Promoting Innovation in Drug Development: Understanding the Current Regulatory Environment

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Developing new drugs is a risky, time-consuming, and costly process: it has been estimated that it takes 12 years and several hundred million dollars to develop a new drug, with less than 20% of drugs evaluated in clinical testing ultimately receiving Food and Drug Administration (FDA) approval. First-in-class therapeutics, which bring new scientific approaches to the treatment of disease, represent the most innovative group of new medicines, and they have transformed patient outcomes in certain diseases. Concerned about the barriers to approval faced by first-in-class therapeutics and other innovative approaches, a group in the House of Representatives has recently launched the "21st Century Cures" initiative. This team of legislators has highlighted the importance of regulators in fostering innovation in its mission statement, noting that there cannot be **"a major gap between the science of cures and the way we regulate these [innovative] therapies"**. Although the FDA dictates the requirements for and cadence of drug approval, little is known about how the agency specifically approaches first-in-class therapeutics. In order to assess how the FDA handles these innovative therapeutics, we compared the use of special regulatory pathways, the clinical trial evidence needed to secure approval, and regulatory review times between first-in-class therapeutics approved by the FDA between 2005 to 2012 and those therapeutics that were not the first in their class.

Using a framework developed by the FDA, I and my coauthors categorized all novel therapeutics approved by the agency between 2005 and 2012 as first-in-class, advance-in-class (i.e., use an existing approach offering material advantages for patients, such as less frequent dosing or fewer side effects) or addition-to-class. Subsequently, **using a database assembled in our previous work**, the use of special regulatory pathways, clinical trial evidence, and regulatory review times were compared between the three groups of therapeutics.

Descriptively, of the 188 therapeutics approved by the FDA between 2005 and 2012, 37% were first-in-class, 21% advances-in-class, and 42% additions-to-class. While orphan status was associated with first-in-class therapeutics, other special regulatory designations, namely accelerated approval and priority review, were not. The quality and quantity of clinical trial evidence required to win FDA approval

differed. Advance-in-class therapeutics were more commonly approved on the basis of a single clinical trial measuring efficacy than first-in-class and addition-to-class therapeutics. However, there were no differences in the use of surrogate endpoints, which are preliminary markers of efficacy that patients cannot always detect, such as lab measurements. On average, the FDA took approximately 90 days more to review applications involving first-in-class therapeutics than those involving advances-in-class, but the agency reviewed first-in-class applications 30 days faster than those involving additions-to-class.

This characterization of the current regulatory environment improves our understanding of how the FDA approaches innovative therapeutics. There appears to be an opportunity for the FDA to work with drug makers to ensure that the use of special designations correlates with therapeutics that are likely to have the greatest impact for patients. The number of clinical trials measuring efficacy was appropriate for first-in-class therapeutics, while the observation that the majority of advances-in-class were approved on the basis of a single trial could raise concern, as the **results of important clinical trials are not always reproducible**. While it may seem surprising that the FDA approved first-in-class therapeutics more slowly than advances-in-class, this may simply reflect the agency's need for additional time to evaluate the new science of first-in-class therapeutics. In aggregate, first-in-class therapeutics are not unnecessarily burdened by an unfavorable regulatory environment; however, there are opportunities to tweak the current framework to ensure that patients have timely access innovative medicines that are both safe and effective.