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May 1, 2007

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Dear Mr Chapman,

I received a Congressman's Dingell's letter of April 25, 2007. In the letter, he asked me to provide answers to questions that were posed by The Honorable Bart Stupak.

Appended to this letter are my responses. As you have requested, I list the questions and then provide the answer immediately following. References for all questions appears at the end of the questions.

I was honored and delighted to participate in the hearing on March 22, and I am pleased to provide these responses. Let me know if you need any additional information.

Cordially,

Bruce M. Psaty, MD, PhD
Professor, Medicine and Epidemiology
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May 1, 2007

The Honorable Bart Stupak

Question 1. Were there recommendations to which the FDA was especially responsive?

The answers to relevant to this question and to several other of the other questions listed below appear in a commentary published by the *Journal of the American Medical Association* (1). Brief answers to all questions are also provided here. The FDA clearly engaged the IOM report (2-4), but offered no opinion on the recommendations that would require Congressional action. Some of the excellent responses include the plans for: (1) the review of AERS (IOM, 4.1); (2) the access to study data from large automate health-care databases (IOM, 4.2); (3) the evaluation of the Risk Minimization Plans (IOM, 4.4); (4) the plans to develop and systematically improve risk-benefit analyses (IOM, 4.5); (5) the new Advisory Committee on communication with patients and consumers (IOM, 6.1); and (6) the development of the risk communication plan (IOM, 6.2);

Question 2. You listed a number of "incomplete" responses to IOM recommendations. Are there others?

The IOM recommended additional regulatory powers in the post-approval setting (IOM, 5.1 and 5.2), yet the FDA did not comment publicly on this recommendation.

Under the assumption that PUDFA might continue, the IOM suggested safety-related performance goals (IOM, 4.3). The FDA, however, described no specific safety-related performance goals.

The recommendation to involve Advisory Committees in the review of all NMEs was essentially ignored (IOM, 4.8).

The IOM recommendation to post all new-drug-application review packages on the Agency's website (IOM, 4.12) was not accepted.

The IOM recommended the review of all new molecular entities by Advisory Committees that included expertise in pharmacoepidemiology and public health (IOM, 4.9). The FDA plan for an occasional increase in the involvement of experts missed the point that the effort to assess risk and benefit almost always involves safety issues that might benefit from a public-health perspective.

The IOM recommended that the Secretary of HHS appoint an external Management Advisory Board to help transform the Center's culture (IOM, 3.2 and 3.3), but the management consultants mentioned in the FDA response, though perhaps a good start, were not the comprehensive approach recommended by the Committee.

The IOM Committee recommended building internal epidemiologic and informatics capacity to improve post-market studies (IOM, 4.6), but it appears that the FDA lacked the resources to respond to this recommendation.

The IOM recommended a public-private partnership to prioritize, plan and organize funding for confirmatory drug safety and efficacy studies of public health importance (IOM, 4.3). The effort still lacks a champion (5).

Question 3. Why is the public-private partnership recommended by the IOM necessary?

In the US, the tradition of leaving to the pharmaceutical industry the task of evaluating the efficacy and safety of its products has permitted manufacturers to make study design choices that largely pre-determine the answers provided by the trials. In active-treatment comparison trials, for instance, sponsors have often chosen inadequate doses or inferior comparison treatments that will make their products look good (5,6). More marketing than science, these studies do not answer important public health questions. The IOM Committee envisioned a public-private partnership that would help define the key public health questions that merit investment in large, long-term trials. This partnership would not only identify studies of greatest interest but also recommend the best design features through an independent unbiased process.

Question 4. You mentioned that 899 post-market commitments are still pending. Why are so many pending?

The number of pending post-marketing commitments has remained fairly constant, about 800 or more, over the past three years (7-9). Some are old and do not have an agreed-upon start date, so they can never be classified as "delayed," and many of them will remain "pending" in perpetuity. These post-market commitments, which are intended to address important questions, often come up so late in the approval process that they are not well designed. Some pending studies should be dropped, others redesigned, and all of those that remain need a start date. Additionally, many FDA reviewers are uncertain about the types of post-market commitments to request (10). The last minute rush to finalize the product label and design post-market commitments has contributed to the weakness of the US drug-safety system.

Question 5. You referred to the value of scientific disagreement. How is it that disagreement helps the FDA in its mission?

FDA has to make binary decisions, often with incomplete information. Uncertainty is the usual source of scientific disagreement, often best resolved by the conduct of additional studies. Scientific disagreements within the Agency during the pre-approval evaluation, as occurred with Ketek, are likely to be excellent predictors of drugs that eventually have post-market safety problems. The disagreement itself is useful information that should not be concealed. Some FDA views--for instance about the need to present a single public voice--seem to be unnecessary and even inappropriate in a science-based organization. IOM reports make a single set of consensus recommendations, yet when necessary, they allow for dissenting opinions. Law courts do so as well. What physicians and patients want is honest information, including legitimate scientific disagreements. Under the PDUFA timelines, 18% of FDA medical officers "felt pressure to approve … a drug despite reservations about its safety, efficacy or quality" (10,11). Suppression of healthy scientific disagreement has perhaps helped to erode the culture at the FDA.

Question 6. You have raised the question of transparency at the Agency. If you could look at internal FDA documents, which ones would you like to see?

I would like to see the approvable letter for muraglitazar and the internal correspondence leading up to the approvable letter. Muraglitazar is the diabetes drug that Dr Nissen talked about at the Oversight and Investigations Subcommittee hearing on February 13, 2007 (12). His work in this area was a great public health service (13). I would also point out that the safety and efficacy reviews by FDA medical officers were also outstanding (14,15). The FDA questions to the Advisory Committee, however, were not well designed to encourage a serious integration of risks and benefits or to elicit a formal risk-benefit analysis (16). The approvable letter for muraglitazar and the other correspondence, if they were written before Dr Nissen's publication, might provide some insight into the FDA division's understanding the public-health risk-benefit problem that Dr Nissen so eloquently described.

Question 7. One of the IOM's recommendations concerned risk-benefit. What did you think of the FDA response to this recommendation?

The FDA response was fairly comprehensive, but surprisingly late for an agency that has made determinations, for many years, about which drugs are "safe and effective for the intended use." Admittedly, risk-benefit analyses present a number of difficulties (17), but they are essential to the health of the public, and the FDA seems committed to adopting a new approach. In addition to their usefulness in counseling patients, risk-benefit analyses are also especially useful for identifying missing information and, thus, important for isolating the scientific questions that merit further study. At several stages, risk-benefit analyses are thus an integral part of the lifecycle approach to drug evaluation. An important corollary to risk-benefit analysis is, of course, transparency--making this information available to the physicians and the public.

Question 8. What is your view of direct-to-consumer (DTC) advertising?

The IOM Committee recommended the use of a symbol like the black triangle used in the United Kingdom to signal the uncertain safety associated with new drugs and a limitation on DTC advertising for up to two years (IOM, 5.3). As a public-health scientist, I would recommend abandoning DTC advertising altogether. It is an indiscriminate marketing technique that helps and harms (18-20)--like a fire department that hoses down all the homes in a neighborhood to put out a kitchen fire in one house. I have clinic on Monday mornings, and one day, all 5 men on my schedule came in asking for a prescription for the same drug. This epidemic of perceived erectile dysfunction was precipitated by Super Bowl ads the previous day. None of these men had ED. When a truly important and innovative therapy such as imatinib (Gleevec) arrives, word about it gets around fairly fast these days without any need for DTC advertising. I myself would not count, for instance, purple pills among the truly important and innovative therapies. The GAO report has also identified problems in the FDA review of DTC ads (21).

Question 9. Is there a conflict-of-interest problem on FDA Advisory Committees?

There is certainly the perception of a problem. Physicians and scientists are notoriously naïve about conflict of interest (22). In one survey of medical residents (23), 61% said that their colleagues were likely to be affected by gifts from industry, but only 16% admitted that they themselves might be affected. How can that be? Well, we tend view ourselves in such a favorable light that conflict of interest is harder to discern in ourselves than our colleagues. The IOM Committee recommended that a substantial majority of Advisory Committee members be free of significant financial conflicts (IOM, 4.10). In the FDA response, there was no commitment to limit conflict of interest. The recent guidance from the FDA on conflict of interest did not go far enough (24). The drug-review process will benefit from truly independent outside review. The more independent, the better. Regardless of whether conflicts may have affected FDA decisions, the issue of public confidence demands that even an appearance or suspicion of the adverse effects of conflicts must be addressed, otherwise the FDA's overall credibility decline.

Question 10. You referred to the industry's lack of interest in safety. Can you provide any examples?

The pharmaceutical industry has a structural conflict of interest. The need to recover their investments in research and development and their fiduciary duty to shareholders lead to pressure or bias in favor of promoting drugs and potentially discounting ambiguous risk signals for as long as possible. Sometimes, the effects on public health can be devastating. Baycol (cerivastatin), a lipid lowering "statin" drug, was voluntarily withdrawn from the market in August 2001 because of a high incidence of rhabdomyolysis, a breakdown of muscle that causes pain and sometimes kidney failure and death (25). The sponsor knew about the high risk of rhabdomyolysis but did not adequately inform the FDA, patients or physicians for about 20 months. When the company's scientists brought this problem to the attention of the head of the pharmaceuticals business group one year before the drug was finally withdrawn, he ignored their concerns and told his marketing staff to "promote the hell out this product" (26). America needs a strong well-funded FDA capable of regulating drugs from manufacturers that are ethical or behavioral outliers.

In a review of materials before my testimony at the Senate Finance Committee in November 2004, it was clear that the sponsor was aware of the possibility that Vioxx, compared with aspirin, might be associated an excess of cardiovascular events as early as 1996 (27). The sponsor sought to design a large study that would selectively maximize the chances of showing favorable results for the prevention of gastrointestinal bleeding and selectively limit the chances of finding any unfavorable results about increases in cardiovascular events. Under these circumstances, the FDA needs to make sure that sponsor's studies ask and answer the right questions in a manner that protects and advances the health of the public (28). Decisions about the study questions and designs are best made by scientists independent of the sponsor.

Question 11. Why did the IOM recommend clinical trial registration?

Some sponsors selectively publish favorable findings (29), sometimes with ghost authors (30); and some fail to publish unfavorable findings, sometimes by omitting data from published

studies (31,32) and sometimes by failing to publish the study at all (25,28). They treat scientific data obtained from human subjects, who volunteered to help advance medical knowledge, as if they were mere marketing efforts. This selective approach to publication distorts the publicly available evidence base and undermines any efforts at genuine risk-benefit analyses. The IOM recommendations about registering clinical trials and eventually making the results public are important for public health (IOM, 4.11).

Question 12. Do you favor the continuing appropriations from user fees?

Under PUDFA, the US became increasingly the country of first launch, the public testing ground for new medicines without any efforts to improve the drug-safety system. Indeed, during the first 10 years, PUDFA prohibited the use of user fees for improvements in drug safety. According to Dr David Kessler, head of the FDA from 1990 to 1997, "PDUFA should have had funding on the safety side from the beginning, but the industry refused to accept that…. We wanted it. The industry said no" (33). When Congress created PUDFA, safety activities were largely entrusted to the pharmaceutical industry, and they were not adequately funded at the FDA. In its implementation, PUDFA has also created at least the appearance that the FDA has industry rather than the public as its primary client. Particularly troublesome is the fact that the FDA enters into negotiations with industry to develop the next round of PUDFA goals and funding (34). No other regulator in the federal government (to my knowledge) negotiates in this way with the regulated. The IOM Committee expressed its preference for funding from general appropriations because drug safety is a public good.

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