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From the editor

The *Canon of Medicine*, completed in 1025 by Avicenna, sets out principles for clinical testing: "Experience does not bring forth the knowledge of the worth of a medicine with confidence unless after the observation of seven conditions." Among them: "The test should be in a simple, not a composite disease." It should be tested in two contrary types of diseases. The result must be seen to occur constantly. And it should be used in the body of a human, not a lion or a horse. (Brater and Daly, Clin Pharmacol Therap 2000;67:447–50).

Thus, for nearly a thousand years, investigators have worked not only to improve therapeutics but also to improve the methods for testing new therapeutics. In this issue of *CCR Focus*, the Phase 0 clinical trial design is examined with Dr. James Doroshow as guest editor. As an implementation of the FDA's exploratory IND guidance, Phase 0 trials have been proposed as a means of reducing the long drug development timeline that afflicts modern oncology. The trials are nontherapeutic studies that assess whether a drug has had an impact on its intended target. The nontherapeutic aspect and the fact that a Phase 0 trial will not obviate Phase I testing have caused reluctance in patients, industry, and academia. However, the advent of numerous new molecular targets and the prospect of rapid determination of whether a target has been modulated by a candidate drug provide the impetus for a close examination of this trial design.

This issue of *CCR Focus* examines the range of issues surrounding Phase 0 design, including precedents in pharmacologically driven Phase I designs, the FDA exploratory IND that opened the door, pharmacodynamic assay development, clinical trial design, ethics, and finally, the feasibility of recruiting patients to such trials. These articles illuminate several points that need to be addressed before Phase 0 trials become an important tool in drug development. One, that there must be a different protocol approval process in academic centers—the many layers of scientific and safety review that precede a traditional Phase I trial will need to be vastly streamlined. If the approval process is the same duration for both Phase 0 and Phase I trials, undertaking the Phase 0 by the traditional process will undermine the goal of developing drugs more rapidly. Given that commercial and medical success can be determined by the speed with which a company gains FDA approval, the need to streamline the protocol process is critical. Two, there must be a willingness to abandon compounds that do not modulate the target. In an era where chemistry outpaces our ability to test drugs, we need to be able to triage compounds rather than continue development solely because so much has been invested already. Three, we should give serious thought to the volunteer aspect of the patient population to be enrolled and find a way to recruit patients in the private practice setting before their referral to an academic center becomes a "last hope". Four, assay development will have to be undertaken much earlier in the drug development process such that lack of an assay will not impede rapid implementation of the Phase 0 trial. Such assays should become a requirement alongside preclinical pharmacology and toxicology in the FDA IND package because, without confidence in the assay, it is unlikely that development of a drug will be stopped on the basis of a Phase 0 trial. The FDA issued the exploratory IND guidance to facilitate development of targeted drugs. The drug development community should seize this opportunity to improve methods for the next millennium in the endeavor to bring new and better agents to patients.

Susan E. Bates, M.D.
Senior Editor
CCR Focus