

## SOUNDING BOARD

## Over-the-Counter Sales of Statins and Other Drugs for Asymptomatic Conditions

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Merck recently submitted its third application to the Food and Drug Administration (FDA) to allow it to sell its cholesterol-lowering drug lovastatin in 20-mg tablets over the counter.<sup>1,2</sup> Targeted consumers are men over the age of 45 years and women over the age of 55 years who have levels of low-density lipoprotein (LDL) cholesterol of 130 to 170 mg per deciliter and an intermediate 10-year risk of a cardiovascular event (5 to 20%) but no previous event.<sup>1</sup> Merck's arguments for the switch from prescription-only to over-the-counter sales focused on the "treatment gap" — at-risk persons who are not receiving therapy — and on the desire of consumers for more control over their health care decisions.<sup>1</sup>

The treatment gap is real. More than 60% of persons who are at intermediate risk for a cardiovascular event are not receiving treatment.<sup>3</sup> Some of these persons do not have physicians; those who do have one may not have been offered treatment or refused it when offered. Over-the-counter statins may help narrow this gap.

Perhaps the most compelling public health argument for allowing statins to be sold without a prescription is that self-management is the most sustainable option for the prevention of the many chronic diseases that plague the developed (and developing) world. Health care systems lack the capacity to provide lifelong preventive care to an entire population. Medications could play a role in self-management, along with behavioral strategies.

Previously approved switches from prescription-only to over-the-counter sales were for temporary or intermittent treatment of symptomatic conditions, such as allergy, pain, and gastric reflux. Long-term treatment of asymptomatic conditions, such as hypercholesterolemia, remains the purview of prescribing clinicians. If Merck's request is approved, other companies will surely follow with their own statins and drugs for other asymptomatic

conditions, such as hyperglycemia and hypertension. Once lovastatin or another such drug successfully navigates the over-the-counter switch, it is conceivable that the process will continue until only a few highly toxic medications remain under the control of prescribing physicians. The implications for the FDA, the pharmaceutical industry, the medical community, and (most important) the public are enormous.

### PROBLEMS WITH NONPRESCRIPTION STATINS

The Durham–Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act states that "any drug limited to prescription use . . . shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed. . . ." Two FDA advisory committees met in December 2007 to review Merck's application. The advisory committees felt that the requested change in status for lovastatin did not meet these criteria and voted, for the third time, to reject Merck's application.<sup>4</sup> The reasons cited by the committees for the rejection included insufficient data on benefits and risks in the target population with over-the-counter sales, the inability of consumers to make appropriate self-selection decisions, a lack of evidence that there will be appropriate monitoring, and inadequate FDA authority over advertising and marketing.<sup>4</sup>

In addition to the randomized, controlled trials that are required for the original approval of a new drug, for the switch to over-the-counter

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 INABILITY OF CONSUMERS  
TO SELF-SELECT DRUGS
 

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sales, pharmaceutical companies must perform short and relatively small studies of “label comprehension” and “actual use.”<sup>2</sup> Under current FDA authority, Merck is not obligated to determine the safety or effectiveness of the drug for over-the-counter sales either before or after a switch approval.

The original randomized, controlled trials showed a reduction of approximately 30% in the relative risk of cardiovascular events associated with the use of lovastatin. Although the extrapolation of these benefits to the over-the-counter setting may be acceptable,<sup>5,6</sup> the extrapolation of risks is not. Existing data are insufficient to judge the toxicity of long-term exposure to lovastatin in persons who have a range of coexisting illnesses and who do not have the oversight of a clinician. Safety data come from case reports or small studies, from the FDA’s inadequate Adverse Event Reporting System, and from randomized, controlled trials that lasted only a few years, involved selected and well-monitored subjects, and lacked sensitive measures of adverse effects.

Well-recognized, but poorly studied, adverse symptoms that are associated with statins include neuropathy, depression, and muscle weakness that falls short of myopathy.<sup>7-9</sup> Although recent data are inconsistent, they suggest that an increase in hemorrhagic stroke is associated with statins and low levels of LDL cholesterol,<sup>10-12</sup> which is a concern, since persons with low LDL cholesterol levels would also be taking over-the-counter statins.

Accurate estimates of risk are particularly important to guide decision making among persons with a low risk of cardiovascular events (5 to 10%). The majority of such persons do not meet the criteria of the National Cholesterol Education Program and would not be prescribed statins.<sup>6,13</sup> Because persons who are at low risk derive few benefits from statins, at best reducing their 10-year chance of an event from a range of 5 to 10% to a range of 3.5 to 7%, evidence of minimal harm is crucial.

Although harm is the concern for low-risk persons, benefit is the issue for those at high risk. Such persons might have a reduced benefit if efforts to encourage the use of higher-potency prescription statins are curtailed or if the response in the LDL cholesterol level is not adequately monitored and treated. Are we ready to abandon efforts to encourage optimal management?

The committee was asked to advise the FDA on the proposed switch primarily on the basis of three studies. Two studies addressed the ability of consumers to comprehend the information on the proposed label and decide whether lovastatin (at a dose of 20 mg) would be appropriate for them. One 6-month study of actual use determined whether consumers made appropriate decisions concerning purchasing and using lovastatin over the short term.<sup>1,14-16</sup> Even among the study volunteers (who were better educated than the population as a whole, knew they were being studied, and had more expertise available than is typical in an over-the-counter setting), the findings raised concern. Less than half the respondents who self-selected over-the-counter statins were in the target group.<sup>14,15</sup> Almost 30% of respondents self-selecting lovastatin had less than a 5% risk of a cardiovascular event in the next 10 years and were therefore unlikely to accrue much benefit. Another 24% had a 10-year risk of more than 20%, had already had a cardiovascular event, had diabetes, or were already receiving aggressive lipid-lowering therapy (or were candidates for such therapy).<sup>14,15</sup>

Among the reasons cited by respondents for preferring over-the-counter statins were a lower cost (although the price of such drugs has not been set) and greater convenience, since they would not need to see a doctor (although 70% said they would rely on their physician to decide whether the medication was right for them). Some respondents reported preferring over-the-counter medications because they were “safer” than those available by prescription only, a response indicating that the respondents did not know that the same drug is sold under the two approaches.<sup>1</sup> Almost 75% were incorrect in their response to the question as to whether lovastatin was appropriate for them (i.e., they were either not in the target risk group or had contraindications).<sup>15</sup> Results were markedly improved when respondents who stated that they would discuss the decision with their clinicians were considered to have responded correctly, which raises the question of whether lovastatin meets the FDA criterion of being “safe and effective for use in self-medication.”

The need to extrapolate from population-level data to individual patients is true for all decision

making regarding drugs. But over-the-counter medications for long-term treatment of asymptomatic conditions, such as hypercholesterolemia, raise unique concerns. The prescribing physician currently is responsible for determining whether the benefits outweigh the risks in individual patients, for monitoring the response to therapy, and for making necessary adjustments in treatment. The switch to over-the-counter sales places the onus of acquiring and applying knowledge of benefits and risks and monitoring responses on the consumer. Self-responsibility already exists for approved nonprescription drugs. Unlike lovastatin, however, the currently approved over-the-counter drugs provide symptom relief, for which consumers are often the best judges of benefit.

For nonprescription drugs, the FDA relies on labeling to provide the information deemed necessary for consumers to decide whether a drug is safe (contraindications and cautions) and appropriate (benefits and indications).<sup>2</sup> The label, along with package inserts and product displays, must also present how to take the drug, what monitoring is necessary, when to talk with a doctor, and other information. The amount and complexity of required information is well beyond a label's capacity.

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#### CONCERN ABOUT MONITORING

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Merck is not required to study whether consumers continue to take the medication indefinitely, monitor their LDL cholesterol levels beyond 6 months, switch to a more potent statin if they do not meet their cholesterol goals, or act appropriately when their health status or medication regimens change. To the company's credit, Merck has developed a voluntary self-management system to aid consumers in initial and long-term decision making.<sup>1</sup> However, the company is not required to test it, maintain it, or monitor its use.

Concern about monitoring raises an as-yet-unanswered question about whether there will be convenient, direct-to-consumer access to lipid testing that does not require referral by a physician but is covered by insurance for those who have it. Without direct access, self-selection and self-monitoring are impossible.

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#### ADVERTISING AND MARKETING

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The timing of Merck's request coincides with the increasing availability of generic prescription stat-

ins, a factor that encourages the search for new markets. For Merck, that means selling lovastatin directly to consumers and expanding the potential pool of customers. Financial incentives can, and do, encourage pharmaceutical companies to get medications to the consumers who can benefit from them. The issue is ensuring that the drugs get to the right consumers safely and effectively.

The FDA has little control over marketing and direct-to-consumer advertising for nonprescription drugs, which remain largely within the purview of the Federal Trade Commission (FTC).<sup>17,18</sup> Inadequate FDA control over advertising is exacerbated by the lack of alternative sources of unbiased information, aside from the bare facts that fit on labels and package inserts. Direct-to-consumer advertising will probably be the primary source of information related to over-the-counter sales of statins for many people. Given the complex information that consumers need to make informed decisions, it is not prudent to leave the content of advertising to pharmaceutical marketing executives and the FTC.

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#### NEED FOR OVERSIGHT

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Unless the FDA, under legislative regulation, articulates the exact benchmarks that must be met to ensure that lovastatin "is safe and effective for use in self-medication as directed," Merck is likely to continue resubmitting the application with minor tweaks, relying as much on its marketing skills to persuade the committee that the company is "narrowing the treatment gap" and "responding to consumer demand" as on its scientific acumen.<sup>1</sup> Merck may also hope that turnover will result in more sympathetic advisory committees and FDA staff.

Existing FDA procedures and rules governing the switch from prescription to nonprescription sales simply are inadequate for long-term treatment of asymptomatic conditions. As a start, in studies of real-world use over several years (not just a few months) and in settings reproducing the over-the-counter environment, pharmaceutical companies must be required to show that consumers make accurate selection and monitoring decisions. Although the allowable percentage of incorrect self-selection is unclear, it is much lower than the 50% seen with lovastatin.<sup>1,2,14,15</sup> We need to know that consumers understand their cardiovascular risk, self-monitor for adverse effects or contraindications, have access to chole-

terol testing and check their LDL level periodically, move to a prescription formulation if the LDL level remains too high (although it has yet to be determined what they should do if the LDL level falls too low), take the statin for life (or while they meet indications), and understand what to do when they start taking a new drug or have changes in their health.

Some experts have advocated a behind-the-counter option, similar to the approach used in the United Kingdom, which would provide consumers access to knowledgeable pharmacy staff. However, there are no immediate plans to institute this option in the United States. Ensuring that consumers receive the necessary professional counseling under this option would be difficult.

The recently enacted FDA Amendments Act of 2007<sup>19</sup> and the proposed Non-Prescription Drug Modernization Act<sup>20</sup> both have provisions that, given the necessary resources, provide the FDA with the authority to develop new procedures for the switch from prescription to nonprescription sales. The FDA Amendments Act provides increased authority to require postmarketing surveillance. This authority theoretically could facilitate the procurement of better data on benefits and risks of long-term use of over-the-counter statins, assuming the data include details from the medical record. The best postmarketing safety studies, however, will rely on electronic surveillance.<sup>21,22</sup> Unfortunately, such tracking of statin use will be lost with the switch to nonprescription sales unless the FDA requires electronic monitoring of statin users, a requirement it should consider.

Section 915 of the FDA Amendments Act requires that the agency maintain a Web site with easily searchable postmarketing safety information, and Section 917 of the bill requires improved communication regarding risks. These complementary provisions allow the FDA to move beyond the label on the drug packaging to convey the unbiased and comprehensible information needed by consumers to make informed decisions.

The Non-Prescription Drug Modernization Act, if passed, would give the FDA the authority to revoke the authorization to market unsafe or ineffective over-the-counter drugs without the lengthy rule-making procedure presently in effect.<sup>20</sup> The bill would also transfer oversight for nonprescription-drug advertising from the FTC

to the FDA, giving the FDA much-needed authority over such drug advertising and marketing.

If these new FDA authorities and procedures are put in place, then the switch from prescription to over-the-counter sales for the long-term treatment of asymptomatic conditions should be reconsidered. Unless self-selection and monitoring are markedly improved, however, the FDA may have to decide whether to approve a strategy for which current data suggest that more than half the consumers will not fall into the population targeted for over-the-counter use and will potentially accrue less benefit or greater risk than the status quo.

No potential conflict of interest relevant to this article was reported.

Dr. Tinetti is chair of the FDA's Non-Prescription Drugs Advisory Committee. The views in this article are those of the author and do not reflect the opinions of the advisory committee or the FDA.

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