

How Many “Me-Too” Drugs Is Too Many?

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ON AUGUST 3, 2009, THE US FOOD AND DRUG ADMINISTRATION (FDA) approved pitavastatin (Livalo), making it the eighth statin approved for use in the United States and seventh currently available for sale. This approval comes almost a quarter century after that for the first member of the class, lovastatin, 8 years after generic lovastatin was approved and 4 years after 2 additional statins, pravastatin and simvastatin, lost patent protection and generic versions of them entered the market.

“Me-too” drugs are common in numerous widely used classes, including angiotensin-converting enzyme inhibitors and selective serotonin reuptake inhibitors. As with pitavastatin, their approval may come many years after the approval of other generic drugs in the class. For example, the proton pump inhibitor dexlansoprazole was approved in January 2009, more than 6 years after generic omeprazole became available. Thus, the approval of pitavastatin raises several questions: are so many agents in a single therapeutic class really needed, particularly when generic drugs are available, and, if not, what should be done about it?

Are Me-Too Drugs Too Much of a Good Thing?

Many arguments can be made on both sides of the debate regarding the need, or lack thereof, for more me-too drugs. In favor are issues of cost, safety, and efficacy. Market competition among similar drugs may reduce the cost of all drugs in the therapeutic class and improve affordability for patients and health systems. The Congressional Budget Office estimates that the “best price discount,” which is the difference between the average price paid by pharmacies and the lowest price paid by any private purchaser in the United States, increases by 10% when the number of brand-name drugs in a class increases from 1 to 5.¹ Follow-on drugs may sometimes have better safety profiles than older medications in the class. In some cases, more options in the prescriber’s armamentarium can improve clinical outcomes because some drugs may have greater potency, such as the low-density lipoprotein-lowering ability of some newer statins compared with those previously approved for the same indication.² From a societal perspective, individuals in the

United States generally believe free market principles effectively determine the appropriate role of competing products, and thus the existence of me-too drugs helps optimize consumer choice and the ability to personalize care.

In contrast, more options in a therapeutic class may make treatment decisions more difficult and may undermine clinical outcomes.³ Producing me-too drugs focuses research and development resources on drugs for conditions for which treatment options currently exist, while neglecting other conditions of more pressing public health importance.⁴ The proprietary nature of rebate information makes estimating the savings from within-class competition a matter of speculation, especially if generic drugs already exist in the class. Even at heavily discounted prices, brand-name drugs almost certainly cost more than generic medications. The associated spending differentials may have important implications for consumers and the health care system as a whole.⁵ Newly approved me-too drugs are much more likely to be heavily marketed than multisource generic drugs, which leads to greater prescribing of brand-name products despite the absence of data that their higher prices translate into appreciable differences in clinical outcomes.⁶ For patients, high drug costs are a central reason for nonadherence to essential medications.⁷ In addition, at the time of approval little information about the benefits and safety of me-too drugs is available to patients, prescribers, and payers compared with the often extensive postmarketing history of products that were previously approved.

A Proposed Approach for the Approval of New Me-Too Drugs

After generic drugs become available in a therapeutic class, the benefits of approving a new drug in the same class are almost certainly outweighed by its downsides. Targeting the most transparent of these negative consequences, the societal resources spent to approve next-in-class agents, is also a potential mechanism to address this issue more in general.

The FDA is legally compelled to evaluate all drugs submitted for approval, including all me-too products, regardless of the number of in-class brand or generic alternatives

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that exist. Drug manufacturers heavily subsidize review costs, but the FDA must devote public resources to the evaluation of each new me-too drug. The costs of these reviews are relatively inelastic with respect to the number of in-class drugs that have previously been approved and, at some point, most likely exceed the expected utility of the next me-too drug. Moreover, although applications for drugs that offer major advances in treatment undergo a priority review, every person-hour spent by the FDA evaluating a me-too drug application is an hour spent not reviewing an application for a drug for another indication for which fewer treatment options exist, or monitoring the postmarketing use of those that have already been granted approval.

An alternative approach is to review me-too drugs through routine mechanisms, such as by requiring that they prove superiority over placebo or noninferiority to another drug, only until a generic version of a drug in the class is approved. After this, manufacturers seeking FDA approval should explicitly demonstrate the superiority of the new product, not just its noninferiority, compared with other products that are already available. Superiority could be based on clear improvements in efficacy or safety. Or indications could be sought for populations other than those for which existing drugs in the class are approved, such as elderly persons or children (where appropriate). Another option would be to seek a new indication altogether.

For pitavastatin, approval was based on its noninferior low-density lipoprotein cholesterol-lowering ability compared with atorvastatin, simvastatin, and pravastatin, which seems to be an insufficient rationale for approving an eighth-in-class product when generic versions of 3 of the products are already available.⁸ Marketing materials suggest that pitavastatin has a low potential for drug interactions because it is not extensively metabolized by the cytochrome P450 system.⁹ Under the proposed approach, this relative advantage could have warranted approval for pitavastatin if the sponsor demonstrated in preapproval studies that it leads to improvements in clinically important safety end points, such as lower incidence of rhabdomyolysis and myopathy.

Critics may argue that changing the drug approval process limits market competition for prescription drugs and that alternative mechanisms already exist to mitigate the effect of me-too drugs, such as the ability of payers to set high copayments for these agents. Relying only on payers to address this issue does not address the public resources consumed by the FDA and still allows for drug makers to provide discounts to insurers for preferred listing on their formularies. Furthermore, the proposal is not intended to limit competition but rather to raise the requirements for approving next-in-class drugs, which may help address the market distortions that patents for me-too drugs currently create. Many aspects of the US prescription drug industry are already regulated¹⁰; this proposed approach is merely a modification of existing regulatory structures to help maximize the return from the societal investment on prescription drug

approval. This is not dissimilar to the regulations imposed to maximize the benefits from products in other industries, such as utilities.

Getting From Theory to Reality

Numerous issues must be addressed for this proposed approach to become a reality. Most notably, because the FDA lacks the legal authority to implement this proposal, granting it the authority to not review an application when a generic competitor has already been approved, unless the new product meets a higher standard, will require congressional action. At a more granular level, the magnitude of efficacy or safety improvement necessary to demonstrate superiority or what constitutes a new indication will need to be precisely defined. Strategies to address situations in which other agents are in the process of FDA review when a generic drug in the class is approved will need to be developed.

Until these obstacles are cleared, the FDA will continue to be compelled to review applications for more me-too drugs, particularly among rapidly expanding therapeutic areas, and often after generic drugs in the same class are already available. If reviewing these applications adds drugs to the market that are not any better than a multitude of existing products, instead those efforts should be devoted to the evaluation of other therapies that may have greater potential for making improvements in resource use, safety, and efficacy.

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