Senator Grassley

Question 1: Do you agree, without reservation, to respond to any reasonable summons to appear and testify before any duly constituted committee of Congress, if you are confirmed?

Answer: Yes I do.

Question 2: Is there anything you are aware of in your background that might present a conflict of interest with the duties of the office to which you have been nominated?

Answer: I am not aware of anything in my background that might present a real, or apparent, conflict of interest under the Standards of Ethical Conduct regulations, and I will seek and abide by the advice of agency ethics counsel in the Office of the General Counsel with respect to these issues.

Question 3: Do you know of any reason, personal or otherwise, that would in any way prevent you from fully and honorably discharging the responsibilities of the office to which you have been nominated?

Answer: No I do not.

Question 4: On what date did you formally and officially resign as Director of the National Cancer Institute? Do you have any formal or informal agreement related to your continued employment at NCI contingent upon the outcome of your nomination to the FDA? Since resigning from NCI, have you had any association with NCI, including, but not limited to, retaining a paid or unpaid position at NCI?

Answer: I officially resigned as Director of the National Cancer Institute on June 10, 2006.

I do not have any formal or informal agreements related to my continued employment at NCI contingent upon the outcome of my nomination to the FDA.

I will continue to be associated in matters pertaining to my professional expertise in oncology as a member of the NIH Consultant Staff (a cadre of professionals not primarily employed at NIH, but who are of recognized professional ability and who may be called upon for advice and assistance on patient care). In this capacity, I can provide professional opinions regarding patient care in my area of expertise in urologic oncology and will approximately once per year deliver a medical lecture.

Question 5: In your appearance before the Senate HELP Committee on August 1, 2006, you stated your belief that there was no need for the Office of New Drugs (OND) and Office of Surveillance and Epidemiology (OSE) to be two, separate centers within the Food and Drug Administration. As you know, OND is responsible for the approval of drugs within specified time periods. However, over the course of numerous investigations by my Committee staff, one particular issue is always there: constant pressure to approve drugs

within deadlines established by the Prescription Drug User Fee Act. The unfortunate reality is that safety has taken a back seat to the fast approval of products by the FDA. The consequences of the FDA's inadequate attention to drug safety is just beginning to be fully understood.

Please explain, in detail, why two separate and independent centers – one for approving drugs as speedily as possible and one for ensuring post-market surveillance and safety of approved drugs – will not improve the FDA's ability to fulfill its mission to protect the public health.

In responding, please articulate whether or not the OSE, formerly the Office of Drug Safety, is on equal footing with the Office of New Drugs. Although these offices appear to be co-equals on an organizational chart, it is evident that OSE is the lesser office when it comes to staff, resources, regulatory authority, and stature within CDER and the FDA. Most recently, the Director of an Office within OND stated to the Committee that post-market surveillance is "overwhelming" and the problem is a resource issue.

Answer: I believe that two separate and independent centers would not improve the FDA's ability to fulfill its mission to protect the public health, and in fact, in the evolving era of molecular medicine, such an approach could have a deleterious effect. Our knowledge of a drug's safety and efficacy profile proceeds along a continuum, which begins with *in vitro* and animal studies (before the drug is ever administered to humans), continues to grow through rigorous clinical trials, and is further refined after a drug is marketed. Because clinical trials are not capable of detecting rare, serious adverse events, and because the population receiving the drug once it is marketed is often different from that in clinical trials, we expect to learn more about a drug's safety and efficacy profile after it is marketed. It is the review and synthesis of this cumulative knowledge base that leads to the most accurate assessment of the drug's safety profile. In CDER, Office of New Drug (OND) staff focuses on the pre-marketing safety data, while Office of Surveillance and Epidemiology (OSE) staff specialize in the post-marketing safety issues. Pre- and post-marketing safety data must be viewed as integral and interrelated, and both should be considered as part of the lifecycle of the drug. Staff from the OSE and OND work closely in the analysis of appropriate regulatory actions, together they take into consideration both risk and benefit information from pre- and post-approval sources. If pre-approval and post-approval functions were split, there would be a loss of continuity in the review of risks and benefits. In the era of molecular medicine, the tools of modern science and technology will be essential to determine the impact of a drug, with regards to both effectiveness and toxicity, in both pre- and post-marketing settings.

Separating these two activities into two centers would be very costly, because of the duplication of the wide range of expertise involved in both. Medical officers in OND whose areas of expertise include the affected patient population(s), medical conditions, and treatments, know the results of animal and clinical studies that supported approval of the product; in addition, they review studies with products that are used in the same patient populations, and products, some still in the investigational phase, from drugs in the same or related classes. This expert knowledge of the patients' medical conditions, availability of alternative therapies, and safety profiles from IND and NDA submissions is a crucial component in the review of newly

identified risks and how they may impact benefits. OSE personnel provide expertise in the areas of epidemiological studies of large populations, evaluation of data from AERS (that is, spontaneous adverse event reporting) and large external data sets purchased for adverse event tracking and evaluation in specific populations, medication error prevention, and risk management techniques.

If the responsibilities were split into two centers, the safety center would have to duplicate the expertise of OND staff, with expert knowledge of patient populations, medical conditions, alternative therapies, and safety profiles from investigational new drug applications and studies in marketing applications to support approval to enable the safety center to make appropriate risk-benefit decisions and the drug approval center would have to duplicate the expertise of the OSE staff.

OSE like OND, reports directly to the Center Director. Center management and OSE management are working to ensure frequent communication between OSE and OND. Also, CDER is increasing the staffing and resources of OSE within CDER

Cross-center consultation cannot substitute for integration within the Center, and would be much more difficult administratively, and therefore, less efficient. With the consolidation of CDER offices into a new facility at White Oak, OND and OSE's close proximity has facilitated this integration with improved and easier communication, leadership, and shared responsibility. For example, OND routinely meets with OSE staff to discuss the current or anticipated safety of marketed products. CDER has recently instituted safety meetings that are held periodically (monthly or bi-monthly) to discuss new safety issues and the status of reviews and analysis of previously identified safety signals. Also, prior to approval of applications to market new molecular entities (NMEs), or non-NMEs, OND and OSE staff have pre-approval safety conferences. OSE staff is also consulted by OND in many pre-approval activities that increase CDER's ability to understand and adequately monitor risk and benefit for marketed products such as medication error prevention and risk management plan review. It is preferable to continue to improve the function of the current integrated model, rather than create a new, discontinuous model with unintended deleterious consequences.

In most cases, OND, through its Offices of Drug Evaluation and review divisions, is delegated the final decision-making and signatory authority for applications assigned to it. For post-marketing safety issues, OSE personnel are key members of the review team and contribute to these regulatory decisions. If there are organizational or individual disagreements with a planned regulatory action between OND and OSE, there are several avenues for all opinions to be heard including routine meetings among review team members from OND and OSE, meetings with supervisors and management within the Center and Agency, dispute resolution, CDER regulatory briefings, Advisory Committee meetings, Drug Safety Oversight Board (DSB) meetings and new procedures for expressing differing professional opinions.

How can you assure Congress that post-market surveillance is as important to the FDA's mission as the approval of new drugs?

I believe that post-marketing surveillance is as important to FDA's mission as the approval of new drugs. FDA continuously takes steps to address post-marketing safety. For example, on April 30, 2001, FDA's regulations implementing section 130 of FDAMA, which requires sponsors of approved drugs and biologics to report annually on the status of post-marketing commitments, became effective. These regulations modified existing reporting requirements for NDA drug studies and created a new reporting requirement for biologic products.

On October 1, 2002, the "Public Health Security and Bioterrorism Preparedness and Response Act of 2002," which includes the Prescription Drug User Fee Amendments of 2002 (PDUFA III) was enacted. PDUFA III goals include the use of user fees to fund pre- and peri-NDA/BLA risk management plan activities in addition to their use for the review of marketing applications and other initiatives. This resulted in the development of a risk management team in the Center for Drug Evaluation and Research (CDER) Office of Surveillance and Epidemiology (OSE) that works closely with the CDER Office of New Drugs (OND) in the review of proposed risk management plans and in the evaluation of existing plans. PDUFA III goals also include the use of user fees to fund improvements in FDA performance management. Two initiatives towards these goals involve post-marketing safety. The first is a process improvement team on post-marketing safety that is working on defining roles and responsibilities for staff in OND and OSE; as a result of this group's efforts, OND is in the process of instituting a post-marketing safety team within each of its review divisions, to better coordinate the review of post-marketing safety issues and to enhance communication between OND and OSE. For the second, a process improvement team within OSE is underway to improve communication, project management, and to enable OSE to more efficiently and effectively respond to emerging safety issues.

In April, 2006, CDER appointed an Associate Center Director for Safety Policy and Communication, with the goal of bringing greater focus, attention and energy to important Center-wide drug safety and risk communication initiatives, as well as efforts that require close coordination with the Commissioner's Office and external stakeholders.

Do you have a vision to strengthen post-market surveillance and improve FDA's ability to fulfill its mission to protect the public health beyond what has been done to date? What are your plans for improving post-marketing surveillance systems and activities? Please be specific and provide time frames for implementation.

My vision is for post-marketing surveillance to serve as an opportunity to detect and analyze the earliest signals of unexpected toxicity or enhanced effectiveness of drugs as they are applied to larger, more diverse populations of patients than were included in selected clinical trials. The cornerstone of FDA's post-marketing safety efforts to detect serious risks with marketed drug products is the review and analysis of passive spontaneously reported adverse events that are submitted to FDA. These reports are entered into the Adverse Event Reporting System (AERS) database for review and analysis. To enhance our ability to better capture safety signals within the system, FDA has integrated the use of data mining techniques into its review of AERS data. Data mining provides an objective method to detect safety signals that might otherwise not be recognized. Data mining identifies adverse events in the AERS database occurring with the use of a particular drug more frequently than would be expected in the database. Such "signals" then can be pursued with more intensive case evaluation. It is important to realize that data mining

looks at associations in the database between drugs and adverse events. It makes no inference regarding a causal role for the drug in the development of the adverse event. FDA plans to investigate other signal management tools, including advanced information management systems, to aid the safety reviewers in the triage, tracking, and management of skyrocketing numbers of adverse experience reports.

To supplement the AERS system, FDA is exploring the feasibility of ways to work with outside partners to develop an active surveillance system. The term "active surveillance" refers to methods that actively identify adverse drug events, rather than waiting for them to be reported as is the case with AERS (passive surveillance). Once methods are developed and validated, we would pro-actively search various data systems for medical events that are likely to be the result of drug therapy, and then conduct in-depth investigations to determine the likelihood that a drug may have contributed to that event. These systems, once developed and validated, may offer the opportunity to further examine known safety issues, or to explore for new events not previously thought to be related to the use of drug products.

An OSE working group is currently exploring active surveillance and has issued a Request for Information (RFI), seeking ideas and potential existing systems from the public. This group has reviewed the responses it received and OSE is now considering what the next steps will be. FDA recently reviewed its partnership with CDC for the National Emergency Injury Surveillance System (NEISS), which looks for new adverse events presenting to hospital emergency departments. A pilot program evaluating this system is ongoing.

OSE currently has contracts for drug use data to quantify the number of prescriptions dispensed to the population and obtain demographic information on the population exposed to pharmaceutical products. These data are also used in association with spontaneous case report data to understand the context within which adverse drug reactions occur.

OSE has an epidemiology contracts program to investigate drug safety questions important to FDA. Four sites are currently funded through this contracts program:

- HMO Research Network
- I3 Magnify Drug Safety (United Health database)
- Kaiser Permanente Research Institute
- Vanderbilt University with Tennessee and Washington State Medicaid

These contracts were awarded in September 2005 and studies are ongoing.

CDER and the Agency for Healthcare Research and Quality (AHRQ) have signed a formal data use agreement that will allow us to conduct a collaborative research project entitled "Data Development for Patient Safety - A Pilot Study Using Medicare Part B Drug Data." The goal is to develop data structures and methodologies for identifying and analyzing adverse drug events using CMS Part B drug data.

OSE currently has a contract allowing access to the General Practice Research Database (GPRD). The GPRD contains anonymized longitudinal medical records from primary care in the

United Kingdom (UK). It is searchable on a patient-level basis for prescription information, health history, details of ambulatory care visits, information relating to hospitalizations and laboratory test results. This acquisition has increased our access to population-based data to enable more formal epidemiologic studies to be performed. We have completed an initial study of the "Association between Non-Steroidal Anti-Inflammatory Drugs and Acute Myocardial Infarction in the UK-Based General Practice Research Database."

In order to fully implement the use of electronic medical data system information, FDA will be adding computing infrastructure and staff and will need to develop policies, standards and methodologies for this type of analysis. FDA is actively evaluating the utility and feasibility of conducting specific studies of high priority safety issues using such linked databases. Studies conducted on these types of databases will provide more evidence about drug use in a broader range of conditions, including more detailed evidence about drug safety in subgroups of patients. CDER is making every effort to ensure that appropriate resources are devoted to the functions managed by both OND and OSE.

FDA is committed to working with other government agencies, professional and patient groups and industry to continue to reduce the incidence of medication errors through better consumer medical information, improved drug labeling and naming, and through enhanced electronic health information architecture to ensure that safety information is communicated efficiently and effectively.

CDER has a number of initiatives underway to improve our internal processes for post-marketing safety review activities. These include the development of a CDER-wide safety tracking system that is anticipated to be completed by early 2007. A process improvement team on post-marketing safety is working on defining roles and responsibilities for staff in OND and OSE; as a result of this group's efforts, OND is in the process of instituting a post-marketing safety team within each of its review divisions, to better coordinate the review of post-marketing safety issues and to enhance communication between OND and OSE. A process improvement team within OSE is underway to improve communication, project management, and to enable OSE to more efficiently and effectively respond to emerging safety issues. OSE began a project to identify best practices and develop optimal procedures for the review of adverse experiences by safety evaluators in OSE. In addition, OSE will host a course for OND reviewers this fall on the tools and methods used in OSE to better familiarize OND staff with OSE. OSE is developing a research agenda to focus activities in areas of the highest priority. As noted in the response to an earlier question, CDER has recently instituted safety meetings that are held periodically (monthly or bi-monthly) to discuss new safety issues and the status of reviews and analysis of previously identified safety signals.

Question 6: Recent oversight of the FDA has allowed numerous employees, at all levels of the FDA, to voice concerns about the insufficiency of the agency's resources and authority. During your testimony you stated the FDA had adequate authority to regulate the drug approval process, while ensuring that drugs are safe and effective and approved within a timely manner. What are your thoughts on additional user-fees to be used exclusively for drug safety purposes? Why do you believe the FDA has sufficient authorities when the GAO, many in Congress, and so many FDA officials currently believe that present

authorities are inadequate to fulfill the FDA's mission to protect the public health, particularly in the post-market setting? For example, the FDA has the authority to require post-market clinical studies as a condition of drug approval. However, the agency can only negotiate with companies to conduct such studies after a drug is on the market. In addition, label changes also are negotiated with a company. What is your position on Congress providing FDA the authority to require drug companies to conduct post-market clinical studies and compel companies to promptly add a warning to a drug's label when a new health risk is discovered? Do you plan to request these authorities from the Congress?

Answer: It has been my focus to use all existing regulatory authority and enforcement powers to assure safety when accomplishing label changes with drug companies or when monitoring or managing drug safety issues. I believe FDA can successfully carry out its mission under its current statutory and regulatory authority.

Question 7: In March of 2006, you spoke at the annual meeting of the Pharmaceutical Research & Manufacturers of America in Washington, DC. During your remarks at the conference, you made some comments noting that the FDA of the future will be a "science-led, facilitating agency that helps new products at a much more rapid rate, in much larger volume." There is a distinct difference between regulating and "facilitating." Your comments appear to suggest a role reversal for the agency. At a time when the American public has lost confidence in the FDA, why are you suggesting that the agency should be a "facilitating agency"? Given the fact that you were addressing the pharmaceutical industry your motivations are quite apparent, but please explain in more detail your vision for the FDA's role as a "facilitating agency" versus its historical role as a regulating agency.

Answer: I don't believe that the terms "regulating" and "facilitating" are mutually exclusive, but rather are complementary. In my remarks to the Pharmaceutical Research & Manufacturers of America, I wanted to emphasize that I recognize that the advances in basic science, in medical technology, and in diagnostic and therapeutic products that have the potential to revolutionize health care and provide unprecedented opportunities for innovative, personalized, life-saving interventions, which must be safe, as well as effective. As FDA works to facilitate such development, the Agency can serve to make available ground-breaking new treatments while also preventing untoward and unexpected problems in the development process that result in products that are not safe and not effective. This is the broad vision of FDA's Critical Path Initiative. I believe it is absolutely essential that FDA's regulatory science evolve to recognize and support the on-going scientific discovery. FDA must modernize our scientific regulatory standards to facilitate incorporation of new scientific advances into safer and more effective medical products. FDA must be a science-based agency that continually modernizes our scientific regulatory standards as science evolves, to ensure that safer, more effective new products, at a much more rapid rate, in much larger volumes, can make it across that bridge of development, in order to be delivered to patients and improve their health.

Question 8: As you know, the Committee on Finance is presently investigating the approval and post-market surveillance of the antibiotic Ketek. The FDA has consistently denied timely access to both documents and officials necessary to conduct legitimate

Congressional oversight of the FDA. In particular, the FDA has withheld documents related to a closed investigation, as well as access to a line agent involved with that closed investigation. The Department of Health and Human Services and the Department of Justice have stated that it is executive agency policy to not provide line agents in response to Congressional requests for information. Nonetheless, there are numerous legal and historical precedents on record where line agents have been interviewed by or testified before Congressional Committees related to open investigations. The fact that a matter is pending has never been a bar to Congressional oversight. Do you agree with that generalized statement as to the authority of congressional oversight? Will you work with this Committee and reach an accommodation so that the goals of Congressional oversight are met and the institutional interests of the executive branch are met? In responding, articulate your personal position on why the FDA cannot accommodate a congressional request for a line agent, in this case a Committee request related to a closed investigation, and why the FDA has not accommodated the Committee in defiance of numerous legal and historical precedents. Finally, please describe in detail your role, if any, in meetings and/or discussions with HHS and/or DOJ related to providing the Committee on Finance with documents and access to FDA officials pursuant to its ongoing investigation of Ketek. Describe in detail all meetings and identify the individuals with whom you consulted.

Answer: I concur with the Executive Branch's longstanding policy of complying with Congressional requests for information to the fullest extent consistent with constitutional and statutory responsibilities. We strive to work with Congress to accommodate Congressional oversight while maintaining interests of the executive branch. Regarding matters pending before the Agency, disclosure of pre-decisional information would significantly compromise the ability of our staff to consider important public health and safety matters in an objective and independent setting. Moreover, I am concerned that there would be a chilling effect in the deliberative process if employees believed their frank and initial opinions may be the topic of debate in Congressional hearings, and possibly in the press, simultaneous with the deliberative decision-making process. It is critically important that FDA experts be able to thoroughly evaluate and candidly discuss available information related to drug safety and other matters. The Agency's ability to protect and promote the public health depends on its ability to conduct objective analyses and to base its decisions on sound science. Likewise, the disclosure of information that might relate to any open investigation in response to Congressional inquiries poses an inherent threat to the integrity of the Executive Branch's enforcement and litigation functions. Such inquiries create the risk that the public and the courts will perceive undue political and Congressional influence over enforcement decisions.

Regarding the Committee's request to interview a line agent, line agents conduct investigations that are central to enforcing the laws enacted to protect the public health in relation to FDA-regulated products and activities. The Agency needs to ensure that its agents can exercise the independent judgment essential to the integrity of law enforcement and prosecution functions and to provide public confidence in those decisions. I believe that the prospect of a Congressional interview about their actions may have a chilling effect on the actions of our agents. At the same time, I recognize that Congress has an oversight duty. Line agents are accountable to their supervisors. Therefore, by questioning supervisors, Congress can fulfill its oversight responsibilities without undermining the independence of line agents, without raising

the appearance of political interference in investigational and prosecutorial decisions, and without compromising potentially successful prosecutions.

Question 9: As you know, FDA's advisory committees are an essential part of the review and approval of drugs, biologics and medical devices. The committees consist of members from academia, the government and industry. Advisory committee members, however, often have financial and/or other interests in the products being reviewed for approval. This sometimes purports the appearance of a conflict, especially when they may be tangentially vested in one of the products they are responsible for evaluating. Describe your views with regard to conflicts of interest among FDA employees and FDA advisory committee members. What actions, if any, do you plan to take to minimize and address any apparent and/or perceived conflicts of interest among FDA employees and committee members and ensure that conflicts of interest are fully disclosed?

Answer: I am committed to improving the effectiveness of the advisory committee processes, ensuring the integrity of FDA employees and reassuring the public about the basic integrity of both.

It is important that the public understand the key principles that must be kept in balance for the advisory committee process to effectively function:

- The public benefits from top scientific deliberation and advice in medical product decision-making.
- Expert scientific knowledge and clinical experience are in high demand by government, patients, and medical product developers. The people who have this kind of expertise, especially in narrow therapeutic areas and rare diseases, are widely sought, and often just as widely employed.
- FDA has a rigorous process for soliciting and vetting candidates to minimize any potential for bias. FDA screens members broadly for financial interests and covered relationships that could present even the appearance that they have a conflict of interest that could affect their impartiality. Not all financial interests and covered relationships are equivalent, and so our process does not treat them all the same. For example, FDA might, based on a case-by-case analysis, grant a waiver to allow an individual to participate on an advisory committee despite his employment relationship as a member of a data safety monitoring board, which is an expert, independent body. Likewise, FDA's process also gives careful consideration to the employment relationship of an academic department chairman who is employed in a university department where a junior faculty member received a research grant from a drug company that may be affected by the work of the advisory committee, even though the chairman had no role in obtaining the grant and may not even have been aware of the grant when it was awarded. Because we try to identify all potential conflicts, the agency may grant waivers to allow individuals to participate in meetings where it concludes, after close scrutiny, that the benefits of participation outweigh any potential conflict. When a conflict exists and the magnitude of the conflict outweighs the agency's need for the expertise the committee member will provide, we recuse that individual from the proceedings.

We announced several steps to help make FDA's advisory committee processes more effective at providing timely, top-tier, independent scientific advice to the agency and at reassuring the public about the basic integrity of this process. This effort includes the development of guidances to provide greater clarity and transparency in the disclosure of waivers of financial interests and covered relationships that could present actual or apparent conflicts of interest, as well as additional efforts to implement more streamlined approaches that will improve the transparency in the appointment of members. We plan to:

- Revise FDA guidance to identify more clearly the conditions under which conflict of interest waivers are granted.
- Revise our guidance that specifies when waivers of conflict of interest will be disclosed to the public and what information will be made available.
- Revise our guidance that specifies when briefing materials used at advisory committee meetings will be made publicly available.
- Provide greater public dissemination of advisory committee schedules through increased mailings to public groups and provide electronic notifications through an FDA advisory committee listserve.
- Implement a more streamlined approach to the appointment of members to the agency's drug-related advisory committees.

With respect to conflicts of interest among FDA employees, the employee's service is a public trust and employees that engage in unethical conduct diminish that trust. It is important for every employee to follow the conflict of interest laws and regulations in order to maintain a positive public perception of the way the Agency conducts its operations.

Actions are already in place to minimize and address any actual, apparent and/or perceived conflicts of interest among FDA employees and ensure that conflicts of interest are fully disclosed. FDA employees are subject to strict regulations regarding financial interests and participation in outside activities. The reporting of such interests are mandatory per Government-wide and HHS ethics regulations and the process is strictly monitored by FDA's ethics office. Employees are also held accountable under Title 18 of the U.S. Code governing criminal conflicts of interest. Employees receive detailed training on these and other conflict of interest issues upon entrance on duty and periodically each year including mandatory ethics training for all Public and Confidential financial disclosure filers.

Question 10: According to 21 CFR § 10.65, "An official transcript, recording, or memorandum summarizing the substance of any meeting described in this section will be prepared by a representative of FDA when the agency determines that such documentation will be useful." It has been the long established policy of the FDA to document its meetings with drug and device sponsors. For instance, many times during a meeting, a Regulatory Project Manager will be present to take notes and handle administrative matters. Describe in detail how FDA enforces this requirement across the agency. Are policies, procedures, and guidance consistent between the Centers? What actions does FDA take when employees fail to document their contacts with sponsors? Please document actions taken by the FDA since January 1, 2001, in response to violations of 21 CFR § 10.65 and/or FDA policies.

Answer: I believe that FDA's policies, procedures, and guidance regarding documentation of meetings with drug and device sponsors are consistent across Centers though they may not be identical. As you know, CDER, CBER, and CDRH, each have their own infrastructure, and accordingly may have different policies and procedures. Our goal as an Agency, however, is that policies and procedures be consistent across Centers to the extent that such policies and procedures would have a significant impact on our stakeholders.

FDA trains employees on Agency policies and procedures to help ensure compliance. If an employee failed to appropriately document industry contacts, if the incident was brought to the supervisor's attention, the supervisor would discuss the omission with the employee and monitor the employee's behavior on this issue more closely. In addition, supervisors discuss with employees how they have performed in relation to policies, procedures, and guidance during semi-annual performance evaluations.

Question 11: In your opinion, should FDA employees be allowed to submit articles to scientific journals without the advance approval of FDA management, if they clearly state in the article that they are expressing their own opinions and not those of the agency? If not, why not?

Answer: As a general matter, FDA encourages employees to share medical and scientific information that will benefit the public health. We believe that the publication of articles in scientific journals can result in several important benefits, such as:

- Discussion of important public health issues. Such discussions can generate debate or further study on a complex issue or convey important information to the public;
- Demonstrating the scientific, medical, or other expertise within FDA. This may increase public confidence in staff expertise and in the agency's ability to deal with novel or complex matters; and
- Professional development. Scholarly publications may help an individual's professional development in his or her chosen field.

However, we also believe that agency review of employee articles prior to their submission to scientific journals is important, and in some cases is required by regulation (as discussed below). Such pre-submission review can:

- Prevent inadvertent disclosure of trade secret, confidential commercial information, or other information that cannot lawfully be disclosed. Several statutes, including the Privacy Act (5 U.S.C. § 552a), the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §§ 301 et seq.), and the Trade Secrets Act (18 U.S.C. § 1905), as well as FDA's implementing regulations (21 CFR Parts 20 and 21), limit public disclosure of certain types of information;
- Avoid generating premature conclusions based on incomplete information or generating confusing, conflicting, or misleading information. For example, an article could suggest, but not establish, that an FDA-regulated product can malfunction in a specific situation, while other information at FDA, which the employee has not seen, disproves that such

malfunctions occur. If the article is published, the initial public reaction to the article might include decisions based on this incomplete information (thereby complicating or delaying an individual's treatment); and

- Avoid creating misleading expectations. For example, an employee may write an article about a future initiative, but be unaware that resource limitations or subsequent priorities or events necessitate postponing, modifying, or cancelling the initiative. Pre-submission agency review may alert the employee to those resource limitations or subsequent priorities or events and enable him/her to revise the article appropriately.

Pre-submission review of articles, therefore, can provide important benefits. Such benefits and protections of integrity would be lost, and the damage done to the Agency's credibility would not be mitigated by employees simply attaching a disclaimer to their articles and, as a result, avoiding agency review altogether.

Moreover, all employees are required by agency regulations governing ethical conduct to obtain approval before undertaking a writing activity in their personal capacity where the subject matter relates to their official duties or the invitation was extended by a person or entity regulated by FDA or otherwise considered a "prohibited source" (of gifts to employees) under the ethics regulations. The process for obtaining this approval is prescribed by the regulations and includes a review by agency management and ethics officials of a syllabus, outline, summary, synopsis, draft or other similar description of the content and subject matter involved. In addition, the pre-approval process involves advice and guidance to the requesting employee regarding the use of a disclaimer or other biographical description of the employee's qualifications to avoid inaccurate attribution.

Question 12: On July 20, 2006, the Union of Concerned Scientists and the Public Employees for Environmental Responsibility released findings of their survey of FDA scientists. According to that survey, almost one-fifth of the FDA scientists said that they had been asked, for nonscientific reasons, to inappropriately exclude or alter technical information or their conclusions. One-fifth said that they have been asked explicitly by FDA decision makers to provide incomplete, inaccurate or misleading information to the public, industry, the media and government officials. What specific actions will you take to ensure that FDA scientists are not pressured to ignore their concerns and change their conclusions and to hold accountable those who pressure or intimidate these scientists?

Answer: I am committed to ensuring FDA makes decisions based on sound science and will make myself personally available to staff who want to appeal decisions made by FDA management. I believe that the need to appeal to me will be rare, however, because I will ensure that there are strong policies and procedures in place for resolving issues involving dissenting opinions. Efforts towards that end will include promulgating new policies and procedures as necessary, and strengthening, by process improvement and best practices measures, many of those that are already in place.

For example, we are working to ensure a rigorous ombudsman program through which staff are welcome to promulgate dissenting opinions. Staff may also invoke standard written procedures for facilitating and resolving differing professional opinions. In addition, under the Secretary's

leadership, FDA established a Drug Safety Oversight Board whose charter includes responsibility for deliberating on any dissenting opinions raised during evaluation of drug applications and surveillance of marketed products. Through these and other traditional management techniques, I believe we will successfully address any dissenting opinions, and I am committed to evaluating our processes and refining them as necessary to ensure that there is a healthy, open, unsuppressed scientific debate of issues at FDA.

Question 13: The insights of whistleblowers help keep agencies accountable. When employees who voice concerns or who raise allegations of fraud, waste and/or abuse are retaliated against or are forced to assert their legal rights as a whistleblower, there is a chilling effect on other employees who see the consequences of speaking the truth. By letter dated April 27, 2006, I wrote you regarding the Committee's investigation of Ketek and requested that you advise FDA employees that:

> **they have the right to speak directly and independently to Congress, or to a Committee of Congress, without interference from the FDA if they wish, in accordance with 5 U.S.C. § 7211. Retaliation against these individuals, or any other FDA employees, who communicate with the Committee in reference to Ketek will not be tolerated. Such conduct is further punishable by 18 U.S.C. § 1505 and false statements and perjury are likewise punishable pursuant to 18 U.S.C. § 1001. Further, under 5 U.S.C. § 2302(b)(8), a federal employee authorized to take, direct others to take, recommend or approve any personnel action may not take, fail to take, or threaten to take any personnel action against an employee because of protected whistleblowing. Protected whistleblowing is defined as disclosing information which the discloser reasonably believes evidences: a violation of law, rule, or regulation; gross mismanagement; gross waste of funds; an abuse of authority; or a substantial and specific danger to public health or safety. Please also note that P.L. 109-115 enunciates a government-wide prohibition on the use of appropriated funds to pay the salary of any federal official who prohibits or prevents or threatens to prevent or prohibit a federal officer or employee from contacting Congress, and "any punishment or threat of punishment because of any contact or communication by an officer or employee with a Member, committee or subcommittee."**

Nonetheless, I understand that in June you held a meeting with FDA staff involved with Ketek. According to a number of FDA employees present, your speech used a lot of sports metaphors regarding being "team players" and keeping opinions "inside the locker room" and not voicing them outside the locker room. Apparently, among a number of troubling comments, you stated that a team member who spoke outside the "locker room" might find themselves "off the team" as a consequence. Your meeting with Ketek staff was held in the midst of an ongoing congressional investigation and followed a number of critical reports in the media about the FDA's handling of Ketek. It is apparent that some FDA employees were offended by your comments, found them highly questionable, inappropriate, and potentially threatening. Personally, I am greatly troubled by your decision to hold this meeting at all, let alone making comments about kicking anyone off the team. For the record, state whether or not you believe your comments raised even the appearance of

being inappropriate, chilling, and/or threatening? What assurances can you provide that you take seriously that some FDA employees found your comments threatening and that all employees within the FDA will be protected and not subjected to retaliation?

Answer: Any FDA employee who has concerns about fraud, waste, and/or abuse has both the right and the responsibility to make those concerns known to organizational management, Agency leadership, and all appropriate authorities. In public and in private, I have consistently affirmed my commitment to that principle and to providing protection to those who have the courage to exercise this important right and responsibility.

My comments at the meeting to which you refer did not address this subject, but rather the issue of my experience in organizations like FDA, in which leadership must promote a culture of diversity, including academic freedom in expressing differences of thought. However, in an organization such as the Agency, that thought process has an important purpose and it must lead to a conclusion and an action. This is, in fact, the very process in which you engage in the Legislative Branch - rigorous debate and discussions occur at a proper time, in a proper place, in a proper fashion (the locker room, if you will). However, this is a team effort, with universal respect for opinion and perspective, and once this open process leads to a decision being made (a law is passed, a drug is approved), that decision is organizationally supported and executed.

FDA thrives on a scientific/academic decision-making process that welcomes, and in fact depends on, the vigorous exchange of diverse and differing opinions. However, as a result of a healthy process such as this, many times a consensus, or majority, decision will be reached, with which an individual who was part of the decision-making process may not agree. For individuals who participate in this team activity, so to speak, there must be respect for the process and recognition that in some cases the opinion of the majority of their peers may take precedence over their own.

Question 14: Senator Dodd and I introduced the Fair Access to Clinical Trials Act, the FACT Act, which would create a publicly accessible national data bank of clinical trial information to create greater transparency and accountability in clinical trials and the scientific process. This national data bank will include both a clinical trial registry and a clinical trial results database. The bill also will require the FDA to make its internal drug approval and safety reviews publicly available. What is your position with regards to a mandatory public clinical trials registry and results database? What is your position on making all of FDA's internal drug approval and safety reviews publicly available?

Answer: The Administration does not have a position on this bill.

Question 15: What is your position on requiring full disclosure of industry contributions to pre-market and post-market approval research?

Answer: Almost all of the marketing applications filed with the FDA are supported by industry contributions to pre-market and post-market research. We have the ability to review all of this data, even its raw form, to ensure the integrity of the data. In addition, 21 CFR Part 54 requires certain financial disclosures by clinical investigators of financial arrangements with the sponsors

to be submitted with the marketing application to ensure that any bias in the clinical investigation has been minimized and to allow FDA to assess the reliability of the data.