Statins: A Success Story Involving FDA, Academia and Industry

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A few years back, when prescribing lovastatin to help lower my cholesterol level, my physician asked me if I knew how the drug came to be approved by the Food and Drug Administration (FDA). I confessed to my own ignorance. He remarked that "pharmacologists are joking that it is so effective it should be put in the drinking water supply," and acknowledged that he was taking it himself. That certainly piqued the author's interest.

I recently had an opportunity to talk with Dr. Sol Sobel, currently the Associate Director of the Office of Pharmaceutical Sciences, about the development and approval of the statin class of drugs. Dr. Sobel joined FDA in 1977 as a reviewing medical officer and was appointed to the directorship of the Division of Metabolic and Endocrine Drugs in 1981. His recollections, along with supporting documentation and publications, show that the class of statin drugs was introduced into the practice of medicine as a result of a complex interplay of events and environment.

In 1959, FDA had approved the marketing of Triparanol as a cholesterol-lowering agent. In 1962, the drug was withdrawn from the market after FDA discovered that the company had provided falsified laboratory data. The falsified data had omitted reference to the cataracts found in rats and dogs in pre-clinical trials, and some patients who had taken the drug for a year did develop cataracts. [1] FDA also seized safflower oil for making "heart healthy claims."

Merck Terminates Trials

In 1976, Japanese researchers isolated a compound, compactin, which was shown to block cholesterol synthesis in vivo, and by 1979, Merck scientists had isolated the inhibitor – lovastatin. Around this time, however, the World Health Organization released the results of a large and well designed clinical trial of clofibrate, used to treat severe blood lipid disorders. Patients treated with the drug had a significantly higher mortality rate than the placebo group, and the drug narrowly escaped removal from the market. It still carries an extensive black box warning. This, according to Dr. Sobel, led to a general sense of pessimism surrounding the possibility of developing drug treatments for hypercholesterolemia. When rumors surfaced that compactin itself might have caused some cancers in dogs, Dr. Roy Vagelos, Merck's CEO says that he "made the decision to discontinue clinical trials of lovastatin."[2] Following Merck's decision to terminate clinical trials, FDA became actively involved in maintaining interest in the development of the "statins."

In July 1982, Merck made lovastatin available, under an arrangement approved by the FDA to Roger Illingsworth of Oregon Health Sciences University and Scott Grundy and David Billheimer of the University of Texas. Although Merck did not have an IND at the time, IND's were granted to Illingworth and Grundy under a process that included Merck's agreement to allow FDA to provide the researchers access to the Drug Master File, which contained information about the chemical identity of lovastatin and its manufacture.

Scott Grundy recalled that in 1982, the climate for lipid-altering drug development was not particularly good. Treatment for elevated LDL was based, he said, on "a conjecture known as the lipid hypothesis." Namely, that pharmacologic or dietary reduction of the "harmful" cholesterol would benefit the patient by arresting atherosclerosis. There was no proof at that time that drugs or diet used to lower cholesterol would be the clinical equivalent of patients with "spontaneously occurring" low cholesterol. Dr. Illingworth's patients, however, were all patients with cholesterol exceeding 400mg/dl who had already failed therapy with known treatment modalities. They were fully informed of the potential benefits and the known risks of lovastatin and agreed to participate in the trial designed to lower their cholesterol, either with lovastatin alone or in combination with other hyperlipidemic drugs. In 2001, Dr. Illingworth thanked FDA for allowing him to have the original IND for lovastatin and wrote Dr. Sobel that he had followed 17 patients with familial hypercholesterolemia for more than 10 years on lovastatin with "good efficacy and safety."[3]

Cholesterol Study Changes Thinking

The atmosphere surrounding development of lipid lowering drugs began to change following publication in *JAMA* (Jan. 20, 1984) of results from the Lipid Research Clinic Coronary Primary Prevention Trial (LRCCPPT), a multi-center, randomized double-blind study that tested the efficacy of cholesterol lowering in reducing the risk of coronary heart disease in 3,806 asymptomatic middle-aged men with high cholesterol. The trial did not use lovastatin; rather it relied on dietary changes and cholestyramine and the results were modest, but they did demonstrate that lowering cholesterol levels for 7.4 years, on average, did support a 19 percent reduction in the endpoints of heart disease, death or heart attack. Dr. Sobel noted, "Although the results of this study were quite modest by our present day standards, they served to effect a change in attitude towards pharmacologic means of lowering LDL-C cholesterol as a definite help in reducing coronary heart disease." Synergistically, the work of Michael Brown and Joseph Goldstein, who, studied the genetic basis for high cholesterol in some patients, elucidated the mechanism for LDL disposal by the liver. In 1985, they received the Nobel Prize for their discoveries concerning the regulation of cholesterol metabolism. Taken together, the LRCCPPT trial results and Brown and Goldstein's work, spurred new commercial interest in lipid-altering drugs.

On March 23, 1984, Merck submitted a company sponsored IND for lovastatin and the approval work proceeded apace.[4] The new drug application for lovastatin was approved nine months after its submission to FDA, which was one of the shortest approval times for an NDA by FDA up to that time. The decision by the Division of Metabolic and Endocrine Drug Products to approve agents for marketing based on the surrogate of lowering LDL cholesterol was a key component in shortening the review time for lovastatin. Lovastatin was released for marketing in 1987.

The key to successful post-marketing regulation in the case of this drug was the management of risk factors. Developments in the field of recombinant DNA technology facilitated the investigation and classification of the P-450 enzyme system, which FDA used as a tool to further minimize the risks of the clinical use of lovastatin. According to Dr. Sobel, this system became a prime tool in the post market surveillance process, predicting potential deleterious drug interactions for the statins. At the time of approval, FDA had residual safety concerns about this class of drugs in three areas: lens (eyes), liver and muscles. Although the mechanism by which cataracts were formed in patients taking triparanol was entirely different than that of patients who took the statins, FDA erred on the side of safety when lovastatin was first marketed, and required that labeling recommend yearly "slit-lamp" exams which would have detected early cataract formation. A Phase 4 investigation for cataract monitoring produced no evidence for cataract formation and eventually the recommendation for slit lamp examination was dropped.

In 1988, labeling expansion on the issue of drug interaction did note some concern about concomitant therapy with other lipid-lowering drugs and immunosuppressive drugs. In 1990, FDA scientists in the Division of Metabolic and Endocrine Drug Products and the Division of Epidemiology published an article on myopathy and rhabdomylolysis associated with combined use of lovastatin and gemfribrozil in a dozen patients, and recommended the discontinuation of concomitant therapy.[5] Initially very frequent monitoring of liver enzymes was recommended but over time it became clear that severe hepatotoxicity rarely occurred and the interval for liver monitoring was lengthened and then made discretionary.

Conclusion

The most important concern at present is the potential for the development of myopathy and rarely muscle destruction with consequent renal failure. The labeling makes recommendation for the monitoring with respect to this toxicity. Surveys now show that between 50 and 75% of Americans "know" their cholesterol number(s). That alone is testimony to the revolutionary nature of the statin drugs as a class. Moreover, the approval process for the first statin drug, lovastatin, illustrates how FDA, academia, and industry were able to work together to nurture the full potential of a drug that might otherwise have not been developed. Risk management approaches helped insure safe use of the drug for a large and growing segment of the population post-market, by anticipating potential drug interactions as well as the potential for causing other serious, but rare conditions.

Endnotes

1. Laughlin, RC and Carey, TF, "Cataracts in Patients Treated with Triparanol," *JAMA* 181: July 1962, pp. 339-40.

2. Vagelos, PR, "Are Prescription Drug Prices High?" Science, 252: 5010 (May 24, 1991), pp. 1080-4. Pedro Cuatrecasas, "Drug Discovery in Jeopardy," *Journal of Clinical Investigation* 116:11 (November 2006), p. 2840.

3. U.S. Congress, Office of Technology Assessment, Pharmaceutical R&D, Costs, Risks, and Rewards, OTA-H-522 (Washington, D.C., GPO), p. 74. The report does not make it clear that FDA, rather than Merck, was the party that made the decision to allow clinical trials to proceed after considering the pre-clinical toxicological data, including the compactin findings which had initially deterred Merck.

4. Long before the approval of Mevacor, Merck understood the need for large-scale clinical trials to expand use of the drug. Merck's Phase V studies involved over 7,000 patients. According to Greene, Phase V studies "were a set of expensive, large-scale, long-term trials conducted with the aim of developing additional therapeutic indications for an already approved drug or broadening the terms of an existing indication. In other words, these were trials of market expansion." Greene, p. 197.

5. "Myopathy and Rhabdomyolysis with Lovastatin taken with Gemfibrozil," *JAMA* 264:23 (December 19, 1990), pp. 2991-2. Comment: *JAMA* 264:1 (July 4, 1990), pp. 71-5