LAST MONTH, THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) ANNOUNCED THAT IT PLANS to draft new guidelines for testing and approving the use of multidrug treatments for diseases. For cancer treatment, the need for this approach and its attendant guidelines are based on an advanced understanding of the disease that has emerged from 30 years of research. If we are to achieve breakthrough cancer therapies, current FDA regulations must change.

An extensive characterization of the altered signaling pathways in cancer cells has spurred the development of targeted pharmaceutical agents that disrupt individual aberrant pathways. This strategy is predicated on preclinical evidence that the malignant properties of tumors depend on such pathway alterations. Examples of effective targeted agents include imatinib (Gleevec), which targets the enzyme c-Abl in chronic myelogenous leukemia, and trastuzumab (Herceptin), which targets the protein HER2 in certain breast cancers.*

In the best cases, targeted agents have changed the natural history of the diseases they were designed to treat. However, too often, the clinical benefit has been modest, if not disappointing. This lack of efficacy is increasingly explained by our current understanding of biological mechanisms. A cell decides whether to proliferate, differentiate, remain in a resting state, or die depending on the output from signaling networks that are characterized by pathway redundancies and crosstalk. These features can overcome the effect of single-agent interventions. For example, inhibitors of the enzyme mitogen-activated protein kinase kinase (MEK) have proven disappointing as single agents against pancreatic and non–small-cell lung cancer, despite frequent MEK pathway activation in these cancers. Mouse models have shown that combining a MEK inhibitor with an agent that targets part of another signaling pathway [phosphoinositide 3-kinase (PI3K)] can result in substantial tumor regression by inhibiting parallel signaling pathways. Other potential drug combination approaches to enhance efficacy and prevent rapid development of resistance include targeting different points of the same signaling pathway with different drugs or using drugs that target the same altered protein but in different ways.

Current regulatory burdens confound attempts to develop two new molecular entities (NMEs) as a combination therapy. The “combination rule” of the FDA’s Code of Federal Regulations was designed for therapies that use fixed-dose combinations (drugs combined into one physical form), but it also applies to non–fixed-dose combinations of drugs. The contribution of each drug to the combination product must be determined for regulatory approval. Hence, large multi-arm, factorial-designed phase III clinical trials are required to provide statistical proof that the combination product is superior to standard-of-care therapy and to each drug administered separately. This has been acceptable for drugs that treat non–life-threatening diseases, such as hypertension, but it is less acceptable for diseases such as late-stage cancer, where treatment with potentially ineffective therapies should be kept to a minimum.

The FDA’s willingness to devise guidelines that examine the totality of data (clinical and nonclinical) when assessing the contribution of each NME to an effective combination, without requiring statistical superiority for the combination over each single drug, is welcome news and will probably spur more collaboration between companies to develop these novel combinations. The FDA’s recent announcement of a new initiative (in partnership with the U.S. National Institutes of Health) to accelerate the process from scientific discovery to the availability of new therapies is also good news. I urge the FDA to expedite the development of new approaches that will enable efficient clinical evaluation and potential approval of the combination of two NMEs to treat cancer, while maintaining appropriate standards to ensure patient safety. It is time for regulatory science to catch up with basic science in the quest for breakthrough cancer therapies for the patients who desperately need them.

— Arthur D. Levinson

*Genentech produces Herceptin and is developing inhibitors of MEK (GDC-0973) and PI3K (GDC-0941 and GDC-0980).