning sickness. The pills were sent to about 1,000 physicians in the United States, who gave them to their patients on an experimental basis, meaning there was no requirement to inform the FDA about experimentation with this unmarketed agent. These "experiments" were not actual trials; there were no comparator groups, no informed consent, and no systematic data collection. The NDA for thalidomide was submitted to the FDA in 1960, but a new FDA reviewer, Dr. Frances O. Kelsey, believed the safety data on the drug was inadequate and refused approval despite pressure from both the pharmaceutical manufacturer and her FDA supervisors. Affecting her rejection was the lack of data indicating whether the drug could cross the placenta and affect the fetus. The consequences of this drug use were devastating; tens of thousands of babies were born with phocomelia, affecting 1 in 100,000 live births in Europe in 1957 and 1 in 500 by 1961. The thalidomide disaster led to the 1962 Kefauver-Harris amendments to the FD&C Act, stating that drugs must be proven to be safe and effective based on substantial evidence, consisting of adequate and well-controlled trials conducted by experts qualified by scientific training and experience. This introduced to the FDA the informed consent requirement and reporting of adverse events (AEs) in clinical trials and provided the modern standards of regulatory evidence to support drug approval.⁴

While drug safety and effectiveness was paramount, the demand for accelerated drug approval by the FDA reached a peak in the 1990s with the accelerated approval regulations in 1992, brought forth in response to serious and life-threatening diseases such as Acquired Immune Deficiency Disorders (AIDS) and cancer. Approval in this setting was based upon surrogate endpoints reasonably likely to predict clinical benefit and the fact that the new drug must be better than available treatment, with a need for post-marketing trials to confirm benefit and convert the agent to receiving regular approval.⁵ This was then followed by the Food and Drug Administration Modernization Act (FDAMA) of 1997, designed to expedite drug development for life-threatening disease, allowing a fast track approval process and priority review with a 6-month NDA review time for products addressing unmet medical needs. It also called for creation of a public clinical trials registry, now found at www.clinicaltrials.gov.⁶ Later, the 2007 FDA Amendments Act (FDAAA) gave the FDA new post-marketing safety authorities, mandating post-marketing requirements (compelling safety-related labeling changes and development of and compliance with risk evaluation and mitigation strategies (REMS)) and requiring submission of direct-to-consumer advertisements prior to their dissemination to the public (and imposing monetary penalties for publication of false/misleading information).⁷

Despite all of these historical acts and amendments, challenges remain in oncology drug development and regulatory decision-making. Oncology drugs are developed for life-threatening diseases, and there is a balance and tension between providing patients access to the drug and adequately investigating it. Approvals may be based on small populations and relatively short exposures, and severe toxicities may be considered allowable to achieve even modest efficacy gains. Plus, indications for usage may span a spectrum from prevention to treatment of incurable disease. Registration trials may poorly predict actual real-world experience with any given agent, including whether AEs are caused by the drug or the disease (or both). Trial exclusion of patients with real-world challenges, including marginal performance status, end-organ dysfunction, diminished marrow reserve, and end-stage disease such as brain metastases also create challenges, along with frequent off-label post-marketing use.⁸

The drug approval process involves key elements, including substantial evidence of efficacy with acceptable safety in adequate and well-controlled trials and the ability to generate product labeling that defines the appropriate patient population for the agent and sufficient information to enable safe and effective use.⁹ Expedited review and documentation surrounds fast-track designation of a drug, priority review, accelerated approval, and a breakthrough therapy designation. Agents following this track are granted review and approval early in clinical development, prior to an NDA submission.¹⁰ In oncology, fast-track approval is routinely granted based upon even a single significant clinical response, use for a specific indication, and an acceptable development plan. Priority review is granted if the drug represents a significant improvement compared to marketed products for treating, preventing, or diagnosing disease and no satisfactory alternative therapy exists. This expedites the goal date for regulatory action. Whereas standard review takes 10 months, priority review may only take 6 months.⁸ On the standard approval track, a drug must demonstrate evidence for clinical benefit and improvement in an established surrogate for clinical benefit (eg, a durable response). In contrast, accelerated approval is based upon an endpoint other than this direct measure of clinical benefit or surrogate validation. However, it is not an approval based upon borderline evidence in an established endpoint of clinical benefit, nor is it a means to salvage a failed clinical trial.^{9,10} Data on first approval action from the Office of Hematology/Oncology, Center for Drug Evaluation and Research (CDER) on novel drug approvals between 2012 and 2015 show that 29 were approved through the standard track and 17 through accelerated approvals.¹¹

Methods to confirm benefit in accelerated approval include interim analysis of a surrogate endpoint in a randomized trial with confirmation of benefit at completion of the same trial and evaluation of refractory patients with confirmation of benefit in less refractory patients. The breakthrough therapy designation is for drugs intended to treat a serious or life-threatening disease where preliminary clinical evidence indicates potential substantial improvement over existing therapies on at least one clinically significant endpoint. The designation is granted for a drug and its indication, not the drug alone, and it may be rescinded later if approval criteria are not met. It is not a guarantee of future drug approval.⁹ That said, it does allow early expert input and early consultation with the manufacturer for use of clinically relevant specifications, an "all hands on deck approach" to the development of a drug and the review of the NDA and biologic license application (BLA). Through September 2016, the breakthrough therapy request disposition in the Office of Hematology and Oncology had a 41% grant rate.⁸

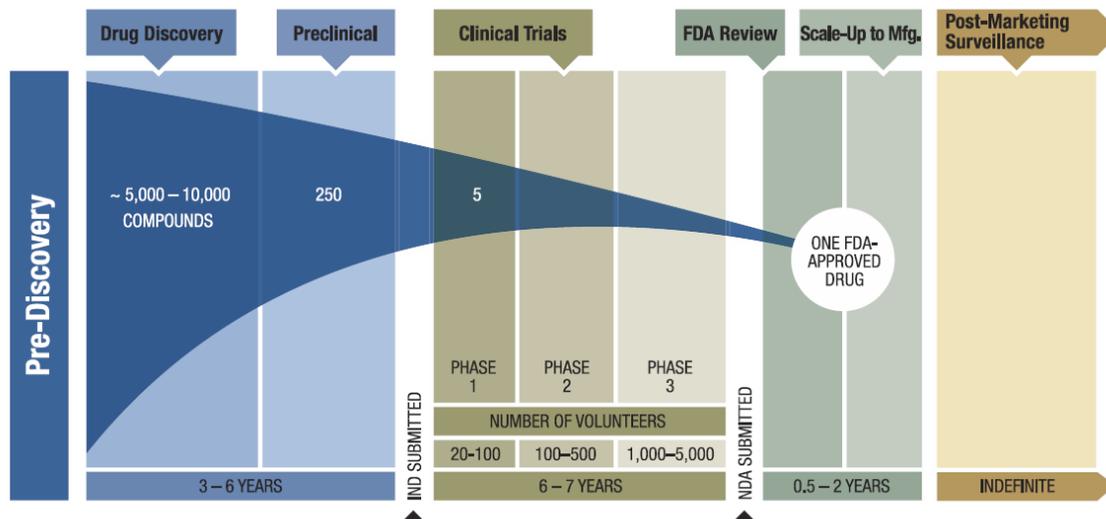
The main endpoints for drug approval in oncology include overall survival (OS), progression-free survival (PFS), and overall response rate (ORR). OS remains the gold standard, defined as the time from randomization of the patient in a clinical trial until death. It has the advantages of being an objective and direct measure that assesses both efficacy and safety, but it requires larger sample sizes and longer studies, and drug crossovers and use of subsequent therapies may confound the results. PFS is comprised of the time from randomization to disease progression or death from any cause, whereas time to progression (TTP) is the time from randomization to disease progression or death *from disease progression*. As it is often difficult to determine the exact cause of death in a patient with cancer, PFS is the preferred measure. For PFS measures, a smaller sample size and shorter follow-up are appropriate, stable disease is included, and the results are not confounded by crossover or subsequent therapies. These measures have supported both regular and accelerated approvals, depending on disease setting, magnitude of effect, toxicities, and the robustness of the study itself. That said, PFS results may be complicated by missing, incomplete, infrequent, or asymmetric assessments. Non-measurable disease such as bone metastases also presents challenges, as does inadvertent unblinding leading to bias. There is also uncertainty surrounding the clinical benefit of PFS alone, particularly if the effect is small, there is no OS advantage, the drug is very toxic, and other treatments are available. Discordance between the investigator and independent radiologic review can be common. This may occur when the investigator determines there is progressive disease based on clinical or radiographic data not submitted to the independent review committee (IRC), selection of different target lesions, inter-reader variability, or investigator bias in unblinding situations.⁸

The ORR isolates treatment effect from the natural history of disease and lends itself well to use in single-arm trials, because the ORR in most untreated cancer is presumed to be zero. However, it does not take into account stable disease and poses challenges in settings such as use of immunotherapy. ORR has also historically not been viewed by the FDA as a clinical benefit endpoint, although it may be the basis for accelerated approval in some cancer, especially hematologic malignancies. The response rate (RR) is also used, reflecting direct clinical benefit in some cases. Key considerations here include the magnitude of the RR, nature of the response, association with disease symptoms and amelioration of those symptoms with treatment, the depth of the response, and its durability and persistence. Overall, the nature and extent of the response are important. Regular/standard approval may be granted on the response rate and duration along with the high likelihood of tumor-related symptom relief and cosmetic improvement (depending on the malignancy).⁸

Patient-reported outcomes (PROs) should also be taken into consideration, considering that clinicians tend to underreport symptoms. Patient-reported symptoms demonstrate a better correlation with disease status than clinician-reported symptoms. PROs directly assess the clinical benefit of a treatment; however the difficulty is how to measure these benefits.¹² Challenges with reporting PROs include reliability, content development, appropriate recall periods, language translations, clinically meaningful score changes, and the ability to detect change over time in response to a clinical intervention/change. In oncology, PROs present unique challenges, including open-label designs in trials, single-arm trials, major drug-related toxicities, missing data, and the tendency to limit trials to patients with Eastern Cooperative Oncology Group (ECOG) 0-1 performance status. Successful studies using PROs include enrolled patients symptomatic from their disease (vs concomitant comorbidities), trials that are engaged early with the FDA to discuss strategy and registration, development of a simple PRO tool relevant to the patient population with data submitted real-time via the EMR, and situations in which superiority is the target goal and the RR and change in symptom score are assessed, including any relationship between these two parameters.⁸

Even when all the relevant data and processes are followed optimally, the drug approval process often remains long¹³:

Drug Discovery and Development Timeline



Common errors in the development and approval process in oncology include lack of drug dose optimization, failure to consider the agent's actual relevance to the United States population, failure to isolate the effects of the new drug, and statistical mistakes and pitfalls. The maximum tolerated dose is the usual historical endpoint for dose optimization in phase II/III trials. However, this may not be appropriate for non-cytotoxic drugs which may be able to achieve similar or greater efficacy with less toxicity (or greater efficacy with no difference in toxicity) or may be inappropriate for treatment goals or less relevant to drugs that will be taken chronically. One-third of NME drug approvals since 2011 have had a postmarketing requirements or commitments (PMC/PMR) study related to dosing.⁸

Importantly, trials undertaken in the United States should be relevant to its population to support US regulatory approval. The patient population and the treatment should both be relevant to this country's population and reflect the United States

standard of care. In addition, statistical pitfalls can impede trial progress, including poorly planned or unplanned interim analyses, over-prioritization of statistical significance vs clinical significance, and misuse of subgroup analyses. Interim analyses may help in these trials, providing timely information if designed correctly. However, problems may arise if they are not pre-specified or are inappropriately designed, result in early trial termination for statistical significance without clinical significance, or impair ability to collect long-term data appropriately. In regard to significance, the p-value should be used to determine the statistical “truth” of a clinically important outcome but not to define a clinically important outcome.⁸

One other important area to cover is compassionate use of drugs. The objective of expanded access through the FDA's 21 Code of Federal Regulations (CFR) 312.300, Subpart 1 was to facilitate the availability of investigational new drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patients' conditions.¹⁴ Key elements necessary for expanded drug access and compassionate use include that the drug must be an investigational agent for serious, life-threatening disease and other available/approved therapies for use have already been exhausted or are contraindicated in the individual patient.¹⁵ The intent is to provide access to an investigational agent to treat a patient, not to collect data. Providing the drug in these cases does not compromise an investigator's/clinician's ability to gain future marketing approval for this agent. Multiple steps must be followed in compassionate use, including a comprehensive discussion of the treatment with the patient, inquiry to the manufacturer of the investigational drug, and written request for follow-up. If the company agrees to provide the drug, all relevant information regarding efficacy, safety, and dosing will be provided by them. The FDA must then be contacted to file a single patient IND for use of the agent before the drug is shipped.⁸

Summary:

The development of pharmacologic therapies for treatment of malignancies can often be a long and drawn out process, with multiple regulatory guidelines and processes to follow. That said, a clear understanding of the regulatory processes surrounding standard and accelerated drug approval (and compassionate use of investigational drugs), best targets and endpoints for clinical trials, and the importance of optimizing collaboration with the patient and the regularity in all aspects of therapy are paramount to successful investigation and use of new and emerging treatments for malignant diseases.

RELATED PRESENTATION

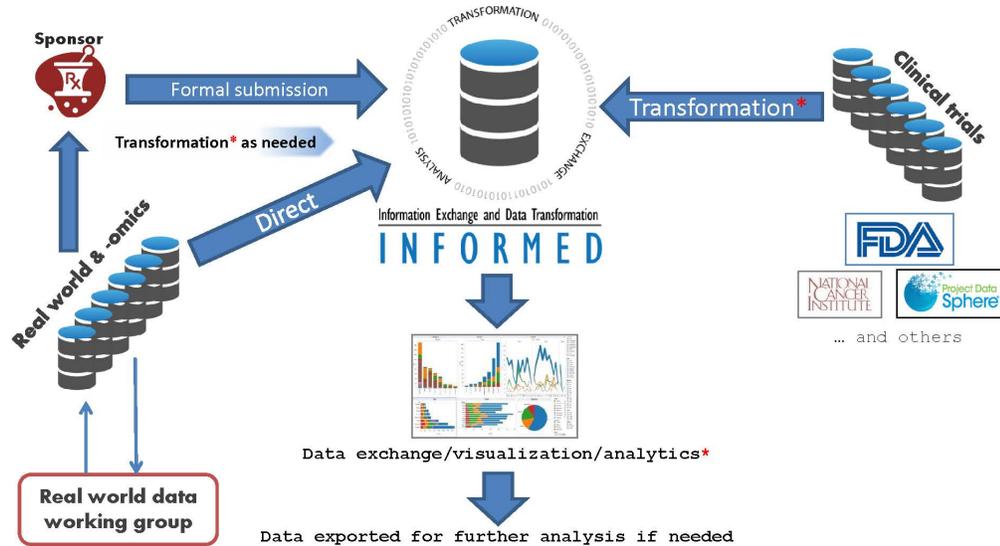
Data Sharing, Research Parasites, and the Korean Alphabet

Faculty Presenter

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In brief, another area that will be of more concern in drug development and research is that of data sharing, especially the potential for data to be used by those other than the original researchers for their own purposes, including potentially trying to disprove what the original researchers had proposed. This can further complicate the approval and regulatory processes for drug approval and use and can hinder optimal collaboration between investigators and investigation groups.

INFORMED: Framework



*Technology and software development

Summary:

Overall, there should be an emphasis on data sharing for the common purpose of improving research and product evaluation in the overall field by reducing unnecessary redundancy in investigations and developing better study designs to optimize research and potentially improve results that down the line could result in improved patient outcomes.

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