Questions from the Honorable Bart Stupak (from Dr. Ray Woosley):

1. In an article you co-authored in 1998 entitled "Making Medicines Safer," you cited figures indicating that adverse effects of drugs is one of the top six causes of death in this country. Is that still the case?

> I am not aware of more recent data and I suspect that it has changed significantly. The estimates that I cited in 1998 were based on the rates of adverse events in hospitalized patients. There is another component that occurs in outpatients and nursing facilities that has not been quantified and should add substantially to the number of deaths.

2. In the same 1998 article, you noted that, given the state of information technology in 1998, it was remarkable that the Food and Drug Administration (FDA) lacked a systematic program of post-marketing drug surveillance. Does it exist today?

> Not at this time. However, a potential program of post-marketing surveillance does exist but it is only partially utilized. The eleven AHRQ-funded Centers for Education and Research on Therapeutics (CERTs) have the potential to serve as such a system. They have the potential to establish access to the electronic medical records for over 100 million patients and they have the required medical and pharmacologic expertise. They are not now funded to conduct independent post-marketing safety surveillance but could do so if adequately supported. In addition to conducting post-marketing safety assessments, these Centers could also confirm drug effectiveness in the real world of medical practice, assess comparative effectiveness and confirm appropriate use. All of these functions are included in the authorizing language for the CERTs. AHRQ and FDA simply need the appropriations to jointly implement an active surveillance system utilizing the existing network of CERTs. Funding for FDA is an essential component of such a network so that the surveillance can be fully informed and any necessary regulatory action can be taken promptly.

3. How does FDA's voluntary reporting system (AERS – Adverse Event Reporting System) compare with France's post-approval drug safety surveillance system?

> France has an active surveillance system of 31 regional pharmacovigilance centers positioned throughout the nation at major universities and hospitals. They are staffed with scientists who are trained to detect, analyze and characterize the risk factors associated with adverse drug events. The centers receive spontaneous adverse event reports and gather the data to better understand the reliability and nature of any reports. Unlike AERS which relies only on voluntary reporting, the French system actively examines the medical records of patients who receive newly marketed drugs and obtains comprehensive information about those who have adverse experiences that might be drug reactions.

.4. How does FDA's voluntary reporting system compare with the United Kingdom?

According to experts at the FDA, the UK's General Practice Research Database (GPRD) is the largest pharmacoepidemiologic database in the world with the highest quality data. The database covers about 3 million lives with data going back 10 years. The data are collected from the computerized medical record systems of 5% of all general practitioners in the UK. This database resource is superior in many ways to any US-based database known to the FDA.

The UK also has a "yellow card" system in which they ask physicians to complete a survey reporting outcomes for a fixed number of patients who receive a newly marketed drug. This system allows the UK's regulatory body (MHRA) to, not only detect adverse events quickly, also provide an estimate of the frequency of the adverse event.

The AERS system can never accurately estimate incidence because of under-reporting. Mandatory reporting would not be a solution to the problem because of the likelihood of over-reporting of events that could obscure the detection of real adverse events.

5. The article you co-authored entitled “A New System for Moving Drugs to Market,” contains your recommendation that newly approved drugs should be given to a defined population under observed conditions only. Wouldn’t this require an initial ban on most direct-to-consumer marketing since a newly approved drug would be approved for a carefully defined population?

Yes, but not necessarily in every case. The original intent of those who approved direct to consumer (DTC) ads was to enable patients to learn that a new treatment for their illness had become available and that they should contact their physician to determine if it would be of value in their care. It was not their intention for the ads to be used to market the drugs. The attempts to balance the marketing components by requiring that the ads convey risk/benefit information in the limited time available is, not only futile, it raises false expectations that understanding will result.

DTC ads promote drugs to the general public although prescription drugs, by their very nature, require a trained intermediary to diagnose whether the drugs are likely to be safe and effective for the patient. Such broad promotion fosters overuse of the drugs and a lack of true appreciation of their potential risk. In the system of accelerated but limited access that we proposed, the ads could be prohibited unless the public needs to be informed that a new drug is now available. However, the ads should not be promotional in nature and should be more in accord with the original concept of a "public service announcement." The ad should also emphasize that the newly approved product is only recommended for a limited population, i.e. the types of patients for whom it has been studied and found to have an acceptable risk/benefit ratio.

6. How would the FDA enforce such a limitation on drug prescriptions given that states regulate medical practice not the FDA?

The FDA should not be expected to try to guide the use of prescription drugs, other than by providing information about the safety and efficacy of drugs. AHRQ is the element of government responsible for improving the outcomes in healthcare. The educational and research programs of the AHRQ-funded CERTs could be better utilized to help provide the data/information needed to adequately guide and manage the use of new medications.

Professional societies can also become even more involved in setting prescribing standards through the use of guidelines for the appropriate prescription and monitoring of new therapies. Professional societies establish standards of therapy but they need to be more specific. For example, they recommend a "beta blocker" for treating hypertension, but which of the many should be tried first. It is not always the least expensive to purchase. HMOs have effective systems to monitor and guide the use of therapies. The major problem is the absence of data to inform those who wish to guide therapy. The lack of data on comparative effectiveness and comparative safety is the limiting factor.

As Alastair Wood has suggested, in order for companies to receive market exclusivity for innovative new therapies, companies should be expected to conduct reasonable post-marketing studies (and, I would add, use their detail force to encourage the appropriate use of their drugs by rewarding the sales force when the drug is prescribed appropriately). In order to provide an incentive for companies to fully evaluate their drugs for safety early after entry into the market, the FDA should encourage companies to also monitor for evidence of effectiveness as a basis for expanded claims to treat broader populations.

Unfortunately, regulation of use is likely to be ultimately left to the plaintiffs bar. However, most Health Maintenance Organizations, the Veterans Affairs Medical Systems and others are increasingly able to track drug use and reward those who prescribe drugs appropriately.

7. Does providing warnings, product labels or package inserts adequately protect patients from adverse events?

No. We need better ways to manage risk by informing and protecting patients. Also we must recognize that some risk management tools that appear to be reasonable may not be effective and could cause unanticipated and unintended harm. Restrictions on the use of the drug, dofetilide, led to greater use of other drugs that had lower efficacy and even greater risk of harm. Also, the "Black triangle" warning for newly released prescription drugs has never been tested to

be certain that it will produce a net positive impact. We should not assume it will work for every product and could result in non-compliance to therapy and patient

8. In your 1998 article, entitled "Making Medicines Safer," you called for establishment of a post-marketing drug-safety program independent of the FDA to assure objectivity and to avoid conflicts of interest. Do you still recommend the creation of an independent body responsible for oversight and investigation of post-market drug safety?

Yes, we recommended the creation of an independent Board to evaluate the overall safety process and programs available to the FDA and to inform the FDA of its findings from active surveillance. However, we did not recommend that this body assume any of the responsibility for regulating the industry and its products. Our suggestion was to have the Board gather data, submit it to the FDA and make recommendations on safety, not take away the regulatory responsibility. The regulatory decisions are best made by those government employees who have been trained in medicine and the regulatory sciences and who are experts in the science of simultaneously assessing benefit and risk for populations. Physicians are trained in assessing risk and benefit for a patient, not populations.

9. Given that the FDA permits the same reviewers in the Office of New Drugs who approve a drug to make the final decision on post-market status of the drug, is this not an inherent conflict of interest?

I think it is can be a "perceived" conflict of interest, not an "inherent" conflict of interest. The reviewers' responsibility must include the counterbalancing assessment of effectiveness in addition to safety. Post-market assessment must include an ongoing assessment of benefit and risk simultaneously. I don’t believe it would be wise to change the current system and create one in which the "approvers" and the "removers" are pitted against one another. Recommendations for the market status of drugs require complex assessments, a synthesis of the scientific information and a consensus decision. It is very likely that there will be dissenters on the team that makes these assessments. The dissenters must be given a opportunity to express their opinions but at some point, only one recommendation can be made by the Agency. Public airing of "split decisions" only result in chaos and loss of credibility for the FDA. The best way to minimize disagreements and maximize the accuracy of the decision making process is to have an independent source of highly accurate information on the post-market experience with new drugs.