

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## Talking to the FDA About Dose Optimization and the Aims of Project Optimus



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### **H&O** What is Project Optimus, and what prompted the creation of this project?

**MT** Project Optimus is a new initiative from the Oncology Center of Excellence at the US Food and Drug Administration (FDA) to reform the dose optimization and dose selection paradigm in oncology drug development. A wide range of expertise is represented among the entire project team, which includes medical oncologists, clinical pharmacologists, pharmacologist toxicologists, and statisticians. The Project Optimus leads are Drs Mirat Shah and Atiqur Rahman.

The correct dose and schedule are the foundation of drug development. Project Optimus was created because too often the current paradigm for dose selection, which is based on cytotoxic chemotherapeutics, leads to doses and schedules of molecularly targeted therapy that are inadequately characterized before the initiation of registration trials. Patients may be receiving these novel therapeutics for longer periods of time to maximize the benefit, which ideally includes not only longer survival but also improved quality of life. Poorly characterized dosing schedules may lead to selection of a dosage that provides more toxicity without additional efficacy, severe toxicities that require

a high rate of dose reductions, intolerable toxicities that lead to premature discontinuation and a missed opportunity for continued benefit from the drug, and potentially persistent or irreversible toxicities that limit subsequent therapeutic options.

### **H&O** What are the goals of Project Optimus?

**MT** The overarching goal of Project Optimus is to educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities, and patients to establish a dose finding and dose optimization paradigm across oncology that emphasizes selection of a dosage that maximizes not only efficacy, but also safety and tolerability. There are several specific goals. The project aims to communicate expectations for dose finding and dose optimization through guidance, workshops, and other public meetings. It also aims for drug developers to discuss dose finding and dose optimization with FDA Oncology Review divisions early in the development program—well before conducting trials intended for registration. In addition, Project Optimus will describe existing approaches to this process, as well as support the development of novel strategies for dose

finding and dose optimization that leverage nonclinical and clinical data in dosage selection, including randomized evaluation of a range of doses in trials. The emphasis of such strategies will be placed on performing these studies as early as possible in the development program and as efficiently as possible to bring promising new therapies to patients.

### **H&O** How are drug doses currently evaluated and selected, and what are the limitations to this approach?

**MS** As Dr Theoret mentioned, the current dosing paradigm evolved largely based on investigations of cytotoxic chemotherapies that aimed to identify a maximum-tolerated dose. Currently, the highest dose administered (or close to the highest dose administered) in an early trial is carried all the way through development of the drug and then ultimately tested in a registration trial. This approach is followed even when there is no evidence that the higher dose is better than a lower dose. This is one limitation to the existing paradigm.

Another limitation is that drugmakers consider only the most serious or life-threatening toxicities when selecting a dose. They do not consider lower-grade toxicities, such as diarrhea, which might not be severe enough to require hospitalization, but still have a negative impact on a patient's quality of life. These lower-grade toxicities could also impair a patient's ability to continue treatment with a drug that would otherwise be beneficial.

### **H&O** What are the considerations in determining the optimal dose for an oncology drug?

**AR** From the patient's perspective, an optimal dose is expected to ideally increase overall survival without compromising quality of life, and will be tolerable for long-term use. As a clinical pharmacologist, I would say that an optimal dose should be based on an understanding of the dose exposure-response relationship, both for efficacy and safety.

### **H&O** Does the focus on precision medicine in drug development impact dose optimization?

**MS** Throughout the past few decades, precision medicine has shaped drug development in oncology. Identification of biomarkers has allowed tumors to be classified beyond the tissue of origin and into molecularly defined subsets, and allows some patients to receive targeted therapies based on these biomarkers. In some cases, this shift in the paradigm has led to dramatic signals of efficacy much earlier in the drug development process. An example is

BRAF inhibitors for the treatment of melanoma. Scientific advances within precision medicine have made oncology drug development an even more rapid process with more compressed timelines vs the traditional approach.

Within these shifts, the dose optimization paradigm has largely not changed. Drugmakers need to take into account the fact that newer targeted therapies have different pharmacologic properties than cytotoxic chemotherapies and therefore must sufficiently characterize the dose.

On the FDA side, we need to be cognizant that patients may be grouped into small subsets to conduct clinical trials that focus on these targets. We also need to be aware that speed remains very important to drug development in oncology. It will be necessary to ensure that the advice given to companies is consistent with this paradigm.

### **H&O** What are the benefits of dose optimization, particularly in terms of current management strategies?

**AR** Dose optimization helps to define the shape of the exposure-response relationships for drug activity and toxicity. During drug development, dose optimization will help guide selection of a dose or a number of doses for testing in registration trials to establish the benefit/risks of a product. This approach will identify an optimal dose for the indication, as well as a range of doses that might be included in the labeling (depending on the quality and verification of the data), to help physicians select an optimal dose for an individual patient.

The disposition of a drug can be impacted by factors such as organ dysfunction, concomitant medications, and age. The exposure-response relationships generated through dose optimization will also help to tailor a dose for specific patient populations, such as patients with organ dysfunction or those receiving concomitant medications.

### **H&O** At what point in the process of drug development does the FDA begin to interact with manufacturers?

**MS** At the FDA, we start interacting with drugmakers relatively early in the drug development process. Even before the drug is first tested in humans, we start interacting with drugmakers to consider their protocol and plans. We continue to interact with them throughout submission for approval, and then beyond in the postmarketing space.

Through Project Optimus, we have been emphasizing to drugmakers the importance of dose optimization, particularly early in the process at initial meetings, before the drug is even tested in humans. We are seeing that

drugmakers are receiving this message. They are asking questions about the dose-selection paradigm. They are trying to meet with us early to obtain input regarding the overall development program.

### **H&O** Can guidance from Project Optimus help inform the design of clinical trials?

**MS** Through Project Optimus, we are working to develop general guidance that would be broadly applicable to drug development in oncology. We are emphasizing the importance of testing a range of doses and performing randomized dose trials where applicable. The overarching principle is that we want drugmakers to understand what happens with efficacy and toxicity at different doses and to then use that information to select a dose, rather than just choosing the highest dose.

We also understand that there is no “one size fits all” approach for all oncology drugs. Drugmakers have the opportunity to meet with us throughout their entire development program, starting early and going all the way through approval. At those meetings, we try to provide advice that is consistent with our general principles, but also tailored to the type of drug and the patient population.

### **H&O** What are the challenges in changing the dose of a drug that is already approved?

**MS** It can be difficult to conduct these trials in an efficient way so that the information regarding the dose is not delayed. Project Optimus is currently focusing on the preapproval and premarket space, for several reasons. We believe that an understanding of the dose is central to establishing the drug as safe and effective. Because of the importance of the dose to the overall development program, it should be evaluated and optimized early in the process. It is much more impactful to have good information on the dose early on. This information can facilitate the development of the drug beyond the initial patient population. Drugs are often developed as part of a combination rather than as monotherapies. An understanding of the dose can guide development of these combinations. In some cases, new dosing regimens or formulations might be more convenient to patients.

Furthermore, there is more flexibility to evaluate a range of doses early in the drug development process. In the postapproval setting, a drugmaker may have a certain manufacturing plan in place, which would be difficult to change.

**AR** Another challenge is the size of the dose optimization trials in the postmarketing setting. The trials usually provide very limited information about dose comparison related to the exposure, safety, and efficacy.

### **H&O** Do you have any other observations regarding how to optimize drug dosing?

**MS** Patients have options among many more efficacious drugs than were available historically. In this time of unprecedented opportunity, however, it is important to pay attention to the dose and consider safety and tolerability. As more effective treatments allow patients with cancer to live longer, there is an increasing focus on being able to do so with a better quality of life. Patients should be able to receive an effective treatment for as long as possible. Safety and tolerability are integral to this overall conversation.

**AR** Both the FDA and the drug manufacturers must recognize the importance of an early dialogue during drug development. Data generated from the nonclinical setting should be used in the clinical setting to assess and help optimize dosing during drug development, not after the drug is approved.

**MT** It is important to understand that robust dose finding and dose optimization are key objectives of early drug development programs that are too often overlooked for oncology drugs. We welcome the opportunity to work with stakeholders to develop strategies for incorporating more informed dose optimization into development programs. These strategies include the randomized evaluation of a range of doses in trials—potentially, seamless oncology trials. The goal is to promote efficient evaluation of novel therapeutics for the treatment of patients with cancer, while maximizing the efficacy and minimizing the toxicity of these agents.

### **Disclosures**

*Drs Theoret, Shah, and Rahman have no conflicts of interest to disclose.*

### **Suggested Readings**

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