The Honorable Bart Stupak

1. *What problems do you see in connection with the restricted use of fees contained in Prescription Drug User Fee Act (PDUFA) IV?*

   The overemphasis on meeting "deadlines" for approval has shifted FDA efforts away from drug safety. Pursuing safety signals during the pre-approval phase takes time and could, at times, delay approval. Since more safety problems are now detected post-approval, it suggests that the pre-approval safety evaluation is less thorough. The presence of an adequately staffed and funded Drug Safety Office could restore the balance.

2. *Do the deadlines in PDUFA contribute to an excess of unrecognized safety problems in connection with new drug applications?*

   As stated above more safety problems are now detected post-approval. Today, 20% of new drugs have a Black Box warning added after they are on the market and 4% are withdrawn. This should not be considered acceptable public health practice.

3. *Has PDUFA affected the "culture" of the Food and Drug Administration (FDA)?*

   It would be hard to prove. However, it would not be overreaching to conclude that the degree to which PDUFA dictates how FDA must interact with industry could create tensions within a public health agency.

   One reason for the isolation and alleged mistreatment of the small drug safety staff may be that they can delay approval by bringing up potential safety concerns. These concerns may require more sponsor and FDA analysis of trial data and possibly even new studies. Any such delays may be at odds with management's need to meet PDUFA deadlines in order to realize user fee revenue.

4. *What changes in FDA's drug safety structure would be most likely to obviate another "Vioxx" tragedy?*

   Drug safety has to be brought to parity with drug benefit. This can not be accomplished without the creation of an *independent* Office of Drug Safety with a Director who reports directly to the Commissioner. This Office needs adequate funding to secure sufficient numbers of appropriately skilled staff and its own Advisory Committee.

5. *Should the Office of Surveillance and Epidemiology share authority with the Office of New Drugs in postmarket setting?*

   Since monitoring of drug safety is the main FDA mission post-approval, there ought to be an independent Office of Drug Safety responsible for post-marketing. The currently weak and understaffed Office of Surveillance and Epidemiology lacks authority. Sharing

authority is fine in principle and should be done both pre-and post-approval. But, the final decisions pre-approval ought to rest with the Office of New Drugs and decisions post-approval with a new Office of Drug Safety, or alternatively, an expanded Office of Surveillance and Epidemiology.

6. *What is your opinion of direct-to-consumer marketing of new drugs?*

DTCA has led to over-utilization of very costly and typically non-essential drugs. There are often much better understood and less expensive alternatives are available. If DTCA is a first amendment commercial free speech right and cannot be restricted, then new rules requiring thorough FDA reviews of the advertisements for scientific accuracy prior to them being aired or printed should be introduced.

7. *How can the use of new drugs, with relatively unknown safety records, be reduced?*

Absolutely.

(a) Strict risk management programs should be linked to their approval.

(b) When there is inconclusive or incomplete data to support safety, drugs should only receive time-limited conditional approval.

(c) The rationale for the conditional approval due to safety concerns should be made public.

(d) Restrictions ought to be placed on DTCA. A prominent Black Box warning detailing any potential safety concern ought to be included in the advertisement.

8. *What are the problems associated with post marketing safety studies?*

(a) There are no legal consequences (fines, drug withdrawal) for drug companies who choose to ignore or stall the completion of a post-market safety study commitment.

(b) Every study commitment should have a clear deadline for completion and submission to FDA.

(c) Cleaning up the current backlog ought to be of highest priority.

9. *Does the FDA have sufficient authority to sanction pharmaceutical companies that suppress or delay submission of unfavorable trial information?*

FDA appears to believe it does, however it fails to behave accordingly and take meaningful action against regulatory violations by industry. Whether it actually has sufficient legal authority may be a question for regulatory experts to determine. However, FDA does need an expanded toolbox of available sanctions so it can deal appropriately with different kinds and degrees of violations.