Navigating Project Optimus and the Rapidly Changing Oncology Development Landscape

Imagine a world where cancer treatments are more effective while also being safer for patients. This vision is quickly becoming a reality with Project Optimus,[1] the U.S. Food and Drug Administration's (FDA's) groundbreaking initiative from its Oncology Center of Excellence (OCE).[2]

The initiative, which brings a stronger focus on the patient, has altered many aspects of oncology clinical development. Specifically, for small to mid-sized biotechs, the impact of Project Optimus on clinical development planning, timelines, and funding needs are significant. Understanding and leveraging this initiative are key to enhancing patient safety while maximizing the chances of regulatory success in oncology drug development.

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Goals of Project Optimus

By focusing on dose-optimization and patient-centric approaches, Project Optimus aims to maximize the efficacy of new cancer treatments while minimizing toxicity. More details are provided for the industry in "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases," a final guidance document effective August 2024. The initiative aims to improve the therapeutic index of oncology drugs, accelerating the development of safer and more effective treatments. This approach is a departure from the traditional maximum tolerated dose (MTD) that has long been the standard for dose selection in oncology, but did not consider the quality or longevity of a patient's life.[1, 3]

The FDA's rationale for implementing Project Optimus stems from recognizing that the traditional MTD model, while effective for cytotoxic chemotherapies, is often inappropriate for targeted therapies and immunotherapies.[1] These newer next-generation oncology treatment modalities often achieve optimal efficacy at doses lower than the MTD, reducing unnecessary toxicity and improving patient adherence, outcomes, and quality of life.[1, 3] This paradigm shift is expected to enhance the overall quality of cancer care and may lead to more personalized treatment regimens.[4]

With the finalization of the guidance, the FDA confirms the study design advice for biotech companies that Catalyst Oncology has suggested since the draft guidance was published in January 2023. (See Table 1.) While the final guidance holds true to the intent of the initial draft, some language in the final version is stronger than the draft guidance, such as the following for dosage optimization and for pharmacokinetics (PK).

Dosage Optimization

"Sponsors are therefore strongly encouraged to discuss their plans for dosage optimization with FDA during formal meetings, including early in clinical development."[1]

PK

"A PK sampling and analysis plan should be included in each protocol. The PK sampling and analysis plan for all clinical trials should be sufficient to support population PK and dose- and exposure-response analyses for safety, activity, and efficacy."[1]

Table 1. Brief Overview of Changes to Oncology Drug Development

Prior to Project Optimus	Project Optimus
MTD	Range of doses, randomize for dose optimization prior to pivotal
28-day toxicity standard	Long-term toxicities
End-of-study analysis	Interim data analysis
Quick expansion	Safety, pharmacodynamic (PD), biomarkers, and efficacy endpoints
Serious adverse effects (SAEs) focused safety	Overall toxicity, patient-centered outcomes
Optional pre-investigational new drug (pre-IND) meeting	Pre-IND meeting to ensure agency buy-in on dosing strategy and trial

Optimizing oncology clinical trial design

Project Optimus ushers in a new approach to early-phase oncology study designs, including the integration of dose-finding and efficacy studies, the use of adaptive trial designs, the incorporation of PD and biomarker assessments, and the application of model-informed drug development (MIDD) approaches.

Project Optimus is designed to maximize not only the efficacy of a drug but patient safety and tolerability.

These trial design strategies are intended to optimize oncology research by streamlining the trial process, shortening development timelines, and enhancing patient outcomes. Sponsors not collecting enough data to justify a dosing strategy could face significant regulatory delays. The FDA may issue clinical holds, refuse to file (RTF) decisions, and complete response (CR) letters requesting additional studies to explore alternative doses or regimens.

Dose optimization and efficacy studies

One of the core components of Project Optimus is the integration of dose optimization and efficacy measures earlier in the development process. Traditionally, early-phase trials focused solely on dose-finding, stepping through dose levels with three to six patients per dose level (i.e., a classic 3+3 design) to help determine an MTD. Efficacy was always an endpoint but was typically evaluated in later phases via a separate protocol (Phases II and III). In the past, an MTD was all that was required to proceed to registrational studies, and dose optimization didn't typically occur until post-approval.

Project Optimus encourages the simultaneous assessment of safety and efficacy, allowing for a more comprehensive understanding of the dose-response relationship. It is designed to maximize not only the efficacy of a drug but patient safety and tolerability.[1, 5] This integration manifests in larger early-phase sample sizes, and most commonly a seamless Phase I and II study design that explores dose-finding, dose optimization, and early efficacy signals all in one protocol.

As a result, a first-in-human (FIH) trial can require upwards of 60 patients to complete dose escalation and optimization, whereas Phase I oncology studies historically would enroll ~20 patients and stop. Efficacy assessments are often built in from there, exploring one or more indications or biomarker-specific arms (for targeted therapies), combination dosing, or randomization between two dose levels as specifically noted in the FDA's guidance. All of this leads to large Phase I/II sample sizes, often looking to enroll well over 100 patients in total for escalation and expansion before the period.

Adaptive trial designs

Adaptive trial designs allow for modifications based on interim data. These designs enable more efficient dose exploration by adjusting dosing regimens in real time based on emerging data, thus optimizing the trial process and reducing development timelines. Historically, early-phase studies leveraged a rule-based design to enroll patients, most commonly the 3+3 design that dosed three or six patients at a given dose level. [6]

While it was the gold standard escalation design for decades, 3+3 does not provide much flexibility for dose optimization and, in fact, carries a risk of exposing more patients to sub-therapeutic doses than might be necessary. Under Project Optimus, more adaptive designs have become prevalent such as model-based designs like the continuous reassessment method (CRM) or model-assisted designs like the modified toxicity probability interval (mTPI) or Bayesian optimal interval (BOIN). The BOIN design has particularly become common, gaining momentum since the FDA designated it fit-for-purpose (FFP) in December 2021 for Phase I dose-finding clinical trials. [7]

PD and biomarker assessments

PD and biomarker assessments are critical for understanding the biological effects of different doses. By incorporating these assessments into early-phase trials, researchers gain insights into the mechanisms of action and identify optimal dosing strategies that balance efficacy and safety. [1, 3, 8]

MIDD approaches

MIDD leverages mathematical algorithms and statistical models to predict drug behavior and optimize dosing regimens. MIDD helps integrate diverse data sources to inform dose-optimization decisions, which is valuable where patient heterogeneity and complex disease biology complicate dose selection. [9, 10]

Advanced clinical strategies

Project Optimus also enables advanced clinical strategies to achieve comprehensive dose optimization for oncology therapies. Such strategies include evaluating multiple doses in parallel cohorts, conducting long-term tolerability assessments, and leveraging nonclinical data for dose selection.

Evaluating multiple doses in parallel cohorts, referred to as backfill cohorts, allows for a more robust comparison of dose-response relationships. Combining this approach along with the more adaptive escalation designs discussed above helps identify the optimal dose faster than traditional sequential dose-escalation studies. [1, 3] The backfilling BOIN design (BF-BOIN) is an example of a recent approach that addresses both. [11]

Long-term tolerability assessments are essential for understanding the chronic effects of cancer therapies. Historically, the standard 28-day toxicity window didn't always uncover longer-term effects. Project Optimus emphasizes the need for extended observation periods to capture delayed toxicities and ensure the selected dose is effective and tolerable over the long term. [1, 4]

One example of a newer design that addresses long-term tolerability is the time-to-event-BOIN (TITE-BOIN), which "accommodates late onset toxicities and rapid accrual, allowing dosing decisions even with pending DLT [dose limiting toxicity] data from some of the patients in the current cohort." [12] This may be particularly beneficial for immunotherapies or antibody-drug conjugates (ADCs) that can see toxicity after an initial 21- or 28-day dosing window, or that want to incorporate data across multiple dose levels for dosing determinations.

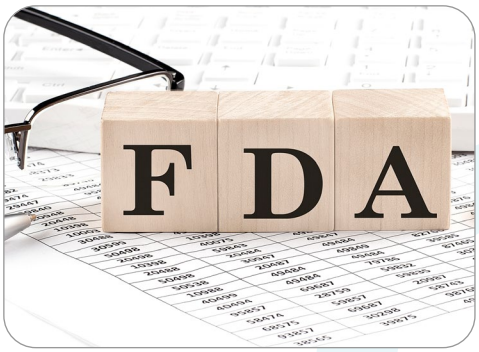
Nonclinical data, including preclinical pharmacology and toxicology studies, play a significant role in dose selection. By leveraging these data early in the development process, researchers can better predict human responses and refine dosing strategies before initiating human trials.[1, 3]

Innovative approaches, including the use of real-world evidence and advanced statistical methods, are encouraged within the regulatory framework of Project Optimus. These approaches enhance the robustness of dose-optimization studies and support more informed regulatory decisions. [1, 4]

Emphasizing early, strategic regulatory engagement

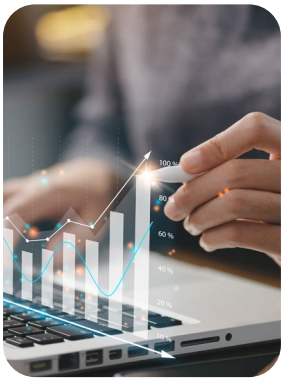
Proactive engagement with regulatory authorities is essential for the successful development and approval of oncology therapies. Project Optimus emphasizes the importance of early and ongoing interactions with the FDA, the presentation of data-driven rationales for dose selection, and strategic regulatory negotiations. These practices help ensure that development strategies align with regulatory expectations and streamline approval processes.

Successful regulatory negotiations require clear communication, robust data, and a thorough understanding of regulatory guidelines. Engaging with the FDA early and often, being transparent about the data, and demonstrating a commitment to patient safety and efficacy are key strategies for navigating the regulatory landscape. [1, 3]



At the start of clinical development, proactive engagement with the FDA through pre-IND and INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meetings is vital for aligning development strategies with regulatory expectations. [13] It's important for sponsors to prepare for such meetings at an earlier stage than prior to Project Optimus and provide opportunities to discuss dose-optimization plans, get regulatory feedback, and ensure study designs meet requirements. [1, 4]

Presenting data-driven rationales for dose selection is essential for successful regulatory negotiations. Sponsors must provide comprehensive evidence, including PK and PD data, biomarker assessments, and clinical trial results, to justify the chosen dose. Incorporating interim analyses—coupled with additional meetings in early stages—can now increase a sponsor's costs at the front of a clinical trial. [1, 4, 9]



Navigating new financial challenges

Since Project Optimus shifts the focus of oncology drug development to require more data earlier in the development paradigm, this directly impacts the financial implications of developing an oncology asset. Small biotech companies need to invest more in early-phase trials to meet the new regulatory expectations. [1, 4]

Sample sizes are larger, as discussed above, requiring more time or more sites to enroll the patients. PK/PD and biomarker assays are more prevalent, and patient outcomes are assessed earlier in development, often electronically. All of this requires additional investment that was typically reserved for later stages of development.

A sponsor could previously run a Phase I oncology study for a few million dollars. This would return an MTD for Phase II with hints at efficacy and would often generate enough data for proof of concept and further funding. Now, tens of millions of dollars are required to run a seamless Phase I/II design with more than 100 patients. Applying the new guidance will generate a more robust data package with optimized dosing, better clarity on efficacy, and a higher probability of regulatory success, but requires more investment dollars earlier to reach initial proof of concept.

The good news is that this is often sufficient to move straight into registrational studies, negating the need for a stand-alone Phase II trial and effectively reducing the overall cost of bringing a drug to market. This will also reduce the probability of post-marketing commitments, all with the oncology patient journey in mind.

Financing strategies to mitigate risks

Creative contracting and financing strategies can help startups manage the financial impact of optimized oncology drug development. Finding a partner that understands the biotech funding environment and can help manage cashflow and contain capital while sharing the risks and rewards of drug development is important.

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For example, a biotech with $10 million in Series A funding may not have the capital to run a FIH study design from start to finish with all the elements that Project Optimus necessitates. That said, there are mechanisms to begin the study and start dose-finding and optimization while looking for additional funding levers. To help offset the impact on timelines and cost, small biotechs can explore strategies like:

- Splitting a contract or upfront payment to focus on the escalation portion of a protocol
- Contracting with milestone-based payments that align with funding datapoints
- Leveraging adaptive trial designs to streamline dose exploration [1, 4]
- Focusing the development strategy to a specific indication or proof-of-concept output
- Incorporating strategic feasibility to optimize the countries for rapid patient enrollment
- Utilizing real-world data to supplement clinical trial data [1, 9]

The FDA's Project Optimus initiative has dramatically shifted the oncology drug development landscape. The new approach to early-phase oncology study designs, including the integration of dose-finding and efficacy studies, encourages the simultaneous assessment of safety and efficacy. It also calls for more frequent engagement with the FDA and data transparency. Small biotechs need to invest more capital earlier to align with the requirements and timing of data. While this generally negates the need for a stand-alone Phase II and reduces the overall cost of drug development, creative financing strategies are required to help small biotechs manage this larger upfront investment.

Finding a contract research organization (CRO) that can partner with biotechs to understand their program goals, develop a roadmap that is Project Optimus compliant, and offer creative financial terms is critical to optimizing the chances of development success.

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