

File Jane Henney

August 24, 1998

The Honorable James Jeffords  
Chairman  
Senate Labor and Human Resources Committee  
428 Dirksen Senate Office Building  
Washington, DC 20510

Dear Mr. Chairman:

First, let me take this opportunity to thank you for the courtesy you and your staff extended to me at our initial meeting in mid-July. I found our discussion helpful, and I appreciate the opportunity to respond to the questions you submitted to me on behalf of members of the Committee on Labor and Human Resources.

The leadership provided by you and the members of the Committee in enacting the Food and Drug Administration Modernization Act has established not only a new direction but a new philosophy for the Food and Drug Administration. The Act and its full implementation will ensure that the fruits from the investments made by the public and private sectors in biomedical and biotechnology research will expeditiously move from the developmental phase into the marketplace and will, therefore, expedite patient access to safe and effective medical products. I am also committed to working with the Committee to enhance the Agency's scientific base and on other critical public health issues.

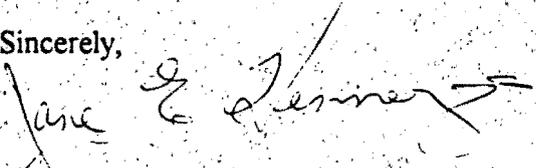
Please be assured that if I am confirmed by the Senate, I will bring my full energy and experience to the tasks at hand. I have enjoyed over two decades of managing change in leadership positions at large and complex health care organizations at the state and federal levels. I am fully committed to leading an agency that makes scientifically-based decisions, and uses processes that are open, timely and responsive. Those who have worked closest to me know that I am an advocate of listening before acting, and expecting excellence and integrity from myself and those who work with and for me. It is my strong conviction that this approach will assure the strong relationships envisioned in the Act between the Agency and the regulated industry, consumers, and health professionals.

With respect to the responses I have enclosed, due to my four year absence from the FDA, I have relied to some degree on information provided by staff at the Department of Health and Human Services and the Food and Drug Administration. This has been a helpful exercise, particularly in reacquainting me with Agency procedures and the many new issues that have arisen since I last served with the Agency in 1994. If confirmed, I will look forward to listening closely to the views of members of Congress, the regulated industry, the consumer and patient community, and other interested parties as well on the important issues raised in the Committee's questions.

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In conclusion, Mr. Chairman, I want to thank you for graciously agreeing to schedule a timely confirmation hearing on my nomination. I look forward to the opportunity to discuss with you and other Committee members the range of important issues concerning FDA.

Sincerely,

  
Jane E. Henney, M.D.

Enclosure

## RESPONSES FROM DR. JANE HENNEY

### Drugs

**1. The number of generic drug approval applications has increased from 300 in FY 1991 to 462 in FY 1997, while staffing in the Office of Generic Drugs (OGD) has remained relatively constant during this period. Do you believe that if the FDA does not significantly increase the number of OGD reviewers, many generic drugs will not be approved on a timely basis?**

I believe that it is very important to have generic products made available on the market as soon as possible. Therefore, the Agency needs to ensure that the generic drug review program is as scientifically sound and efficient as it can possibly be. If confirmed, I will work hard to ensure that the generic drug program is doing the best job that it can, and will assess on an ongoing basis the resource needs of OGD with the Administration and Congress relative to the Agency's other priority activities.

**2. Despite the best efforts of FDA's Office of Generic Drugs (OGD), the median review time for abbreviated new drug applications is still more than three times longer than the 180 days mandated by statute. The FDA recently estimated that it would take about 75 more reviewers--which would cost about \$6 million--to meet the 180 day review requirement. As a policy matter, do you believe that the FDA should put in place a strategic plan and budget designed to enable the OGD to meet its statutory review and approval requirements? Would you support the creation of an Agency Strategic Planning Work Group to develop a FY 1999 program plan for OGD?**

I believe it is important to have generic drug products available as less expensive alternatives for consumers. If confirmed, I am committed to ensuring that generic drugs are brought to the market as expeditiously as possible. I have been made aware that the Agency has not been able to review all generic drug applications within the statutory timeframe of 180 days. I think it is worth noting that the OGD has undertaken a number of streamlining initiatives that I am told have already enabled it to maintain the median review time of 180 days even as the workload has increased. At the same time, these initiatives have helped to reduce overall approval times by reducing the number of cycles to approval. However, the Agency must constantly strive to find new ways of improving this very important review process. I look forward to working with you on how best to ensure the efficiency of the generic drug approval program, including a strategic planning initiative.

**3. Will you commit to establishing a process that ensures periodic review of requests for additions to the list of bulk drug substances which may be used in compounding pursuant to Section 127 of the Food and Drug Administration Modernization Act (FDAMA)?**

I believe that developing the list of bulk drug substances that may be used in compounding, clearly, should be an ongoing process. I have been informed that FDA intends to publish a proposed rule for comment that addresses the 30 nominations for bulk drug substances received to date and, after the final rule is published, to promptly evaluate requests for additions to or deletions from the list as they are received by the Agency.

**4. Section 127 of FDAMA requires that FDA consult with healthcare professionals, representatives of patients, and state regulatory boards in developing regulations to implement this section. Do you intend that the advisory panel required in this section hold public meetings and solicit the input of the public in developing the regulations?**

It is my understanding that the Pharmacy Compounding Advisory Committee meetings will be public meetings, in accordance with the Agency's regulations regarding advisory committees. These regulations provide that every committee meeting must include an open portion which constitutes a public hearing during which interested persons may present relevant information orally or in writing. In addition, I anticipate that the Agency will use the normal mechanisms, including notice and comment rulemaking, to obtain public input into the development of the regulations on pharmacy compounding.

**5. What plans do you have to communicate provisions of FDAMA and related implementation to FDA field inspectors to ensure they're up to date with the requirements of the statute? For example, in the context of Section 127 of FDAMA, how will you train field inspectors to work with State Boards of Pharmacy and Medicine to ensure that FDA's role is confined to issues related to manufacturing?**

I understand that a section-by-section analysis of the new law was prepared for FDA's field staff to ensure that all field personnel, including investigators, were made aware of the statutory requirements under FDAMA. In addition, formal presentations were made at two senior-level management conferences. Implementation status reports have been provided on a regular basis in an effort to keep field staff informed of the various documents that have been issued to implement FDAMA. In addition, I am told that field staff are participating on the working groups developing the documents that are specifically required by the new law, as well as those documents that are needed to ensure appropriate implementation of the statute.

**6. The FDA's mission statement specifically states that the administration shall protect the public health by ensuring that human drugs are safe and effective. Do you believe that this statement conflicts with the potential approval of RU-486 by the FDA?**

FDA is required by statute to assure that human drugs are safe and effective for their intended use. Although I am not familiar with the specific review of this product, this should have been the test that FDA applied to RU-486 or any other product intended for human use.

**7. If you believe that no conflict exists, could you explain why the safety of RU-486 should not be examined with respect to an unborn child carried by the individual taking RU-486?**

The statute requires FDA to evaluate the safety and effectiveness of all human drugs based on their intended use. My understanding is that the intended use for RU-486 proposed by the sponsor and reviewed by the advisory committee prior to its recommendation for approval is the termination of pregnancy within 49 days from the first day of the last menstrual period. While I was not involved in this review, I am informed that the FDA advisory committee of scientific experts and consumers, as well as FDA staff, therefore evaluated the safety and effectiveness of RU-486 for its intended user: by pregnant women who wish to terminate their pregnancies within 49 days from the first day of the last menstrual period. I have been advised that because this was the intended use, the Agency did not evaluate the safety and effectiveness of RU-486 for the embryo.

**8. The following questions refer to the planned transition from the use of metered-dose inhalers that use chloroflourocarbons (CFCs) to non-CFC-based alternatives, and the advanced notice of proposed rulemaking published on March 6, 1997:**

**(a) Is there any situation in which patient access to medications that are safe and effective should be sacrificed for environmental concerns? If so, what do you believe is the best way to strike this balance?**

I believe that FDA's core mission is to ensure patient access to products that are safe and effective. Obviously, Congress may decide that environmental concerns should override these or any other values. In the case of CFCs, my understanding is that Congress in the 1990 amendments to the Clean Air Act balanced environmental concerns (which for ozone exposure caused by CFCs involve public health) and patients' needs for safe and effective products by requiring that the CFC-containing drugs be removed from the market only if they are found not to be essential to patient care.

**(b) What flaws, if any, do you see in the March 6, 1997, ANPR? What policy modifications do you suggest to fix these flaws?**

My understanding is that the concerns that have been raised about the March 6, 1997 ANPR focus primarily on whether the criteria for eliminating an essentiality designation for a particular product are sufficiently protective of the patients who rely on the product, and whether the public has been afforded a sufficient opportunity to comment on and participate in the Agency's deliberations on this important issue. While I have not reviewed these issues in detail, I understand that the Agency is giving these concerns very careful consideration in preparing the proposed rule. Should I be confirmed, I would want to review this matter in detail to assure that critical patient needs are given maximum consideration.

**(c) The March 6, 1997 ANPR outlined a "therapeutic class" approach to this transition, in which two broad classes of MDIs -- short-acting bronchodilators and corticosteroids -- were defined and, within each class, individual drugs were considered to be "treatment alternatives." Do you believe that, within each class, these drugs are in fact appropriate "treatment alternatives", i.e., they are interchangeable?**

I understand that the ANPR did outline a therapeutic class approach as one of several possible alternatives. One of the reasons for publishing the ANPR and outlining the various approaches was to get comment on the very issues raised by this question, such as whether it would be medically appropriate to consider all of the drugs in a particular class treatment alternatives for the other drugs in the class. There certainly are classes of drugs where such a finding would be medically appropriate, but I would need to know more about the possible classes and the degree to which their efficacy or toxicity profiles might vary before I could respond specifically with respect to these drugs. If confirmed, I would assure that FDA carefully reviews all of the approaches set forth in the ANPR.

**(d) When it does become necessary to take a safe and effective drug off the market, what is the most appropriate way to do this? Is it appropriate to deem the drug adulterated and misbranded, or are less drastic measures called for?**

When it becomes necessary to remove a violative product from the market, I think it is appropriate, as a first step, to work with the company to withdraw the product voluntarily. I understand that Congress, through the 1990 amendments to the Clean Air Act (CAA), banned CFC-containing medical products unless these products are determined to be essential. If a company did not remove a non-essential CFC-containing medical product voluntarily, EPA could institute action under the CAA, and FDA could bring action under the Federal Food, Drug, and Cosmetic Act because the product would be adulterated and misbranded.

**9. The following questions concern requirements for pediatric studies:**

**(a) Do you expect that mandates of pediatric tests as a condition for FDA approval of a drug will delay the approval of any drugs? If so, is this appropriate?**

Today, most drugs used by pediatricians have never been tested in children and are not labeled for use for children. As a result, physicians often do not have important information they need to choose the appropriate dose of drugs they prescribe, or to make the basic medical decision to prescribe the drug. For these reasons, I strongly support efforts designed to produce data on use of drugs in children.

However, these efforts must not delay the availability of new therapies in adults. I believe that mandates for further product testing as a condition for FDA approval should not delay approval of any drugs. My understanding is that FDA has stated in its proposed rule that the pediatric study requirement should not delay the approval of new drugs and biologics. To ensure that drug approval is not delayed, FDA has built into the pediatric study requirement the ability to defer submission of pediatric studies until after approval for their use in adults. I am told that this authority would be used in those cases where pediatric studies cannot be completed before the application is otherwise ready for approval or where medical or ethical considerations counsel a delay in the initiation of pediatric studies.

**(b) What impediments remain to actual implementation of section 111 of FDAMA? That is, what still must be done before FDA begins to work with pharmaceutical companies to develop protocols for pediatric tests that would qualify for the incentives? What should FDA do to make sure this program is in place as quickly as possible?**

I understand that FDA already has taken the steps necessary to begin implementation of section 111 of FDAMA. As required by the statute, FDA published, on May 20, 1998, a list of approved drugs for which pediatric studies may produce health benefits in the pediatric population. Companies that study the drugs on this list may be eligible for pediatric exclusivity, if the pediatric studies satisfy the other requirements of section 111, such as conducting the studies in accordance with FDA's written request and completing the studies within the time specified by FDA. I also understand that in June 1998 FDA issued a guidance document describing for the pharmaceutical industry the steps necessary to obtain pediatric exclusivity under section 111. FDA already has begun to issue written requests to conduct pediatric studies under section 111. FDA is reviewing submissions from manufacturers according to the dates on which relevant patents and exclusivity periods expire, to ensure that those drugs whose patents or exclusivity expire soon will get an opportunity under section 111 to extend their exclusivity.

**(c) What are your thoughts on how to address the lack of pediatric testing and labeling for off-patent drugs?**

I understand that FDA's proposed rule authorizes the Agency to require pediatric studies of off-patent drugs in compelling circumstances. Even with this authority, it may be difficult to obtain pediatric studies on some drugs for which there is already generic competition. In such cases, other options to explore might include publicly funded research programs and further streamlining of the supplemental application process.

**(d) Section 111 of FDAMA provides incentives for pharmaceutical companies to test drugs for pediatric populations, whereas the proposed rule of Aug. 15, 1997, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New drugs and Biological Products in Pediatric Populations," envisions mandated pediatric tests for some drugs. The proposed rule, which authorizes the Agency to require sponsors to perform studies, is arguably inconsistent with Congress' intent that such studies be requested rather than required. If you are confirmed as Commissioner, will you withdraw this proposed rule? If not, why not? If you will not withdraw this rule, how will you apportion Agency resources to these two approaches? Which deserves higher priority?**

If I am confirmed, I look forward to reviewing the relationship between section 111 of FDAMA and FDA's proposed rule. I know that the Administration's goal is for section 111 of FDAMA and FDA's proposed rule to be complementary and mutually reinforcing. Section 111 provides an important incentive for some pediatric studies and, because of the substantial value of the incentive, may provide a needed infusion of resources for pediatric testing in general. Because the decision to conduct studies under FDAMA is voluntary, however; the Administration has been concerned that without a requirement, some number of drugs for which pediatric studies are needed will not be studied. In addition, section 111 does not provide incentives for studying certain products, including many biologics, antibiotics, and off-patent drugs that commonly are used in children.

**10. Many uses of drugs that are considered to be useful, or even considered to be the standard of care for a particular illness, are not approved by the FDA. In this context how do you respond to the statement, "a double-blind placebo controlled trial is unethical if the clinical benefit of the product is already known?"**

There certainly are clinical situations in which the use of a double-blind placebo controlled trial would be inappropriate, notably those in which failure to use an established treatment might cause patient harm. In evaluating the safety and effectiveness of uses of drugs that have not been approved by FDA, the Agency should always be guided by the highest scientific and ethical standards. Although whether a particular unapproved use of a drug is commonplace, or even the standard of care, does not necessarily establish the clinical benefit of the product, it certainly

would be something that should be taken into consideration in developing an appropriate testing protocol.

**11. Do you think that industry should pay user fees to fund more post-marketing surveillance activities within the Agency?**

Historically, user fees have succeeded only when they resulted from consensus among the Congress, FDA, the industry, and consumers. The current Prescription Drug User Fee Act, which has such support, does not expire until 2002. New user fees for postmarket surveillance activities would need to enjoy similar consensus for them to be practical at this time.

**12. Please define FDA's role in responding to post-approval adverse drug events in contrast with other organizations and individuals including U.S. Pharmacopeia, hospitals, physicians, pharmacists, nurses, patients and their families, medical schools, managed care companies, and researchers.**

Each of the entities referenced in the question has an important, distinct contribution to make to a comprehensive system of post-approval adverse drug event reporting and monitoring. FDA's role is to assure that approved drugs are safe and effective for their intended use, and to do so on an ongoing and continuous basis using all of the information available to the Agency about a particular drug. To do that as effectively as possible, the Agency needs to maximize the contribution of each of the significant participants in the health care system, to ensure that there are adequate and effective mechanisms for communication and coordination.

Drug safety is a matter of continuously developing information. To identify unknown adverse events more rapidly, there should be enhanced communication with health care providers (including hospitals, physicians, pharmacists, and nurses) that builds upon the ongoing work of MedWatch, the FDA Medical Products Reporting Program, in which the recognition and reporting of adverse events are strongly encouraged. Health care professional organizations, including the U.S. Pharmacopeia (USP), have a long history of cooperation with FDA. They encourage their members to report adverse events and help them stay abreast of new findings by expanding dissemination of this vital safety-related information. In addition, the USP is an active MedWatch Partner that works closely with FDA on drug safety, in particular by sharing information derived from the USP Practitioners' Reporting Network.

**13. Will you affirm that the "competent and reliable" standard used by the FTC and included in Section 114 of FDAMA will be the basis for the Agency's review of health care economic data? When will the Agency issue guidance to clarify to manufacturers the Agency's thinking on this provision? Given the strong statutory direction on the standard**

**to be used for health care economic information, do you believe that FDA may not reinterpret this standard or substitute a new standard?**

It is my understanding that Congress determined in section 114 of FDAMA that "competent and reliable scientific evidence" should be the standard for review of health care economic information. Further I am told the Agency has assembled a working group to determine how that standard should be applied to FDA-related products and is in the process of developing guidance on this provision. I understand the working group is gathering information and reviewing documents from many sources, including the Federal Trade Commission (FTC) and Pharmaceutical Research and Manufacturers Association (PhRMA). Several professional associations and individuals also have submitted or notified the Agency of their intention to submit formal comments for the working group's consideration. If I am confirmed, I will ensure that this FDAMA provision is implemented in a manner consistent with the legislative mandate that FDA has been given.

**14. What are your views on direct-to-consumer advertising? Do you believe that such advertising can educate consumers and benefit the public? Under what circumstances is this the case?**

As a general matter, I think that giving consumers information that is truthful and balanced is helpful. I believe that direct-to-consumer promotion can help consumers play a more active role in their health care by providing them with information about products and the conditions such products treat. However, information directed toward patients is useful only when presented in a truthful, balanced, non-misleading fashion that does not minimize the potential side effects of the product, provide unrealistic promises regarding benefits or suggest unique attributes when none exist. Until we have had more experience with FDA's policy permitting direct-to-consumer advertising, we will not know its true impact. I support the commitment the Agency has made to study the effect of direct-to consumer advertising on patient care.

**15. Do you believe that FDA is the appropriate entity to regulate prescription drug advertising directed at patients or should it be regulated by the FTC? Do you think that the division of duties and authorities shared between the two agencies on OTC drugs is the appropriate model for such prescription drug advertising?**

I believe that Congress made the correct determination in the 1950's when it gave FDA the responsibility for regulating prescription drug advertising. Because FDA reviews prescription drugs before they can be marketed, the Agency has the medical and pharmacological expertise necessary to judge the validity of the information presented in prescription drug promotion, regardless of the targeted audience.

**16. Do you think putting a clinical trial "on hold" is an appropriate mechanism to encourage the inclusion of more women in clinical trials?**

I think it is important that the clinical trials for products that are going to be used in diverse populations reflect that diversity. At the same time, I think it is very important that the research community continue to explore mechanisms, such as statistical modeling, which may enable us to be inclusive without necessarily requiring the active participation of diverse populations in every clinical trial. I understand that in September 1997 FDA proposed an amendment to the clinical hold regulations that would permit the Agency to impose a clinical hold on a study involving a serious and life threatening disease if that study prohibited women from volunteering solely because of their child-bearing potential. This approach reflected the recommendation of the Presidential Advisory Council on HIV/AIDS. I understand that the Agency currently is reviewing the comments it has received. If confirmed, I plan to consider this important issue carefully.

**17. Do you believe that there are other special populations that should be specifically included in clinical trials for new drugs? If so, what are they and how would you prioritize them?**

Again, I think it is important that the clinical trials for products that are going to be used in diverse populations reflect that diversity. I believe, and the Agency has emphasized in guidance, that drugs should be studied prior to approval in the patient groups that are likely to use the drug once it is marketed. This is because drugs have the potential to behave differently in different populations, for example, producing a quantitative difference in dose response or other effects or in the risk of an adverse event. FDA's efforts to assure such inclusion have focused on the overall data base in support of a drug, not on inclusion in specific trials. Which populations should be targeted for inclusion in a study would depend on both the drug and the disease to be treated.

**18. What balancing test will you apply and what form would it take (regulation, guidance, etc.) to the twin goals of approving new medicines for the general population and ensuring that products are tested in special populations?**

The balance should be to ensure that there is appropriate information available about how the drug works, or does not work, and what its safety profile is in those likely to use it, without making the drug development unreasonably burdensome or so time intensive that no population receives benefit from a new therapy.

If confirmed, I would plan to continue using the present Agency approach of combining regulation, guidance, and active participation in drug development planning by FDA's new drug

reviewing divisions to ensure that promising products are appropriately tested in different populations, yet are brought to the market as quickly as possible. I believe FDA should continue to monitor the enrollment of special populations to ensure that they are adequately represented in the diseases being studied.

**19. Does the IND process and discussion between companies and FDA provide any opportunity to work together on designing trials that will specifically include special populations?**

Yes. The current product review process provides many opportunities for sponsors and the Agency to work together on all aspects of drug development, including those related to designing trials that evaluate drugs in special populations. Specific occasions that provide opportunities for FDA to work with sponsors include: pre-IND meetings, protocol-specific discussions, end of Phase 2 meetings, and pre-NDA meetings.

**20. Do you think the current IRB process works to protect patients? Do you support expanding IRB oversight to research that is not currently IRB-regulated? If so, what kind of research do you think should be IRB-regulated?**

The critical function of institutional review boards is to ensure informed consent by human subjects. I think experience suggests that the system has worked reasonably well, but we are now seeing some warning signs that should be addressed. For example, new and more complex research has expanded IRB workloads and stressed the system. I understand that the Department of Health and Human Services (DHHS) Inspector General has just released a report that recommends some changes for regulation of IRBs as well as increased IRB oversight of ongoing research. I have not had an opportunity to review this report, but should I be confirmed I would work diligently to see how these concerns might be addressed.

I also think when there are areas of experimentation not currently subject to IRB review, we should be concerned as to whether the human subjects are being protected adequately. Along with FDA there are many entities, including the President's National Bioethics Advisory Commission, that need to be involved in such determinations since there are legal, regulatory, and resource issues that would need to be addressed.

**21. The "fast track" provision (Section 112 of FDAMA) builds upon, but also goes beyond, FDA's existing regulations with respect to accelerated approval for drugs and biological products. Will you implement "fast track" by amending the existing accelerated approval regulations so as to reflect the provisions of the new law, or will you promulgate separate "fast track" regulations while retaining the accelerated approval regulations as a separate**

**but parallel program?**

I would like to see the provision authorized by section 112 of FDAMA widely and effectively used to bring more quickly to the marketplace safe and effective products for serious and life-threatening diseases. I understand that FDAMA directed the Agency to issue guidance that describes the fast track policies and procedures. As the Agency gains experience in the implementation, it may determine that additional guidance or regulatory changes are appropriate.

**22. Who in the Agency will be authorized to grant "fast track" designation-division directors, office directors, center directors, or a new "fast track" program director? How will you ensure that designations are made on a timely basis using consistent criteria?**

Decisions of this type currently are made at the division director level. This eliminates the need to have each decision reviewed through the entire administrative chain. It is my understanding that the Agency plans to issue guidance that describes the fast track policies and procedures. Further, it is my understanding that the Agency is planning to ensure compliance with the legislatively mandated time frame of 60 days for designation by using management tools similar to those which have contributed to FDA's success in meeting PDUFA goals.

**23. The "fast track" provision does not define "a serious or life-threatening condition," but House Committee report language references the broad discussion of this concept contained in the preamble to the proposed accelerated approval regulation published in the *Federal Register* in June 1992. Please indicate whether you intend to adopt a formal definition of this term and, if not, how you intend to ensure its consistent application.**

I know that section 112 mandated FDA to provide guidance that describes the policies and procedures that pertain to the "fast track" program. It is my understanding that the guidance will include the Agency's definition of "a serious or life-threatening condition." I support this approach.

**24. The "fast track provision provides for an alternative basis for approval, under which a product may be approved "upon a determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit." Please describe the criteria by which you will determine whether to issue a "regular" or a "fast track" (i.e., accelerated) approval with respect to a product studied on the basis of its effect on a clinical endpoint.**

FDAMA directs the Agency to issue a guidance document to clarify this provision. It is my understanding that the Agency currently is working on this document in order to meet the

statutory deadline of November 21, 1998. Under FDA's accelerated approval regulations, which have been in effect since 1992, a drug that may be a meaningful improvement over existing therapies for a serious or life-threatening illness may be eligible for accelerated approval where the evidence of its effectiveness establishes an effect on a clinical endpoint other than survival or irreversible morbidity. For example, a clinical endpoint measuring short term benefit in a chronic condition, which is not sufficient for traditional approval, may suffice for accelerated approval. I think that this approach will effectively implement the provision.

**25. The "fast track" provision requires FDA to "establish a program to encourage the development of surrogate endpoints that are reasonably likely to predict clinical benefit for serious or life-threatening conditions for which there exist significant unmet medical needs." Please explain your plan for implementing this program.**

It is my understanding that, in accordance with the statutory mandate, FDA currently is working with NIH toward meeting this requirement. Additionally, FDA is working with sponsors and its advisory committees in the timely evaluation of proposed surrogate endpoints. For many years FDA has been working with sponsors to develop surrogate endpoints that are reasonably likely to predict clinical benefit for serious and life-threatening conditions. In fact, it was Agency scientists who led the way in assessing the use of CD4 cell counts as a surrogate endpoint for AIDS drugs. In addition, the Agency's oncology initiative identified tumor shrinkage as a surrogate endpoint for demonstration of effectiveness in patients with refractory tumors. I support this approach and believe that it will effectively implement the program.

**26. Sponsors whose products receive "fast track" approval may be required to submit copies of all promotional materials relating to the product not only during the preapproval review period but also following approval "for such period thereafter as the Secretary determines to be appropriate" The House Report proposes that such postapproval review occur only for that period of time necessary to establish that the sponsor understands, and is prepared to comply with, FDA's requirements with respect to such materials, or for 6 months (whichever is shorter). Will you commit to adhere to these guidelines with respect to post approval review of "fast track" marketing materials?**

As I understand it, one of the goals set forth in FDAMA is to ensure that only factual and clear information that will facilitate the safe and effective use of "fast track" products for serious and life-threatening illnesses by the medical community be disseminated. However, if confirmed, I would strive to assure that such post-approval submissions continue only for the time necessary to accomplish this goal and will plan to evaluate the effectiveness of this initiative.

**27. Do you believe that drugs to treat the most serious medical conditions, and where there is a tremendous unmet medical need, deserve special treatment by the FDA in its review process?**

Yes. As a medical oncologist, I bring a longstanding commitment and passion to assuring that those who have serious diseases are served by prompt review and early access to such drugs.

**28. Aside from applying 6 month priority review status to such drugs (as compared to the normal 12 month user fee time frame for approval decisions), what mechanisms might FDA apply to expedite patient access to these drugs?**

FDA has long had a number of mechanisms to ensure that patients have access to experimental therapies, particularly for persons with serious and life-threatening illnesses. Single-patient INDs, emergency INDs, and protocol exemptions have been used to ensure "compassionate use" for such patients, usually on an individual basis. In the 1980's, treatment INDs were instituted to facilitate more widespread availability of promising new drugs before general marketing begins. During my earlier tenure at FDA, we developed additional mechanisms for speeding access -- accelerated approval and "parallel track" (access to experimental drugs for AIDS patients for whom standard therapy is not available). FDAMA has codified many of the administrative programs FDA put in place to expedite patient access to these types of drugs.

**29. A study was published in Drug Information Journal earlier this year that showed that the Agency, since the 1992 enactment of its Subpart H accelerated approval authority, has applied accelerated approval 17 times for AIDS and cancer drugs, and only 3 times in all other life threatening diseases combined. Why has the Agency not utilized accelerated approval authority more frequently, particularly in serious and life-threatening conditions other than AIDS and cancer? How would you ensure that this authority is utilized more frequently in other serious and life-threatening conditions?**

Accelerated approval was designed to expedite marketing of certain new drugs and biological products by permitting marketing approval based on their effect on a surrogate endpoint reasonably likely to predict clinical benefit or on the basis of a clinical endpoint other than survival or irreversible morbidity. Because the clinical progression of certain cancers and AIDS is often predicted based upon laboratory tests or the progression of symptoms, these diseases are particularly amenable to the application of accelerated approval. Other life-threatening diseases generally have well-defined and easily measurable clinical endpoints. The effectiveness of therapy for these diseases need not depend on the evaluation of surrogate endpoints; rather, approval based on those well-defined and easily measurable clinical endpoints can be achieved expeditiously. Nevertheless, if confirmed, I would be committed to using all of the regulatory authorities available, including the accelerated approval process, to expedite review and approval

of therapies for individuals with serious or life-threatening illnesses.

**30. Congress enacted Section 112 of FDAMA to codify and expand the Agency's existing mechanisms to speed the development, review, and availability of drugs to treat serious or life threatening conditions. The House, and by agreement in conference, the Senate, concurred on language stating that applications based on clinical endpoint studies, in addition to surrogate endpoint studies, are eligible for fast track designation and approval. In the past, the Agency had stated that only studies that measured surrogate endpoints were eligible for accelerated approval. Do you agree that FDA now has the authority and the mandate to approve drugs on the basis of clinical endpoints (for serious and life-threatening conditions with unmet needs), make them available to patients, and confirm or validate substantial evidence of efficacy on a post approval basis?**

Yes. Section 112 codified FDA's authority to permit ultimate benefit to be confirmed or validated on a post approved basis where effect on a clinical endpoint is established by substantial evidence.

**31. Do you believe the substantial evidence of efficacy standard can be achieved on a post-approval basis? If not, how do you defend the Agency's use of accelerated approvals in situations where the surrogate endpoint is not validated, but rather, is "reasonably likely" to show clinical benefit? How does this demonstrate substantial evidence that the drug will have the effect it is claimed to have? Is not this a flexible interpretation of the efficacy standard where the seriousness of the disease coupled with the lack of current treatment options compels the Agency to expedite availability of drugs on arguably less convincing data than would result in traditional approval?**

As I indicated above, efficacy may be confirmed or validated on a post approval basis where the approval is based on substantial evidence of effect on a surrogate or clinical endpoint. Given the complexity of the decision to approve a drug and the risk benefit analysis on which such approval must be based, I think this approach is consistent with the current legal standard, which was confirmed in FDAMA, that approval require substantial evidence of effectiveness. I do not believe that the use of accelerated approvals reflects an interpretation that less convincing data of effectiveness are acceptable. I believe it reflects flexibility as to appropriate and acceptable endpoints to establish effectiveness. Here again, the Agency is in the process of preparing guidance that I understand will address these issues and I would prefer not to prejudge the content of that guidance.

## Biologics

### **32. Efficiency of Reviews**

**During PDUFA-2 negotiations, the pharmaceutical industry submitted information requests to the Agency. One of these requested an accounting of FDA's actual unit cost to review an IND, a premarket approval application (NDA or PLA/ELA combination), an efficacy supplement, and a manufacturing supplement. The industry's question referenced an FDA audit conducted by a national accounting firm, Arthur Andersen, based on FY93 review activities.**

**(a) In some cases, Arthur Andersen's audit reported costs that are an order of magnitude higher than those reported by FDA's self-audit. Please explain the disparities between these two data sets.**

As I understand this somewhat arcane issue, the two costs are not comparable. Nor are they an accurate estimation of the actual costs of review, as they essentially divide the expenditures for drug review for a year by the number of drug submissions that year. Because a given application's review may run across more than one year, the actual cost of a given review is not computed using either the Arthur Anderson method or FDA's method.

**(b& c) During each of the five years covered by PDUFA-1 (FY93-97), as well as for the five year period as a whole, what was the average unit cost for CDER and CBER to perform each of the following actions? Please provide cost data in both dollars and in full time equivalents (FTEs) using generally accepted accounting practices.**

- (i) Review of an IND**
- (ii) Review of an application for approval to market a new chemical entity/ new biological product**
- (iii) Review of an efficacy supplement for an approved drug/biological product**
- (iv) Review of a manufacturing supplement for an approved drug/biological product**

As the response to 32(a) indicates, actual review costs have not been calculated by fiscal year. The actual costs for submissions received within a given year would stretch across several fiscal years, over the life of a IND, and NDA's review. PDUFA did not instruct FDA to calculate costs in such a way. Indeed, the financial design of PDUFA conforms with traditional government management of expenditures within a given fiscal year.

(d) For each category in which the unit cost of review differs between the two Centers by at least 10%, please indicate what specific actions you intend to take to improve the efficiency of the less efficient Center.

As has been explained in the preceding answers to questions 32a-c, these review costs are not calculated.

### 33. Timeliness of Reviews

During each of the five years covered by PDUFA-1 (FY93-97), as well as for the five year period as a whole, please provide a comparison between CDER and CBER with respect to the average time to perform each of the following activities, and indicate what specific actions you intend to take to improve the timeliness of the less-timely Center.

(a) For priority review products, the average time between submission of an application for marketing approval and the issuance of a complete review, approvable, or non-approvable letter for NDAs versus BLAs (or PLA/ELA combinations).

Having been away from FDA for most of the period covered by these questions, I do not have this information. However, FDA staff have provided me with the following data:

The data presented below show the average time in months between submission of an application and the issuance of a complete review decision (Approved, Approvable, or Not Approvable).

	NDAs	PLA/ELAs
FY93	10.8	9.5
FY94	10.5	6.0
FY95	8.9	9.4
FY96	7.0	9.2
FY97	6.4	5.9
FY93-97	8.4	8.6

**(b) For standard review products, the average time from submission of an application for marketing approval and the issuance of a complete review, approvable, or non-approvable letter for NDAs versus BLAs (or PLA/ELA combinations).**

	NDAs	PLA/ELAs
FY93	14.5	9.1
FY94	13.0	7.9
FY95	12.3	10.3
FY96	12.0	11.8
FY97	11.6	12.1
FY93-97	12.6	10.7

**(c) For priority review products that have been approved, the average time from submission of an application for marketing approval and the issuance of a final approval for NDAs versus BLAs (or PLA/ELA combinations).**

The data presented below show the average time in months from submission of an application to final approval. Please note that the average times shown below and in (d) may increase in the future as additional applications are approved.

	NDAs	PLA/ELAs
FY93	13.2	15.4
FY94	12.7	12.2
FY95	12.6	24.5
FY96	7.1	12.8
FY97	6.1	7.9
FY93-97	10.2	16.6

**(d) For standard review products that have been approved, the average time from submission of an application for marketing approval and the issuance of a final approval for NDAs versus BLAs (or PLA/ELA combinations).**

The data presented below show the average time in months from submission of an application to final approval. Please note that these average times may increase in the future as additional applications are approved.

	NDA's	PLA/ELAs
FY93	23.5	38.6
FY94	20.6	20.1
FY95	17.4	12.2
FY96	14.7	17.8
FY97	11.5	11.7
FY93-97	17.9	20.6

By FY 97, due to both Centers' success in meeting the increasingly stringent demands of the PDUFA performance goals, any differences that may have existed in either review times or approval times had been virtually eliminated.

#### 34. Extensions for Major Amendments

Under PDUFA rules, FDA may grant itself a 3-month extension in the PDUFA review deadline if the sponsor submits a "major amendment" within 3 months of the deadline.

(a) During each of the five years covered by PDUFA-1, as well as for the five year period as a whole, what percentage of NDA's were subjected to one or more such extensions?

FDA staff have provided me with the following information:

Note: Only one 3-month extension is allowed for an original NDA or PLA/ELA.

Receipts	
FY93	29.8% (25 of 84)
FY94	25% (23 of 92)
FY95	22.5% (25 of 111)
FY96	10.1% (11 of 109)
FY97	18% (22 of 122)
FY93-97	20.5% (106 of 518)

**(b) During each of the five years covered by PDUFA-1, as well as for the five year period as a whole, what percentage of BLAs (or PLAs+ELAs) were subjected to one or more such extensions?**

FY93	28.6% (2 of 7)
FY94	0% (0 of 4)
FY95	8.3% (1 of 12)
FY96	22.2% (2 of 9)
FY97	12.5% (2 of 16)
FY93-97	14.6% (7 of 48)

**(c) If there are significant differences in the frequency with which such extensions are granted by CDER versus CBER, please explain the reason for such differences and indicate what specific actions you intend to take to improve consistency between the Centers.**

I am informed that over the five year period of PDUFA, CDER used the 3-month major amendment extension on 20.5 percent of its NDAs while CBER used the extension on 14.6 percent of its PLA/ELAs. For any single year, CDER ranged from 10.1 percent to 29.8 percent while CBER ranged from 0 percent to 28.6 percent. Because of the wide year-to-year variations within each center and the relatively small number of extensions granted, especially in CBER, any differences between the Centers would appear to be insignificant.

In accordance with PDUFA 1 policies, the Centers are granted extensions when a major amendment is received within three months of the decision due date. However, on 41 NDAs and 1 PLA/ELA, the original due dates were met without utilizing the extensions that were granted. These 42 granted but unused extensions are not included in the statistics shown above.

**35. (a) During each of the five years covered by PDUFA-1 (FY92-97) as well as for the five year period as a whole, what percentage of INDs were placed on clinical hold by CDER? During each of those years, as well as for the five year period as a whole, what percentage of INDs were placed on clinical hold by CBER? If there are significant differences in the frequency of clinical holds between the two Centers, how do you account for these differences and what actions will you take to ensure greater consistency?**

I am informed that the following applies to complete holds on commercial, user fee product INDS:

YEAR	CBER	CDER
FY 93	27% (38/141)	16.5% (63/381)
FY 94	33% (62/186)	13.6% (49/360)
FY 95	23% (36/154)	9.2% (33/358)
FY 96	7% (13/177)	6.9% (26/376)
FY 97	11% (21/183)	5.8% (26/446)

It is clear that there were differences between CBER and CDER, especially during the earlier years of the PDUFA-1. There are a variety of possible explanations for these differences, although I am not aware that a specific comparative assessment was ever made. As I understand, both CDER and CBER have taken steps to address the frequency and consistency of clinical hold decisions.

**(b) For each of the five years covered by PDUFA-1, as well as for the five year period as a whole, what percentage of clinical holds by CDER were lifted within 30 days of the sponsor's submission of a clinical hold response? During each of those years, as well as for the five year period as a whole, what percentage of clinical holds by CBER were lifted within 30 days of the sponsors submission of a clinical hold response? If there are significant differences in the time to life clinical holds between the two Centers, how do you account for these differences and what actions will you take to ensure greater consistency?**

I am told that this information was not collected by either CBER or CDER for the five years covered by this question. It is being collected now and will be reviewed closely when comparative data are available.

### **36. Advisory Committees**

**When preparing materials for an advisory committee meeting, CBER generally sends the sponsor a draft of the product review document that the Center intends to send to the committee. Sponsors are then granted an opportunity to offer comments and/or suggest corrections before the document is finalized and sent to the committee. This practice, which both minimizes factual errors in the Agency's document and facilitates sponsor preparation for advisory committee meetings, is followed by some - but not all - CDER divisions. What actions will you take to ensure that all CBER and CDER divisions provide a reasonable opportunity for sponsors to review and comment on advisory committee documents prior to their transmission to a committee?**

Congress addressed the problem of the differing CBER and CDER processes in section 123(f) of FDAMA and instructed FDA to minimize the differences in review and approval for drugs and biologics. I applaud this provision and would apply it to advisory committees.

While I am not familiar with each Center's current practice regarding preparation and review of advisory committee materials, I do know that FDA's various advisory committees differ somewhat by statutory role, composition, and types of subjects considered. I think the important question in assessing whether each component should conform to a single practice is whether such conformance will actually result in better decision making by the advisory committee and the Agency.

### **37. General Administrative Procedures**

**CDER has created a Manual of Administrative Procedures (MAP) so as to ensure consistency in certain review procedures across divisions. CBER has never established any such manual of standard operating procedures. How do you intend to ensure greater consistency between CDER and CBER when there is no consistency within CBER itself?**

It is my understanding that CBER does, in fact, have a manual of standard operating procedures, similar to CDER's Manual of Policies and Procedures (MAPP). I believe such written procedures can make a substantial contribution to ensuring procedural consistency. While CBER's procedures have been better harmonized with CDER through various review practice working groups, I am very open to exploring whether there are other opportunities to expand on this type of consistency.

### **38. Criteria for Regulating Certain Biotechnology Products as Drugs, Biological Products or Medical Devices.**

**FDA does not use consistent or transparent criteria for determining whether a recombinant protein product should be regulated as a drug or as a biological product. Some recombinant protein products have been regulated as drugs, while others have been regulated as biological products. In one case, two competing companies (Cephalon and Regeneron) were each developing recombinant protein products to treat Lou Gehrig's disease; one company's protein was regulated as a drug, while the other's was regulated as a biological product.**

Similarly, some cell therapy products to treat dermatologic and orthopedic indications are regulated as biological products, while other cell therapy products for similar indications are regulated as medical devices.

**Do you intend to establish criteria to ensure that similar products are subjected to similar regulatory requirements, so as to avoid potentially favoring (or disfavoring) commercial competitors by subjecting them to different regulatory regimes? If so, what criteria?**

My understanding is that in 1991 an intercenter agreement between CBER and CDER assigned the jurisdiction for regulation of products to the appropriate center in order to best utilize the available resources and expertise of each center efficiently. This agreement assigned the review of hormones to CDER and other biologic products to CBER, regardless of whether these products are manufactured by traditional methods or by recombinant technology.

If confirmed, I will work to minimize differences in the review and approval of drugs and biologics as mandated by FDAMA. It is important that such designations for review be consistently applied in a manner predictable for the sponsors of such products. Given the rapid development of new technologies and the need for the Agency to be prepared to respond effectively to them, I will make every effort to ensure that the Agency uses criteria that conform to the law and are based on good science and policy, and which lead to consistent and predictable decisions.

### **39. Generic Biological Products**

**(a) Do you agree that, while the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman) established a generic approval system for drugs, FDA possesses no legal authority to approve abbreviated applications for biological products?**

As I understand it, the Drug Price Competition and Patent Term Restoration Act of 1984 codified and expanded in section 505(j) FDA's generic approval system for drugs. By its terms, section 505(j) does not apply to biological drugs that are licensed under § 351 of the Public Health Service Act (PHS Act).

I am informed that neither section 351 of the PHS Act nor FDAMA specifically addresses whether or not abbreviated applications can be filed for approval of biologic products. I am also told that FDA has no plans to allow submission of abbreviated applications for biological products.

**(b) Regardless of whether you believe FDA possesses such authority, will you now commit to Congress that you will not establish a generic approval system for biological products during your tenure as Commissioner?**

I have no plans to establish a generic approval system for biological products if I am confirmed by the Senate.

**(c) It had been reported in the trade press that CDER has formed a Complex Drug Substances Working Group to establish bioequivalence criteria for macromolecular drugs, including recombinant proteins, so as to facilitate approval of generic versions of such products. Do you agree that it is inconsistent with the spirit of section 123(f) of FDAMA to permit generic approvals for recombinant proteins that are regulated as drugs, when generic approvals are not permitted for similar products that are regulated as biological products?**

The scientific issues surrounding macromolecular drugs, including recombinant proteins, are complex and challenging. I cannot tell you whether the recombinant proteins that are regulated as drugs and the biological products referred to in this question are similar products. That assessment should be based on scientific information. Regardless of whether or not 123(f) relates to generic approvals, as a matter of policy, I believe the Agency should treat like products consistently.

**40. (a) Please explain the criteria by which research funds are allocated between and within CDER and CBER and whether you believe these criteria are appropriate.**

Research conducted at FDA must be relevant to the mission of the Agency and contribute to the scientific basis for the Agency's decisions. Often FDA research provides data to support regulatory decisions and policies that are not available from any other source. At present, only FDA can conduct research using the large database of information submitted to it by industry one application at a time.

To stay abreast of newly developing technologies and regulatory issues raised by a rapidly changing array of new products, it is important for FDA scientists to be well grounded in a continuum of research from basic and applied to clinical investigations. A full appreciation of basic research often is necessary to support the critical decisions to approve a new product, retain a previously approved product, or remove a product from the market. Providing opportunities to stay involved in research is also a means to recruit and retain some of the most able regulatory reviewers. Without such scientific talent, the Agency would risk having its decision making compromised.

As I understand it, research is not a specific item in the budget of each Center. However, it is the responsibility of each Center to decide the amount of money that will be allocated to the Center's research program.

Thus, the Center has a process for prioritizing its research program according to certain criteria, including: relevance to FDA's mission, magnitude of the potential health impact, contribution to regulatory decision-making, and the probability of success of the program. Other factors also are considered, such as whether the research is unlikely to be done elsewhere. These seem to be

appropriate criteria for allocating funds for research.

**(b) What steps do you intend to take to ensure that research funds allocated to CDER and CBER are utilized for research that facilitates the Agency's mission of product approval, and not for extraneous activities?**

If confirmed as Commissioner, I would plan to review with each Center its resource needs in all areas, including research. Further, I would receive the advice of the Agency's Science Advisory Board, which would provide an outside view of the need and quality of the ongoing mission related research of the Agency.

#### **41. New Biotechnologies**

**The U.S. is the world leader in the development of biotechnology products. Currently, 40% of all biotechnology INDs are for cellular therapies, and xenotransplantation products. What steps do you intend to take to ensure that FDA possesses resources, expertise, and flexibility to regulate these new products appropriately? How do you intend to create the necessary organizational focus to address this segment of a potentially large industry?**

If I am confirmed as Commissioner, I will be committed to continuing efforts undertaken through the Administration's reinvention initiative, an initiative on which FDA has established an exemplary record.

I understand that through changes made under the Administration's Reinventing Government Initiative and FDAMA, FDA has designed a regulatory framework to address new technologies in a flexible manner. This is the most significant overhaul of the regulation of biotechnology products ever attempted. This new approach takes into account scientific advances that have been made in the area of biotechnology. This approach also attempts to minimize premarket requirements, so as to allow innovation to proceed while ensuring that proper and appropriate levels of controls for safety and effectiveness are followed.

Ensuring the efficiency of the Agency's scientific base is critical to its ability to protect the public health in an era of constantly emerging new technologies. Addressing the adequacy of the research and scientific infrastructure will be one of my highest priorities.

## **42. Merger of CDER and CBER**

**Please discuss the advantages and disadvantages of merging CDER and CBER into a single Center and indicate whether you intend to proceed with such a merger.**

As a general matter, I believe the Agency's primary focus for the immediate future must be full and successful implementation of FDAMA. As I have indicated, that will be my highest priority. Given this challenge, my current view is that it would not be wise to contemplate major organizational restructuring. However, I intend to be very open to identifying and adopting the best practices to improve FDA's performance. If this requires a new organizational framework for parts of the Agency, I will not hesitate to consider and implement such a restructuring.

### **Food**

**43. GAO reported that the FDA does not effectively target its resources on imported foods that pose the greatest health risk. Specifically GAO reported that:**

**FDA's annual work plan is not useful in making selection decisions in district offices;**

**FDA inspectors cannot readily access relevant health risk information; and**

**FDA does not ensure the accuracy of importer-provided shipping information.**

**As a result of these problems, FDA inspectors at ports of entry make subjective decisions that may not target the riskiest shipments. For example, one FDA inspector routinely selected samples of food from a country for filth tests - the inspector believed the country did not have sanitary facilities and therefore assumed that all food products imported from that country were contaminated with filth.**

**As the FDA Commissioner, what actions would you take to improve the annual work plan, make health risk information readily accessible to FDA inspectors, and ensure importers provide accurate shipping information?**

First, I would like to restate my personal commitment to improving the safety of the nation's food supply. This is one of FDA's most critical responsibilities, and I look forward to working closely with the Congress and other interested parties on important issues such as the safety of imported foods, research and education, and coordination of resources and responsibilities.

As for the GAO report, I think that several good observations and recommendations were made. I do not dispute that FDA needs to take action to improve its control over imported foods. I agree that the work plan and other guidance documents must accurately reflect Agency priorities.

If they do not, they need to be revised. If confirmed, I plan to ensure that the Agency addresses this issue. In addition, FDA currently is enhancing its OASIS system to make it more efficient and effective by linking various health risk databases so they are more readily accessible to inspectors. Regarding the third point, I believe that the accuracy of shipping information is crucial to ensuring a safe food supply. FDA already is taking actions to improve compliance, such as education and prohibiting error-prone filers from using the paperless entry system. If confirmed, I plan on looking into this matter to determine how best to work with industry to address this concern.

**44. GAO also reported that weaknesses in controls over food imports enable entry of unsafe products into the U.S. commerce. Specifically, GAO reported that:**

**FDA's system for automatically detaining suspicious food shipments pending testing to confirm their safety can be easily subverted because FDA does not maintain control over the testing process; and FDA does not maintain control over known and potentially unsafe imported food products.**

**As the FDA Commissioner, what actions would you take to improve the FDA's control over the testing process for automatically detained food shipments and to improve the controls over known and potentially unsafe imported food products?**

I think the GAO report presents extremely important issues that need to be addressed. Questions related to certification of testing laboratories and control of import shipments pending review may involve the scope of the Agency's statutory authority. If confirmed, I would want to work with the Congress on addressing these issues so that a safe food supply for the American people can be assured.

**45. There seems to be some confusion about S. 1707, a bill that would amend the Federal Food, Drug, and Cosmetic Act to allow the Secretary to declare foods or specific commodities from a country to be adulterated if FDA determines that a particular facility or country's food system does not provide the same level of protection that is provided for comparable domestic products, and thus, refuse entry into the United States. The bill also permits the Secretary to deny entry of imported foods where FDA has been refused access to conduct inspections of the food preparation, packing or holding facilities.**

**FDA officials have publicly made statements that seem to conflict with those made by the President on this legislation. For example, in October 1997, the President stated: "I'm asking Congress to give the Food and Drug Administration the power and the obligation to ban the importation of fruits, vegetables and other foods from countries whose safety precautions do not meet American standards. This law would be similar to a**

law that already requires the United States Department of Agriculture to keep meat and poultry from countries with inferior food safety systems out of our stores.”

Just two months later, in December 1997, a FDA official stated with regard to the legislation providing FDA authority similar to the Agriculture Department:

“ This is a bit of an exaggeration... what the statute would look like if it is ever turned into law, we do not know...one of the things that we would consider doing is perhaps visiting and evaluating agricultural sectors of some of our trading partners,...”

**Please clarify:**

I am not familiar with the statement from the FDA official, but it is clearly incorrect. The legislation that the President proposed has been introduced in the Senate by Senators Mikulski and Kennedy and in the House by Congresswoman Eshoo. The legislation would, in fact, give FDA the authority to ban the importation of fruits, vegetables and other foods from countries where it has been determined by FDA that safety precautions do not meet American standards.

I believe that FDA should continue to work with foreign governments and producers of imported food to take any steps necessary to help ensure that imported food products meet U.S. food safety requirements or otherwise achieve the level of protection required. If FDA determined that the steps needed to address an existing or potential risk had not been taken and that the affected products therefore did not meet U.S. food safety requirements or otherwise achieve the level of protection required, FDA would be authorized to deny such products entry into the United States.

**46. Please clarify your position on S. 1707 by addressing the following questions:**

**(a) If S. 1707 were enacted into law, what role or roles will FDA inspectors play?**

It is my understanding that S.1707 provides FDA with enhanced enforcement authority through evaluation of foreign food safety systems. I do not believe this legislation, in and of itself, requires an increase in foreign inspections. FDA has relied in the past, and will need to continue to rely, on the knowledge and expertise of our counterparts in the regulatory agencies of foreign governments. The Agency plans to work with countries that are major suppliers of food to the U.S. to develop a better understanding of their agricultural production, processing, and handling practices.

I understand that the Administration requested in the FY99 budget an increase to support FDA's foreign activities (i.e. providing technical assistance and evaluating foreign food safety systems). With this increase, FDA would expand its fresh fruit and vegetable inspection and testing program for domestic as well as imported produce. Additional resources also would also be

focused on sampling products from areas, both in the U.S. and abroad, where there is evidence that a potential hazard exists and preventive measures are lacking.

**(b) How would the FDA enforce this law? Specifically, how would FDA determine if imported food has not been prepared, packed, or held under a system or conditions, or subject to measures, that meet the requirements of S. 1707 or otherwise achieve the level of protection required by the legislation for foods produced domestically?**

I am aware that the statute requires an implementation plan, which the Agency would put forward after public participation into the development of the plan. If confirmed, I would work diligently on this important matter.

**(c) Would additional FDA inspectors be placed at U.S. ports of entry?**

I understand that this legislation is not focused on adding or removing inspectors from U.S. ports of entry. The system envisioned under the bill would emphasize the underlying systems of control at their source rather than FDA's current system of finding contaminated lots of food at the U.S. border. This legislation also would allow FDA to evaluate the foreign food safety system and to apply the knowledge gained from the evaluation to determine which food generally should be excluded from our country. The intention for this new authority, combined with the existing authority to have FDA inspectors at the ports of entry, is to strengthen the food safety system in the U.S. I should add that I understand that as part of the Administration's FY99 budget request, the Agency has asked for additional funding for more inspectors at the borders.

**(d) Would FDA inspectors be required to travel abroad to inspect a country's agricultural and manufacturing practices?**

I assume that in order to examine a country's agricultural and production practices, FDA would need to conduct some on-site examination of those practices, which could include inspection of representative foreign facilities. FDA inspectors also would likely travel abroad when a problem detected in the U.S. is suspected to be of foreign origin.

**(e) If FDA inspectors are required to evaluate a foreign country's agricultural and manufacturing practices, what specific qualifications do current FDA inspectors possess to adequately accomplish this task?**

To be an FDA inspector, an applicant must possess certain scientific training at the college level or above. Most, in fact, have degrees in a scientific discipline. Furthermore, all FDA inspectors receive special training that qualifies them to perform an inspection of a domestic facility to evaluate that facility's compliance with US requirements. For the FDA inspectors who will go abroad, additional training on specific items may be needed to conduct an evaluation of the

foreign system.

**(f) Would FDA inspectors inspect and evaluate the adequacy of domestic agricultural and manufacturing practices?**

I am told that if this legislation were enacted into law, FDA inspectors would not change their inspections and evaluations of domestic agricultural production and manufacturing practices. The legislation would give FDA the expanded authority to apply information learned from examinations of the foreign agricultural and manufacturing systems and to make determinations about which foreign products should be excluded from the U.S.

**(g) What specific domestic standards would FDA inspectors use to determine if foreign country's [standards] meet U.S. standards for fruit and vegetables?**

I believe that if this legislation were enacted, FDA inspectors would use existing domestic standards to determine whether a foreign country's standards meet US standards for fruit and vegetables or otherwise achieve the US level of protection for such commodities. Specifically, several provisions in the Federal Food, Drug, and Cosmetic Act (FFDCA) establish food safety standards, including standards regarding the presence of unapproved pesticide residues and pathogens, and unsanitary practices in manufacturing facilities. Similarly, there are regulations, such as those for low acid canned food and seafood HACCP, established under the authority of the FFDCA, which set forth food safety standards.

**(h) FDA is currently developing guidance on good agricultural and manufacturing practices intended to assist domestic growers in meeting the U.S. level of protection. Would you make this guidance mandatory to domestic and foreign growers?**

I believe that, consistent with U.S. trade rights and obligations, FDA will continue to apply the same standards to domestic and foreign growers in order to protect public health and safety. Under FDA's Good Guidance Practices, guidance documents do not establish mandatory requirements.

#### **47. Irradiation Labeling**

Consumers and food safety experts are focusing greater attention on the public benefits of food irradiation. For example, the FDA itself recently approved a petition permitting irradiation for red meat. As part of the national effort to improve public awareness of food safety, FDAMA includes a provision calling for the redesign of the disclosure label for irradiated foods. Further, the conference report to FDAMA stated that the FDA should issue its final regulations regarding the redesign of the irradiation labeling within twelve months of enactment.

**(a) What are your views on the use of irradiation to advance food safety?**

I know that irradiation has been recognized as a step toward curbing foodborne illness. Nevertheless, it is a complement to, not a replacement for, proper food handling practices by producers, processors, and consumers.

Irradiation has been approved by FDA for use on specific foods to reduce or eliminate pathogenic bacteria, insects, and parasites. Although irradiation is not appropriate for use for microbial control for all foods, in certain cases it can add significantly to ensuring safety from risk of food-borne illness. For example, in the case of meat and poultry, irradiation can play an important role in reducing risk from the microorganisms most commonly associated with human illness.

**(b) As the FDA has approved irradiation as a safe and effective technology in the protection of public health, what role should FDA have in educating consumers about this food safety tool?**

FDA's role is to provide the public with information on the basis for its decisions and to ensure consumers that approved uses of food irradiation have been carefully and objectively evaluated for safety. This can be accomplished not only through a detailed discussion of an approval in the Federal Register but also, for example, in consumer literature such as the Agency's FDA Consumer magazine.

**(c) In order to present useful consumer information on irradiation, what labeling requirements do you propose for irradiated foods?**

I understand that Congress has asked FDA to solicit public comment on whether revisions to the current irradiation labeling requirements are needed and, if so, what form such revisions might take. As a general matter, I believe that such labeling should be truthful and not misleading. In terms of specifics, I will await with interest the public's advice.

**(d) As the November deadline provided in the conference report fast approaches, when will FDA publish a proposed rule on irradiation labeling for public review?**

As mentioned above, I understand the Agency plans to solicit public comment on whether revisions to the current irradiation labeling requirements are needed and, if so, what form such revisions might take. I have been informed that because there does not appear to be a consensus regarding changes in labeling of irradiated food, FDA is considering whether an advance notice of proposed rulemaking may be an appropriate vehicle to solicit additional views.

#### **48. Food Safety Enforcement**

**(a) Following the Hudson Foods recall, the FDA and the USDA signaled their intention to seek expanded enforcement authority. While USDA has submitted its regulatory plan, Congress still awaits the FDA's proposal. In your view, in what way, if any, are the current FDA enforcement tools inadequate to the regulation of food safety ?**

Although this event occurred when I was not at the Agency, it is my understanding that at the time of the Hudson Foods recall, Secretary Glickman announced that he would seek mandatory notification and recall authority under the meat and poultry laws administered by the Department of Agriculture. The Department of Health and Human Services announced a similar intention for FDA.

These proposals were directed at producers and their distributors who do not fully cooperate in notifying the government of hazards with their products and in removing contaminated product from distribution. It is my understanding that neither USDA nor FDA has authority to require firms to notify the government of safety problems with products, to require recalls of food products (except infant formula), or to levy civil monetary penalties for violations of our respective food safety laws (except for pesticide residue violations). Moreover, FDA does not have other authorities that USDA has, including records inspection, product embargo, and subpoena power.

FDA's current enforcement options against unsafe or mislabeled foods are limited to seeking the seizure of such food, or injunctions against offending firms through the U.S. court system and issuing publicity about the suspect products. Notification and recalls continue to be voluntary on the part of distributing firms and highly dependent upon their cooperation.

**(b) What is the FDA's time-table for submitting an expanded enforcement authority proposal?**

It is my understanding that the Administration's first priority in terms of FDA's authority regarding food safety is obtaining additional authority for imported foods. I am informed that FDA has no current timetable for submitting a request for expanded enforcement authorities, but should Congress be receptive to this, I would be willing to work on such an initiative.

#### **49. Delaney Clause**

**(a) The rigidity of the Delaney Clause's 1950 "zero tolerance" standard for chemical additives restrains the FDA's capacity to utilize emerging scientific identification of "no harm" levels for chemical additives. In 1996, Congress took action to replace the FDA's blanket pesticide residue standard under Delaney with a focused, scientifically-based**

**standard for measuring harm. Has the FDA identified problems with the 1996 changes for pesticides?**

As I understand it, the Food Quality Protection Act (FQPA) changed the pesticide law administered by EPA, so that the Delaney anti-cancer clause no longer applies to pesticides. Instead, a new health based standard is now being applied by EPA in conjunction with other health-based criteria. FDA's role is to enforce EPA's tolerances for pesticide residues in food. I understand that the FQPA has not caused enforcement problems for FDA.

**(b) What priority would you assign to the modernization of scientific standards for food additives, colors and animal drugs?**

Standards for safety evaluation must always be consistent with the best available science. FDA must continue to be receptive to various procedures for evaluating safety as long as such procedures ensure protection of the public. Consistent with the level of effort needed to complete product evaluation in a timely and acceptable manner, priority must be given to updating those standards that are most likely to improve final regulatory decisions while maintaining public confidence.

#### **50. Food Additive Petition Review**

**The FDA has developed a well-known reputation for its slow review of food additive petitions. For example, the red meat irradiation petition took over three years despite a statutory six-month deadline. In your view, what are the causes of such delays and how do you plan to improve the performance of the FDA's food center with regard to food additive petition reviews?**

If confirmed, I look forward to reviewing FDA's food center procedures. I think there are a number of reasons why food additive petition reviews take longer than most of us would like.

First, deciding whether something should be added to the food supply of all consumers requires a safety review process that is rigorous and complex. The review is an integrated effort of staff with expertise in chemistry, toxicology, environmental science, nutrition, microbiology, and regulatory issues who review very large bodies of data.

Second, petitions often cannot be approved without additional work. Rather than denying the petition, the Agency often works with the petitioner to obtain the additional information necessary for the Agency to approve use of the additive.

Perhaps most important, the limited number of reviewers combined with the large number of petitions results in a considerable amount of elapsed time as reviewers complete earlier

assignments. Thus, elapsed time is considerably larger than review time.

Nevertheless, I understand that FDA has increased productivity, reduced the backlog of food additive petitions, and initiated steps to streamline the process. If confirmed, I will look closely at additional steps that can be taken to improve the center's performance and ensure that its expertise is used most efficiently.

**51. CFSAN Budget.** The repeated use of unapproved user fees to provide the appearance of a higher program level for CFSAN in annual budget submissions raises serious questions regarding the Administration's commitment to this center's national responsibilities. As further evidence of the Administration's neglect of CFSAN, officials of the FDA have testified that resources have been shifted away from the center to support user-fee funded activities, in particular drug reviews. *(From remarks of Linda Suydam, Interim Deputy Commissioner for Operations, FDA before the House Subcommittee on Human Resources and Intergovernmental Relations, June 22, 1995, on FDA's food additive approval process, Hearing Record – p. 28.)*

**(a) As a participant in the development of the President's annual budget request, has the FDA served as the primary advocate for user fees as a funding source for CFSAN?**

It is my understanding that the Agency's primary concern in budget discussions is the level of program funding, rather than the source of such funding.

**(b) If not, who champions that recommendation and what was the basis for selecting that funding source?**

Based on past experience, I know that the President's Budget request is the result of Administration-wide deliberations involving many different individuals. Since I have not been involved in the budget deliberations in recent years, I am not aware of who is the champion of this point of view.

**(c) As FDA Commissioner, how do you plan to reconcile the Administration's low budget priority for CFSAN with its high expectations in the area of food safety regulation?**

My impression is that this Administration, in the past two years or so, has taken a strong and aggressive approach to improving the safety of food. As documented in the May, 1997, report "Food Safety: From Farm to Table, A National Food-Safety Initiative," several agencies of the Federal Government – including FDA – are working together to develop specific steps to improve the safety of the food supply. The goal of this initiative is to further reduce the incidence of foodborne illness to the greatest extent possible. In addition to this work, the Administration also has launched a number of other initiatives to improve food safety, such as

implementation of HACCP-type inspection systems for different segments of the food industry.

I understand that the President's FY 1998 Budget request included \$43.2 million -- of which \$24 million was for FDA -- for the Food Safety Initiative. The President strengthened this commitment by requesting an additional \$101 million in the FY 1999 budget, of which \$50 million would be for FDA.

**(d) In light of CFSAN's relatively weak budgetary position compared to other Centers within the Agency, what food regulatory activities, including those not central to assuring food safety, may be undertaken in cooperation with industry, self-regulatory organizations, or state and local entities to improve CFSAN's performance?**

I understand that a central feature of the Administration's Food Safety Initiative is cooperative activities with the Agency's external stakeholders -- both its fellow regulators, such as USDA and the states, and the regulated industry. With the states, for example, I know that efforts are underway to develop a "vertically integrated" food safety system. In a vertically integrated system, FDA will provide guidance and training to states in the conduct of inspections. Such inspections will be complementary to FDA inspections, rather than redundant. Certainly, the HACCP initiative in seafood is one example of FDA reliance on industry's own preventive control systems as part of the food safety equation. Another important component of the Initiative is working with states to establish uniform food codes to guide the actions of food retailers throughout the country, and contribute to improved food handling practices. Another example is the two consortia in which FDA currently participates. The National Center for Food Safety and Technology and the Joint Institute for Food Safety and Nutrition will leverage resources by collaboration in research and other activities and shared facilities, research equipment, and scientific expertise. These efforts should result in a better food safety system that reduces duplication of effort and promotes the most efficient use of resources.

## **52. State and Local Role in Food Safety**

**(a) Responsibility for food safety inspection and enforcement is held by local, state and federal authorities. Based on your assessment of our nation's food safety system, what action could be taken to reinforce collaborative partnerships among government entities in order to maximize man-power and resources?**

It appears to me that federal food safety authorities have been increasingly coordinated in recent years. In developing a "vertically integrated" food safety system, FDA will provide guidance and training to states in the conduct of inspections. Such inspections will be complementary to FDA inspections, rather than redundant. Use of consistent, uniform food safety oversight practices across the country by federal and local officials would greatly expand the food safety capability.

**(b) Is the FDA's upcoming enforcement proposal premised on its capacity to build upon state and local systems or to serve as a comprehensive, parallel food safety system? Please explain in detail the reasoning for the FDA's policy change.**

I understand that the administration's intent is to establish a "vertically integrated national food safety system" under which state and federal food safety activities will be complementary and coordinated, not redundant. To the extent the Agency intends to address the adequacy of its enforcement authorities, it would be doing so in the context of its role in this vertically integrated system.

**(c) With regard to measures that can reduce the incidence of foodborne illness, do you plan to educate the public and media on where FDA's role in assuring food safety stops, and that of state and local agencies and consumers begins? Please explain.**

I believe that an effective food safety system requires that all parties -- including all levels of government as well as industry and consumers -- understand their respective roles and responsibilities. For example, FDA's new seafood HACCP regulations clearly place the responsibility on seafood processors to develop and implement an effective HACCP plan. The HACCP plan is audited either by an FDA or a state inspector. And consumers, through the Fight BAC campaign, are being educated on the steps they can take -- clean, chill, cook, and separate/not cross-contaminate -- to enhance the safety of the food supply. In addition, under the Food Safety Initiative, response to outbreaks of foodborne illnesses are being closely coordinated among CDC, FDA, USDA, and the state and local health and regulatory agencies.

### Tobacco

**53. The following questions relate to FDA's past and current efforts to assert jurisdiction over tobacco products:**

**(a) Please give a detailed account of the extent, if any, to which you participated in the FDA's consideration of whether the Agency has authority under existing law to assert jurisdiction over tobacco products.**

I did not participate in the FDA's consideration of whether the Agency has authority under existing law to assert jurisdiction over tobacco products.

**(b) Please explain any involvement on your part in the preparation of the February 25, 1994 letter from Commissioner Kessler to Scott Ballin regarding the petition of the Coalition on Smoking OR Health seeking FDA regulation of low-tar and low-nicotine cigarettes. What does the following passage in the February 25, 1994, letter mean to you:**

**“We recognize that the regulation of cigarettes raises societal interests of great complexity and magnitude. It is vital in this context that Congress provide clear direction to the Agency.”**

I was not involved in the preparation of the February 25, 1994 letter from former Commissioner Kessler to Scott Ballin regarding the petition of the Coalition on Smoking OR Health seeking FDA regulation of low-tar and low-nicotine cigarettes.

**(c) Taking into account the FDA's position in 1994 and its subsequent rulemaking to assert regulatory authority over tobacco products, please explain whether you believe it is appropriate for an Agency to reverse, without any congressional enactment, its longstanding and consistent interpretation of a statute, so as to expand its statutory authority. What factors distinguish the FDA's policy reversal from the constitutional principle that laws be modified only through legislative action?**

Given the recent decision by the panel for the U.S. Court of Appeals for the 4th Circuit, and the Administration's subsequent announcement that it would seek further review of that decision, I believe that this issue will ultimately be decided by the courts, or by Congress through comprehensive tobacco legislation. If I am confirmed as Commissioner, I would obviously abide by any final judicial or congressional action.

As I understand it, if statutory authority exists, the courts have held that it may be appropriate for a regulatory agency to change a long-standing position, if circumstances have changed and the agency provides a reasoned explanation for its change in position. In the case of its jurisdiction over cigarettes and smokeless tobacco, I understand that FDA provided a detailed explanation of the important new evidence that had emerged since the last occasion on which the Agency concluded that it lacked jurisdiction over tobacco products. This new evidence included: (1) the universal recognition in the 1980's that nicotine is an addictive drug, and (2) a wealth of documents revealing that the tobacco product manufacturers have known for decades that consumers use tobacco products for the pharmacological effects of nicotine, and have designed their products to provide sufficient nicotine to satisfy consumers. I am told that none of this evidence was available the last time FDA was asked whether it had jurisdiction over tobacco products. I understand that with this new evidence, FDA felt it was reasonable to conclude that the nicotine in cigarettes and smokeless tobacco is a drug and that these products deliver nicotine to the user like a number of other drug delivery devices and, therefore, that cigarettes and smokeless tobacco products are within the Agency's jurisdiction.

**(d) What is your interpretation of the states' responsibility under the Synar Amendment to the Public Health Service Act? Do you have any indication that the States are not taking adequate measures to enforce their minimum age laws? Pursuant to the Synar Amendment, what authority does the FDA have in relation to minimum age enforcement powers of the States and the U.S. Department of Health and Human Services?**

It is my understanding that under the Synar Amendment, States are required to have in effect laws which prohibit the sale of tobacco products to minors as a condition of receiving federal substance abuse prevention and treatment grants. Further, States must conduct certain monitoring activities and attempt to meet certain negotiated rates of compliance in order to receive the full amount of their grants. Although the Synar program creates incentives for States to enforce their prohibitions on sales to minors, my understanding is that it does not require any particular type of enforcement program. The disturbing prevalence of youth smoking and the studies indicating that in many locations children can easily purchase tobacco products are some indication that historically, state laws prohibiting the sale of tobacco products to children have not been adequately enforced. I am not aware that the Synar Amendment grants FDA any specific authority over tobacco products.

**(e) Dr. Kessler initially rejected a nicotine ban while serving as FDA Commissioner but has since recanted this decision to push vigorously for FDA authority to ban nicotine. Based on your experience at FDA when Dr. Kessler formulated his initial position, what factors define your position as FDA Commissioner on the extent of FDA's authority to regulate nicotine? Would you support such a ban?**

As I stated in response to an earlier question, FDA's authority to regulate tobacco products is currently before the courts. If I am confirmed as Commissioner, I would obviously abide by any final judicial or congressional action.

Although FDA under Dr. Kessler concluded that a ban on tobacco products would not serve the public health because of the large number of adults already addicted and the probability of such a ban creating the black market, my understanding is that the Agency did not conclude that it lacked authority to regulate nicotine. Instead, FDA determined that other steps, including restrictions on access and advertising, would better serve the public health by preventing young people from becoming addicted to tobacco. Based on the reasons given above, I do not believe that a ban on nicotine would best serve the public health.

**(f) The Clinton Administration has utilized executive orders to implement aspects of the FDA's tobacco rulemaking when disputes over its implementation have arisen. Is it your intention to pursue an executive order track should Congress continue its work on legislation regarding teen access to tobacco beyond this session? What factors justify the use of executive orders to bypass Congressional action on this issue? Are there other areas of concern to FDA where executive orders are or may be used in this manner?**

I am aware that the Administration has recently issued executive memoranda with respect to tobacco, but I do not believe these executive actions related to implementation of FDA's tobacco rule.

**(g) Do you believe Congress should approve any action by FDA to ban nicotine before it is to take effect? What role, if any, would reducing or eliminating nicotine in cigarettes play in reducing the overall risk to the public health posed by cigarettes?**

As I stated in response to an earlier question, FDA's authority to regulate tobacco products is currently before the courts. If I am confirmed as Commissioner, I would obviously abide by any final judicial or congressional action.

As I also mentioned in response to an earlier question, based on all the information currently available, I do not believe that a ban on nicotine would best serve the public health. And, it is my understanding that the regulations issued by the Agency in August 1996 do not affect the nicotine in cigarettes and smokeless tobacco products. However, if the Agency ever took steps to ban nicotine, under existing law Congress would have the opportunity to enact legislation to block such a ban before it takes effect. I believe that Congressional review in this context would be appropriate.

**(h) Do you believe that cigarettes should be regulated as drug delivery devices? Please explain.**

As I stated in response to an earlier question, FDA's authority to regulate tobacco products is currently before the courts. If I am confirmed as Commissioner, I would obviously abide by any final judicial or congressional action.

I would note that Senators Frist and McCain included a provision in the Senate tobacco bill that would have regulated tobacco products under a new, separate chapter of the Act, and would have made it clear that the regulation of tobacco does not affect other FDA-regulated products. In my view, this approach has considerable merit.

**(i) Whether your answer to (h) is yes or no, do you believe that FDA should regulate cigarettes on a "performance standard" model or a "substantial equivalence" model? Please explain.**

The performance standard and substantial equivalence models are not mutually exclusive, and both could be used to regulate the same device category. As I understand it, the Senate's comprehensive tobacco bill included performance standard authority, and, for new tobacco products, provisions similar to the premarket review and substantial equivalence authority in device law. While I would like to study this issue further and receive additional information and views concerning tobacco products before proposing the appropriate model or models, the approach taken in the Senate bill appears to provide the Agency with appropriate flexibility.

**(j) Do you believe FDA should regulate tobacco through a separate center? Please explain.**

The tobacco program currently is housed in the Office of Policy within the Office of the Commissioner. I am aware that the Agency has had preliminary internal discussions concerning whether the program should be moved out of the Commissioner's Office, but I believe it is premature to say whether the Agency should create a new center to regulate tobacco. If I am confirmed, I will review this issue and consider such factors as funding, staffing levels, court decisions, and possible impacts on other Agency programs and responsibilities before determining whether a new center should be created.

**(k) In the regulations asserting the jurisdiction over tobacco, FDA defined "intended use" based on "foreseeable effects" and "consumer use." In your view, are there any other product categories not now regulated by FDA that could or should be subject to the foreseeable effects and consumer use theories of the terms "drugs" and "device" as described in the FDA tobacco regulation?**

I am not aware of other product categories currently unregulated by FDA that I am prepared to conclude should be subject to the "foreseeable effects" and "consumer use" theories.

**(l) Is it your view that the purpose of regulating tobacco products at the FDA is only to reduce and/or eliminate smoking by individuals under the age of 18? If yes, is there any circumstance under which you would assert that FDA should execute policies to reduce smoking among those 18 or older?**

My understanding is that FDA's final tobacco rule states that the goal of the rule is to effectively reduce the death and disease caused by tobacco products. The evidence demonstrates that one highly effective method of achieving this goal is by preventing children and adolescents from starting to use tobacco products. More than 80% of adult smokers had their first cigarette prior to their 18th birthday. Approximately one out of every three young people who become regular smokers each day will die prematurely as a result. If the number of children and adolescents who begin tobacco use can be substantially diminished, tobacco-related illnesses can be correspondingly reduced because studies suggest that anyone who does not begin smoking in childhood or adolescence is unlikely to ever begin.

One area in which FDA actions have a direct affect on smokers 18 years of age or older is in the review process for smoking cessation products. In carrying out the Agency's mission to review and grant premarket approval to drug and devices if they are found to be safe and effective for their intended uses, FDA has approved numerous products intended to help consumers quit smoking.

**(m) In the absence of tobacco control legislation providing a dedicated source of funds for FDA's tobacco control activities, please indicate which of the following sources of funding**

for FDA's tobacco control efforts you would propose as FDA Commissioner:

(i) a tax on cigarettes, the proceeds of which are directed all, or in part, to completely cover the cost of FDA's tobacco control efforts;

(ii) a user fee, analogous to that paid by prescription drug companies, levied on tobacco product manufacturers to fund specific regulatory activities that provide an identifiable benefit to the tobacco industry such as timely review of applications for the marketing of new products (if you would select this option, what would be the source of funding for any FDA tobacco control efforts, not covered by the user fee, that benefit the general public);

(iii) a distinct line item in the President's budget submission for the FDA requesting funds to cover the cost of tobacco control efforts, which would be additive to the amounts requested for the Agency in the absence of any tobacco control effort;

(iv) a user fee levied on all FDA regulated products to increase the funds available to FDA which it could then use for tobacco control and other activities, at the discretion of the Commissioner;

(v) diversion of funds from current FDA activities such as the review of generic drugs, food safety efforts, and medical device facility inspections to provide funds for tobacco control activities.

If you would choose options (i), (ii), or (iv), would you put FDA's tobacco control activities on hold pending Congressional enactment of the necessary legislation or find other sources of funding in the interim?

In the absence of comprehensive tobacco legislation, I would expect the Agency to continue to seek funding for its tobacco program through the appropriations process. I am aware that the Administration supported using a portion of revenues derived from tobacco legislation to fund the Agency's tobacco program.

### Medical Devices

54. Section 205(a) of FDAMA contains a requirement that the "Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls." This issue must be considered for both PMA products and 510(k) products. This section was included to carry out the unfulfilled promise of the Safe Medical Devices Act of 1990 which created new postmarket tools in order to reduce premarket requirements, among other reasons.

**(a) What are your views on the extent to which, as a practical matter, the use of postmarket studies could reduce data needs in the approval process? For instance, would you agree that a three year study could be reduced to two years with a one-year postmarket study period?**

My understanding is that postmarket studies already are being used with many PMAs and some 510(k) devices to minimize premarket data needed. Optimizing the use of postmarket testing may reduce premarket data requirements for some devices. For example, postmarket studies may provide additional information about long term use of a device, or effectiveness in a more diverse population. In these circumstances, data that might have been requested for premarket review can be generated following approval. If I am confirmed, I will continue to examine steps that can be taken, consistent with FDAMA, to minimize the amount of premarket data requested when postmarket studies can provide the appropriate consumer protection envisioned in the Act.

**(b) Some have suggested, in this context, the concept of a "conditional" approval. That is prior to the receipt of complete data, FDA would allow a product to be marketed, on a limited and conditional basis, until the final results from a postmarket study were obtained, provided the results raised no new questions of safety or effectiveness. What are your views on this suggestion?**

My understanding is that the Agency has begun to develop mechanisms to expedite approval of and expand access to experimental therapies in appropriate circumstances. In doing so, however, the Agency has operated in a manner consistent with its statutory mandate to establish that there is a reasonable assurance that devices are safe and effective before they are commercially marketed. If I am confirmed, I look forward to exploring all options that might be available to improve the Agency's performance.

**55. Critics have alleged that FDA automatically defaults to requiring the most burdensome types of clinical trials---i.e. randomized, double-blind, concurrently controlled--when valid alternative means for providing safety and effectiveness are readily available. How would you ensure that such trials are required only when absolutely necessary?**

As I stated previously, I entirely agree that FDA should require only such data as are necessary for the Agency to make the determinations required under the statute. I would work to ensure that FDA adheres to its current commitment to work closely with the sponsors of clinical trials to decide what type(s) of trials are the most likely to produce the most useful clinical information in the shortest amount of time and, at the same time, to provide adequate protections for clinical trial participants.

One important mechanism to ensure that this approach is utilized is to provide necessary

guidance and training about what "least burdensome" means. I understand that Center for Devices and Radiological Health (CDRH) has issued such guidance and is providing training to staff and industry about how to establish what is least burdensome.

**56. Section 205 requires that, for 510(k) products with different technological characteristics, FDA shall only request necessary information and shall consider the least burdensome means of demonstrating substantial equivalence. How would you ensure that reviewers are limiting requirements to only that which is "necessary information?"**

I am informed that CDRH routinely provides training, including written guidance, to scientific reviewers and Office of Device Evaluation (ODE) management on the 510(k) process, as well as the various provisions of FDAMA that affect 510(k)s. There is supervisory oversight of the review process and the activities of the review staff, and this oversight extends to the level of evidence needed and requested to evaluate substantial equivalence. As I understand CDRH's internal processes, direct supervisory oversight is strengthened by periodic retrospective review by ODE management of select 510(k) decisions.

**57. One of the more controversial aspects of the FDAMA debate concerned FDA's tendency to ask questions about possible off-label uses for devices and requiring manufacturers to conduct research into uses not intended by the sponsor. The compromise position that was ultimately included in FDAMA applies only to situations in which the Agency finds that the device is reasonably likely to be used off-label and that such use could cause harm. In such cases, a procedure is required which should result in a timely substantial equivalence determination with the requirement for limitations in labeling to accompany the product. Will you affirm that as Commissioner you will implement this provision such that any consideration of any limitation on the labeling of a device shall occur after the substantial equivalence determination has been made. Please describe any situations in which you would deviate from this sequential approach to this provision and explain why.**

Yes. I agree that under FDAMA any consideration of any limitation on the labeling of a device should occur after other issues related to substantial equivalence have been resolved. I understand that the CDRH has adopted this approach and has issued a guidance document regarding this provision.

**58. During your tenure at the FDA from 1992-1994, product clearance and approval times increased to 184 days for 510(k) applications and 649 days for premarket approval (PMA) applications. These figures are well above the congressionally mandated review times of 90 days for 510(k) and 180 days for PMAs. Moreover, the backlog of over due 510(k)**

**applications reached its all-time high three months before you left the Agency. During this time, European patients were receiving many advanced life-saving medical technologies 3 years or more before patients in the United States. What Agency actions and FDA policies contributed to these increases in review times and delays, and what would you have done differently to prevent the backlog from occurring?**

We all know that CDRH faced a number of difficult problems in the early 1990s, including safety problems with several products. This raised questions in Congress and elsewhere about how the CDRH was doing its job. Congress made significant amendments to the device statute in 1990 and further amendments in 1992. The CDRH's performance was the subject of intense investigation by Congress, GAO, and OIG, and as a result, the Agency conducted a program review based on the concerns raised by these bodies.

As a result of the review, we at the Agency worked to implement changes in the device program. Management deficiencies, resource questions, and the issue of clinical input to product review had to be addressed. I believe the disruption caused by this series of events and the time needed for implementation of the corrections cumulatively caused the development of longer review times and the build up of a backlog in applications. A further contributing factor, I believe, was the increased conservatism on the part of a staff that became risk-averse with respect to review decisions.

However, the program changes that were made, together with increased resources Congress provided in 1994 and with the strong leadership that we put into place at CDRH, have turned the situation around. The CDRH now enjoys greatly reduced review times and has no backlog in any review category.

Finally, I should note that it is my understanding that during the time period referenced in this question many countries in the European Community generally required no systematic review of devices as a condition for marketing, and so, of course, products reached the market in Europe faster than in the U.S. Even today, Europe's premarket review program is only partially in effect. I am aware of a March 1996 GAO Report that indicates that the relative infancy of the European system makes it difficult to gauge its effectiveness, either in public health terms or in the degree of access to new products.

**59. Section 216 of FDAMA permits FDA prospective access to PMA data and information for various prescribed uses six years after approval of a device application. This provision was included in FDAMA at the request of the Agency. Will you apply the six-year rule only to products approved after the effective date of section 216 and apply the "four-of-a-kind" rule from the Safe Medical Devices Act of 1996 (SMDA) to products approved prior to that date? Please explain. In implementing this provision with regard to a specific product, which of the following date will be used: submission of the PMA or**

## **Agency approval of the PMA?**

While I look forward to learning about this issue in greater detail, I understand that FDA has not yet interpreted or applied the "six-year" provision. If confirmed, I will work to implement this new provision.

**60. Since 1992, user fees for medical device product approvals have been included in every administration's budget. Since the vast majority of medical device companies are small businesses, including a great many start-up companies with no sales, and because the nature of device innovation is incremental, the Congress has consistently opposed user fees as a tax on innovation and entrepreneurship that would not be necessary if the FDA managed its budget well or took advantage of other innovative approaches such as third-party review. Do you agree with the Congress that medical device user fees are unwise?**

As I indicated previously, historically user fees have succeeded only when they result from consensus among the Agency, the Congress, industry, and consumers. I do believe that innovative approaches such as third party review can help FDA maximize its resources and speed product review times. If I am confirmed, I will work diligently to ensure that the third party review provision included in FDAMA is implemented and evaluated in a way that is consistent with congressional intent.

**61. CDRH has made a great deal of progress in "reengineering" itself over the past several years, what are your views on the reengineering programs adopted, particularly the PDP, the modular PMA, and the new 510(k) paradigm?**

I think CDRH has done an excellent job of reengineering their processes, including premarket review procedures.

The modular PMA review, which permits FDA to review a PMA in sections as each part is completed, should provide a more efficient way to review certain devices. It will give manufacturers early feedback on areas of concern so that they can generate additional data without delaying final approval. The PDP procedures offer a way for the sponsor and FDA to work together early in the process to design the appropriate study and to agree on what level of performance should constitute success. The new 510(k) paradigm allows CDRH to focus its time and resources on high risk devices, while providing some streamlined approaches for submission and clearance of well understood devices.

I believe that these reengineering efforts will help maximize the performance of CDRH.

**62. We understand CDC and FDA are negotiating the return to FDA of responsibility for the complexity categorization and quality control functions of CLIA (Clinical Laboratory Improvement Amendments of 1988) pursuant to the Senate Report language in FDAMA. This initiative is also consistent with the current CLIA regulations. What is the status of those negotiations? Please describe the funding issues associated with this transfer and plans for addressing those issues. Please also indicate whether, upon transfer of the functions, FDA will adopt CDC's current policies and procedures regarding complexity categorization (including "waived" status) and quality control or will actively work to "reengineer" or otherwise improve the system. What is your position on these issues?**

The Department of Health and Human Services has important responsibilities for regulating in-vitro diagnostic products under both the FD&C Act and CLIA. Currently, the Health Care Financing Administration (HCFA) and the Centers for Disease Control and Prevention (CDC) jointly implement CLIA. In response to congressional direction, I understand that HHS is considering transferring responsibility for the complexity categorization of IVD devices from CDC to FDA, although the responsibility for setting standards would remain with CDC. I have been advised that the heads of CDC, FDA, and HCFA currently are discussing the potential transfer, and that those discussions are evaluating the costs such a transfer would entail as well as its impact on the regulated industry. Although the transfer decision is still pending, I look forward to helping to ensure that diagnostic products continue to be well regulated and that the industry and consumers will benefit from any efficiencies that may result from such a transfer.

**63. CBER has jurisdiction over certain medical devices which are regulated by the medical device laws, rather than biologic laws. However, CBER has not met many of the requirements of the law. For example, many 510(k)s take as long as 24 months for clearance at CBER. Nor has CBER been timely in implementation of FDAMA. What are the Agency's plans to address those deficiencies? What are your views on this matter?**

I have been informed that CBER already has taken steps to increase the efficiency of 510(k) reviews, such as adopting the 510(k) paradigm discussed in response to an earlier question, increasing the number of reviewers, and exempting certain lower risk 510(k)'s from premarket notification. In addition, CBER staff have worked very closely with CDRH staff to develop policies and procedures to implement the FDAMA provisions. If I am confirmed, I look forward to working closely with CBER staff to continue to improve its performance in this area.

**64. FDA has done an excellent job of holding outreach meetings around the country to obtain ideas and feedback on initiatives that would improve the inspection process for medical device manufacturers. Some of those initiatives include preannounced inspections, annotated "483" letters, and the issuance of close-out letters after inspections. What is your position on the continuation of these efforts?**

I believe that outreach initiatives developed in the device area should be continued, and I support their implementation in the other Centers within the FDA as they fit the needs of those specific programs.

**65. The Agency has published a list of devices that are eligible for third party review and has indicated that it intends to expand the list "on a regular basis." How would you ensure that all eligible devices are included on the list? What would be your anticipated time frame? What are your thoughts on eventually expanding this program to include higher risk Class II, Class III, and PMA products?**

I appreciate and understand the extensive consideration that was given to third party device review during consideration of FDAMA. The framework set forth in the statute is both thoughtful and flexible. I understand that the list of devices that the Agency published as eligible for this program has 147 types of devices. I believe this demonstrates a conscientious effort by the Agency to put forward a viable program. I am told that the Agency plans to review the list of eligible devices on an annual basis. Recognizing the significance of this provision, you have my commitment that if confirmed, I will give careful consideration to ensuring the fullest reasonable implementation of this program.

Certainly, the full implementation of this important FDAMA provision will inform us greatly in any consideration of recommendation to expand the program beyond the parameters set forth in the statute.

**66. FDA ran a pilot third party review program for a substantial period of time without success. What do you believe are the reasons the pilot did poorly?**

I understand that one important factor contributing to the industry's lack of interest in the pilot program was the Agency's success in reducing its 510(k) review times. I am told that the average total time for 510(k) final decisions dropped from 184 days to 111 days between 1995 and 1998, and the backlog was eliminated. Other contributing factors may have included: (1) the initial list of devices for the pilot program consisted primarily of low-risk devices with lower-than-average FDA review times; (2) device firms had to pay third parties a fee-for-service; and (3) third party review was still relatively new and firms may have felt less comfortable with this approach because they are less familiar with the process.

**67. What measures would you take to ensure that third party review under FDAMA works well and will attract submissions from industry?**

If confirmed, I will be committed to successful implementation of the third party review provision of FDAMA. A key factor in this will be to apply lessons learned from the earlier third party pilot program. I also believe the fact that the earlier pilot worked well for the limited number of manufacturers who participated in the program, combined with the expanded list of eligible devices under FDAMA, will go a long way toward attracting additional submissions from industry.

**68. What is your view regarding the use of FDA-certified third party reviewers to review the more complex 510(k)s which rely on clinical data to establish substantial equivalence?**

As I have said before, I appreciate and understand the extensive consideration that was given to third party device review during consideration of FDAMA. I think it is important now to focus on full implementation of the statute, a process that can inform our consideration of any program expansion. I know that FDAMA requires the Department of Health and Human Services to provide a report on this issue to Congress within three years of FDAMA's enactment. I believe that the Agency will have substantially more experience upon which to base a conclusion at that time.

**69. Do you see any benefit to the FDA from contracting out device reviews, including PMA reviews?**

If I am confirmed, my top priority will be to implement third party review for devices and the other provisions mandated by FDAMA. Based on this experience, I would be open to careful consideration of proposals and mechanisms that will enable the Agency to do its job better. Conceptually, contracting out device reviews, or portions thereof, could be one of those mechanisms. As Congress recognized in its structuring of the third party review program, the complexity of the review of PMA devices and the significance of public health concerns associated with them would need to be carefully considered.

**70. How would you take advantage of the contracting out authority that Congress gave to the FDA?**

In situations where the Agency determines that contracting out reviews will improve the timeliness of the review without reducing the quality or unduly increasing the cost or time of such a review, I think the Agency should explore that option. I think that the Agency should consider such contracts especially when the evaluation of new technologies requires specialized

scientific or technical expertise.

**71. Should FDA hold up a premarket product review because the Agency believes that a device will be used for an "off label" use?**

I do not think that it is appropriate for FDA to hold up the evaluation of any premarket device submission because of concerns that the device will be used "off label."

**72. How do you define the practice of medicine?**

I define the practice of medicine as the professional pursuit of medicine within the constraints of federal, state, and local laws.

**73. What authority, if any, does FDA have to regulate any aspect of the practice of medicine?**

As I understand it, states generally regulate the practice of individual physicians. I know that FDA has authority under the Federal Food, Drug, and Cosmetic Act, for example, to establish restrictions on the sale, distribution, and labeling of drugs and medical devices. In addition, I believe FDA has authority under the Mammography Quality Standards Act of 1992 to regulate certain aspects of the practice of mammography, including initial and continuing qualifications of medical personnel who provide mammography services.

**74. FDAMA requires the FDA to only review the intended use proposed in labeling for a device undergoing a premarket notification review except if there is a reasonable likelihood that the device will be used for an off label use and such use could cause harm. If the Agency makes these findings, then the ODE director must promptly meet with the 510(k) submitter to discuss FDA's concerns and what limitations FDA intends to impose on product labeling. How can this provision work without delaying the clearance of a device?**

I understand that CDRH has developed a guidance document that outlines the procedures it intends to follow in implementing this provision of FDAMA. Pursuant to the CDRH's procedures, substantial equivalence decisions ordinarily will not be delayed. In situations where the CDRH has a concern about an off label use that could be harmful, the Agency would take no more than the 10 days provided by the statute following a discussion of its concerns with the sponsor.

**75. How often do you expect the Agency will require limitations on the label of a product due to potential off-label uses that could cause harm? Please provide a rough estimate of the number of times a year this authority is likely to be invoked based on the Agency's experience with previous applications and your views on the frequency with which FDA should use this authority.**

I have been advised that off label concerns have not been a frequent impediment to devices getting marketing authorization from FDA. Moreover, I understand that the criteria under FDAMA for imposing limitations in labeling are sufficiently rigorous so that the Agency believes that it will occur infrequently.

**76. FDAMA requires FDA to only request the "least burdensome" information necessary to show that two different device technologies are substantially equivalent. What does "least burdensome" information in this context mean to you?**

I would construe the term "least burdensome" to mean the minimal amount of information that demonstrates substantial equivalence. In some instances, least burdensome may mean relying strictly on comparisons of descriptive data, e.g., comparing device specifications. The least burdensome way of showing equivalence will vary depending on the differences between devices and the public health consequences of those differences.

**77. How would you educate reviewers about the concept of "least burdensome" information in the 510(k) context?**

I understand that CDRH is in the process of implementing a number of changes in the 510(k) program that should help ODE reviewers develop an appreciation for the importance of identifying the least burdensome path to market. Whether it is relying on "declarations of conformity" to voluntary standards or information generated by design controls, the alternatives that CDRH has provided for demonstrating substantial equivalence through "The New 510(k) Paradigm" should help identify the least burdensome path to substantial equivalence. I believe that CDRH should monitor the impact of the changes that recently have been made in the 510(k) area and determine whether additional steps need to be taken to identify the appropriate level of regulation for devices subject to section 510(k).

**78. In your opinion should a manufacturer of a laser intended for ablation of prostatic tissue be able to rely on a laser intended for ablation of urinary tract tissue as a predicate to demonstrate substantial equivalence?**

While it would be inappropriate for me to comment on questions relating to the clearance of individual devices, I understand that the Agency has issued a draft guidance for industry which identifies the general principles that FDA will consider in determining when a specific indication for use is or is not reasonably included within a general indication for use of a medical device in accordance with FDAMA. I am told that the Agency has reviewed the comments it has received and intends to issue a final guidance.

**79. When a device is intended for a general use, and documentation demonstrates the device's use in numerous specific applications within the general use, do you believe FDA should permit the general use device to be a predicate device for the same or similar devices labeled for the specific uses set forth in the literature?**

If I am not mistaken, I believe the specific question being raised here is whether or not a sponsor can use published literature to support a claim for a specific use for a device previously cleared for market with a general use. I understand this issue is addressed in the May 20, 1998 "Guidance for Industry - Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review." Basically, my understanding is that while most product applications are supported by the original sponsor data, reports in the medical literature may sometimes be the vehicle to establish the existence of valid scientific evidence.

**80. What use do you see for standards in the premarket notification review process?**

I believe that standards can play an important role in the assessment of medical device technologies, both in the 510(k) process and in other areas. I know that FDAMA permits FDA to recognize consensus standards and to accept a declaration of conformity to those standards as a way to meet some or all of the data requirements in a 510(k) submission. I understand that CDRH has recognized 174 standards to date, with many more presently under review. FDA expects that the reliance on consensus standards will expedite the clearance of premarket notifications.

**81. FDAMA permits persons who choose to rely on standards that FDA recognizes to declare conformance to such a standard to satisfy a portion or all of a substantial equivalence requirement. FDA has authority to request any data upon which a declaration of conformance is made. Under what circumstances should FDA request the data supporting such a declaration outside of the facility inspection process?**

I believe the Agency should monitor manufacturers' adherence to standards during routine

inspections as well as when the Agency has a reason to be concerned that a particular device does not, or cannot, conform to a standard for which a manufacturer has declared conformity. FDA's concern might result from inconsistencies within a document, scientific reports casting doubt on a declaration of conformity, competitor complaints, or other sources.

**82. How can FDA's reliance on recognized standards and declarations of conformance save Agency resources and benefit the public health?**

FDA spends considerable time reviewing test methods and data during the premarket evaluation of devices. The use of standards, even on a voluntary basis, should reduce the time and effort that CDRH reviewers spend assessing device performance. The concept of a "declaration of conformity" to a standard and the Agency's reliance on such a declaration in lieu of reviewing the underlying methods and/or data should have a significant impact on all premarket device evaluations, whether it is the 510(k) program, the IDE program, or the PMA program.

**83. How can FDA promote harmonization of international regulatory requirements through the recognition of standards?**

There has been a trend toward promoting harmonization of regulatory requirements among nations through the development and acceptance of harmonized standards. The use of standards provides a good foundation for the harmonization of international regulatory requirements because such standards are arrived at through consensus among scientists and engineers in industry, government, and the professions. By actively participating in international standards development, FDA can help to ensure that appropriate regulatory controls are incorporated in those standards. In this way, FDA can help promote congruent requirements by those countries using a standards based regulatory system. I understand that, since the passage of FDAMA, the Agency already has recognized 174 standards that may be relied upon to meet FDA regulatory requirements.

**84. FDAMA requires FDA to meet with companies interested in submitting PMAs at least twice before the submission of an application. The first meeting is to result in an Agency determination of the least burdensome type of valid scientific evidence necessary to establish device effectiveness. In your opinion what is the range of types of valid scientific evidence necessary to demonstrate that devices are effective? Please provide examples of devices for each type of evidence you believe would support a device effectiveness finding.**

Valid scientific evidence necessary to demonstrate that a device is effective may vary depending on the type of device. In some cases where the type of device and the medical condition are well

understood and product performance predictably measures a clinical effect, preclinical laboratory and animal data may be sufficient to demonstrate that a specific device is effective. Data on a series of patients using the device may be sufficient where the natural history of the medical condition being treated is well known and the measurement of success is very objective, outside of the control of the patient and free of potential for bias in measurement. An example of this would be a non-invasive weight control device. Non-randomized concurrent or even a historical control might be sufficient to demonstrate effectiveness where a great deal already is known about how similar devices perform, and it can be demonstrated that the control population is very similar to the test population. This type of study might be appropriate for intraocular lenses. Where the disease course is variable or not well defined, where the effect size is small or where a comparison to some other treatment of similar effectiveness is being made, a randomized control trial may be necessary. Devices such as implantable defibrillators are usually assessed in this way.

**85. What differences are there between drug and device requirements in establishing effectiveness?**

I believe that the "reasonable assurance" standard applied to devices is generally more flexible than the "substantial evidence" standard applied to drugs. Substantial evidence to support drug effectiveness is defined as "adequate and well-controlled investigations," while "valid scientific evidence" other than evidence derived from well controlled investigations may be used to support device effectiveness. I understand that FDAMA clarified that a single clinical investigation may be sufficient to establish the effectiveness of a device, and that, in some circumstances, substantial evidence for drugs may consist of data from one adequate and well-controlled study, and confirmatory evidence.

**86. In your opinion, is there value in early meetings between future PMA applicants and FDA to obtain a FDA determination of the valid scientific evidence necessary to support device effectiveness?**

I believe that there is always value in communication, particularly when it is undertaken at a stage where it can guide the parties in making appropriate decisions. Early consultation between a prospective PMA applicant and FDA can help to define the critical issues that must be addressed in the PMA and define the type of trials that appear necessary, and to avoid unnecessary effort. Early discussion of these and other concerns can contribute to a better working relationship and avoid delays in making beneficial new devices available to the public.

**87. An FDA determination of the least burdensome type of valid scientific evidence**

necessary to show effectiveness is binding unless "contrary to the public health." In this context, what does "contrary to the public health" mean to you?

In this context, I believe it would be contrary to the public health to authorize the marketing of a product on the basis of data that failed to establish a reasonable assurance of safety and effectiveness. I would anticipate that such a failure would occur principally when new scientific evidence emerged subsequent to the original determination about what evidence would be necessary to support marketing approval. This could occur where the specified scientific evidence failed to address an element necessary to the finding of reasonable assurance of safety and effectiveness.

**88. FDAMA requires FDA to meet with future PMA applicants, or persons intending to market implants, and review proposed investigational plans or parts thereof in pre-IDE meetings. From this type of meeting, an agreement between the Agency and an applicant is supposed to emerge. If you become Commissioner, what principles would you establish with your managers and staff to ensure that fair and reasonable scientifically based agreements are reached instead of agreements forced on companies by virtue of FDA's overwhelming leverage in the premarket phase?**

I believe strongly that staff should enter "agreement meetings" with prospective PMA applicants with the goal of reaching a reasonable agreement based on the law and solid science. If I am confirmed, I would encourage feedback from companies that participate in agreement meetings with the Agency and would expect CDRH management to monitor how this particular provision of FDAMA is being applied. In those cases where an applicant believes that the Agency is being unreasonable or overly demanding, I would expect the CDRH to review the situation to ensure the applicant has been dealt with fairly. In addition, I understand that CDRH has established mechanisms and issued guidance to facilitate review of scientific and administrative disputes in appropriate circumstances.

**89. Under FDAMA, any agreement reached between the FDA and an applicant is binding unless there is a "substantial scientific issue essential to determining the safety and effectiveness of [a] device." What does this phrase mean to you?**

I would expect this to be an infrequent situation that would arise primarily when there is new information about a disease or treatment that could significantly affect a finding of safety or effectiveness.

**90. If FDA bound itself to an agreement regarding an investigational plan for demonstrating that a device is safe and effective, and an advisory panel disagreed with the agreed to approach, would that necessitate FDA's abandonment of the agreement?**

My understanding is that the criteria to nullify a binding agreement are described in FDAMA and in the FDAMA Early Collaboration Meetings Guidance for Industry and CDRH Staff. I understand that such an agreement can only change when a substantial scientific issue essential to determining the safety or effectiveness of the device has been identified, and only following an opportunity for the sponsor to meet with FDA to discuss the scientific issue involved. If an advisory panel disagreed with an investigation plan, I think it would be appropriate for FDA to review the panel's recommendation to determine whether the basis for that disagreement meet the test to overturn an agreement.

**91. In the PMA context, what does the phrase "least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval" mean to you?**

I interpret the least burdensome appropriate means of evaluating device effectiveness for PMA approval to mean that, after considering the nature of the device and its proposed conditions of use, the Agency requests only the type and extent of data that are needed to establish a reasonable assurance that the device is effective.

**92. The FD&C Act requires well-controlled clinical investigations "where appropriate" to demonstrate effectiveness. Can you think of situations where the FDA could find a PMA device effective based on well controlled investigations, but not well controlled clinical investigations?**

I believe that there are situations where FDA could rely on such investigations to support a PMA. I understand that the Center has approved PMA applications based on "well controlled investigations" that were based on animal, bench, or laboratory data rather than clinical data. For example, as I explained previously, if the type of device and the medical condition are well understood, and product performance predictably measures a clinical effect, preclinical laboratory and animal data may be sufficient.

**93. As a general rule, do you believe two well controlled studies are necessary to demonstrate device effectiveness?**

No. In fact, I understand that CDRH has seldom asked for more than one study.

**94. How necessary is it to have a masked control in a device effectiveness study?**

Masked controls serve to minimize placebo effect in the experimental group and to reduce evaluator bias. Masking can involve blinding the subject to the actual intervention (single mask) or can mean that neither the subject nor the treatment staff know who is receiving the control or experimental therapy (double mask). While usually part of the most rigorous study design, masking may not be necessary if the study has clearly defined and objective endpoints.

**95. In the typical drug study double masking is required to demonstrate effectiveness. As a general proposition, what type of study(ies) are necessary to demonstrate device effectiveness?**

Some studies need masking, and others do not. As I said before, masking is usually less important where the effect of an intervention is evaluated by use of an objective endpoint. CDRH has considerable experience with study designs that use other comparability methods. I am told that in a recent analysis of clinical trial designs for PMAs, only about half were randomized, controlled clinical trials. Of these, approximately half were masked, and only a small number of these were double masked.

**96. In your opinion, should the FDA be bound to review only the conditions of use proposed in a PMA? If not, why?**

FDAMA directs FDA to rely on the conditions of use included in the proposed labeling as the basis for determining whether there is a reasonable assurance of safety and effectiveness, if the proposed labeling is neither false nor misleading. My understanding is that this is CDRH's current practice.

**97. What role do you foresee for the use of product development protocols (PDPs) instead of PMAs? Why? What benefits can use of the PDP provide to the public?**

The product development protocol, or PDP, provides an alternative to the IDE / PMA processes for class III devices subject to premarket approval. I believe the PDP model offers an extremely

flexible framework for the development of new medical devices. It provides a streamlined method through which an applicant and FDA can reach agreement concerning the criteria and data necessary to ensure the safety and effectiveness of a class III device *prior* to the start of preclinical and clinical trials. This approach can provide more certainty in the device development process, and may encourage the development of innovative devices. CDRH expects use of the PDP authority to increase as the Center and industry gain experience with the process and learn which types of devices are best suited for this approach.

**98. FDAMA permits data from IDEs for earlier approved PMA devices to be used to demonstrate the safety or effectiveness of newer PMA devices if the data are relevant to the device under review and legally available to an applicant. Do you believe that FDA reviewers should be encouraged to rely on earlier safety and effectiveness data from approved devices to approve newer devices after a showing of equivalence, established through bench and animal data and not clinical data, between the approved PMA device and a newer one?**

Yes, I would encourage FDA reviewers to rely on information contained in approved PMAs when it is relevant and available to the evaluation of the newer device.

**99. FDAMA requires FDA to meet with an applicant 100 days after receipt of a filed PMA upon the applicant's request. If FDA finds at the 100 day meeting that deficiencies in the PMA will result in a major amendment and the restarting of the 180 day review clock, does the law require that the Agency provide applicants another 100 day meeting when that time comes in a second or subsequent review cycle?**

If I am confirmed, good communication will be -- as I believe it is now for CDRH staff -- a critical and integral aspect of the PMA review process. CDRH has in place, and continues to use, many procedures for early and continued communication with the applicant. These include pre-PMA and IDE submissions, interactive labeling reviews, and video and teleconferencing to discuss outstanding deficiencies. I am not aware that FDAMA addressed Day-100 meetings for subsequent review cycles and the Agency has not provided for such meetings in guidance on this provision. It is important to note, however, that following the Day-100 meeting, CDRH will continue to promptly communicate any additional information in order to achieve final action on the PMA. CDRH also is committed to providing a status letter by Day-90 for all original PMA applications, whether or not a Day-100 meeting is requested, in an effort to ensure early communication and resolution of outstanding issues.

**100. Do you consider a PMA approval of a device to create specific requirements for that device? If so, why? If not, why?**

It is my understanding that a PMA approval of a device may create specific requirements for that device. For example, some PMA approvals require that certain labeling or certain cautionary statements accompany the device. I believe that those are specific requirements for that device. Similarly, PMA approvals that contain specific design requirements, for example a requirement that a certain size wire be used, also create specific requirements for the approved device.

**101. FDAMA created a notification process for manufacturing changes that affect the safety and effectiveness of PMA approved devices. FDA can permit changes by not acting on the 30 day notice (or accepting the notice) or the Agency can request a 135 PMA supplement. Under what circumstances would you require a PMA supplement for manufacturing changes? Why?**

It is my understanding that the Agency intends to require a 135-day supplement primarily in those situations when the information in a change notice presents unique or complex issues with which CDRH has had no previous experience. For example, changes in a sterilization method generally would be reviewed under a 30-day notice provision. However, if the sterilization change was to a method FDA had not seen before for this device type, it could require further review under a 135-day supplement. The details of this approach are set forth in a guidance that was issued by the Agency, and I support this approach.

**102. When a manufacturer makes an incremental modification to a PMA approved device, what type of valid scientific evidence would you require from the holder of the PMA to demonstrate safety and effectiveness?**

It is my understanding that the Agency's policy is that if an incremental modification has no effect on the device's safety and effectiveness, then the manufacturer can provide a simple summary of the change in the next annual report and need not submit additional scientific evidence. If the modification affects the device's safety or effectiveness, supplemental valid scientific evidence is required. The type and extent of the information needed will depend on the nature of the change, and the type of device involved. This evidence may include additional laboratory, pre-clinical, or clinical evidence, depending upon what is needed to support the change.

**103. What suggestions do you have to improve the PMA supplement review process?**

I think that it is important to assess the effectiveness of the process improvements that CDRH has been implementing. For example, real-time review of certain supplements and the new guidance on modifications and PMA supplement requirements hold considerable promise for process improvement. In addition, FDAMA made a number of changes that are being put into effect. Once CDRH has had the opportunity to implement these steps, we will be able to assess the merit of further potential changes.

**104. Should panels be briefed by FDA staff about PMAs or other matters subject to panel review before meetings? If so, what pre-meeting opportunity, if any, should applicants have to receive the information communicated to a panel?**

Yes. Before individual panel meetings, advisory panel members are sent pre-meeting "panel packages" to assist the members in preparing for the meeting. These packages primarily include the data obtained from the clinical trials and labeling for the product. I understand that under FDAMA, FDA is providing to any person whose device is specifically the subject of a classification panel review, the same access to data and information about the device as that submitted to a classification panel. The Agency's implementation of this new requirement is described in the "Guidance on Amended Procedures for Advisory Panel Meetings."

**105. FDAMA reforms to the advisory panel process require that PMA applicants receive "adequate time" to respond to "differing views." In your opinion what do these terms mean? What procedures should be in place to ensure that applicants have an opportunity to make effective responses to differing views?**

I understand that in the "Guidance on Amended Procedures for Advisory Panel Meetings", the Agency describes how this section of the Act is being implemented. The sponsor of a PMA and the Agency are given an equal amount of time to address the panel, with each presentation generally allotted 60 minutes. If a sponsor makes a request for more time to present its application, the Agency grants such requests as time permits.

However, it is my understanding and experience with advisory panel meetings that one-hour is normally sufficient to clearly present a device and supporting data. It is important in planning an advisory panel meeting agenda to ensure that the panel will have sufficient time to discuss the issues and provide advice to the Agency. Following the initial presentations, the sponsor and FDA each are provided equal opportunities to clarify issues that arise during discussions.

**106. What contributions should a panel make to a PMA review? What weight should panel decisions be given by the Agency?**

The advisory panels provide independent advice and recommendations to the Agency on scientific and technical matters, including clinical expertise related to the development and evaluation of medical devices. I believe that the clinical and academic experts that serve as panel members provide FDA with a perspective that complements the in-house scientific review staff. Consequently, the Agency has given panel advice great weight in making FDA's final determinations, but it is important to note that the advisory panels make recommendations to the Agency not decisions, and that these recommendations are only part of the entire review process.

**107. When scientific controversies exist between an applicant and FDA what mechanism would you use to resolve them?**

My understanding is that FDA's regulations provide applicants with several mechanisms to resolve scientific controversies, including informal appeals through the supervisory chain, consideration by an advisory committee, and more formal administrative review. FDA encourages use of informal mechanisms, particularly review through the supervisory chain, because they ordinarily provide quick and effective resolution of controversies.

**108. In your opinion, does FDA's longstanding general supervisory review regulation provide a specific means to appeal scientific controversies, thus largely mooted this FDAMA provision?**

It is my understanding that these provisions are complementary and, taken as a whole, these mechanisms provide a comprehensive and effective means of resolving scientific controversies.

**109. What suggestions do you have to strengthening the FDA's process for resolving scientific disputes?**

The most important step FDA can take is to better publicize its appeals mechanisms. We need to make clear that FDA is receptive to appeals, that we have a wide range of appeals mechanisms available, that appeals will be dealt with as quickly as is possible, and that parties that bring a dispute to FDA will be treated fairly and need not fear reprisal. I understand that FDA has begun to take steps to make this information more widely available.

**110. What is your view about the scope of a device preemption under section 521 of the FD&C Act?**

Section 521 addresses the general issue of when the Agency's regulation of devices preempts state laws. Recently the issue of how this section affects state tort litigation has become controversial. In fact, FDA recently proposed and then withdrew a proposed regulation addressing this issue. If I am confirmed, I would expect to review this matter closely.

**111. In your opinion, should a lay judge and jury be permitted to find a FDA approved label for a PMA device inadequate and, thus, the basis for a finding of negligence by the device's manufacturer?**

I understand your question generally to be whether an FDA approval preempts or forecloses a finding of negligence under state tort law. The issue of federal preemption of state tort law is a complex area that involves a broad range of governmental and private concerns. For these and other reasons, FDA recently withdrew a proposed regulation that was relevant to this issue, and I certainly support that action.

**112. Generally, under what circumstances should FDA issue warning letters? If a company responds to a FDA inspection which documents manufacturing deviations, and the Agency finds the response acceptable, do you think the Agency should still issue a warning letter?**

It is my understanding that it is FDA's policy to issue warning letters only for those violations that may actually lead to enforcement action if not promptly and adequately corrected. It is my opinion that in the case where a firm responds to an inspection finding and the Agency deems the response to be adequate, a warning letter usually is not warranted. However, a final decision on whether to issue a warning letter should depend on a variety of factors, including the compliance history of the firm and the speed with which the firm intends to correct the violation.

**113. Under what types of circumstances should FDA use publicity to achieve a consumer protection result?**

I believe that FDA should use publicity wisely to provide the American people with critical, useful public health information in an accurate and timely manner. I think that some circumstances in which publicity is effective are announcements of recently approved products that may provide significant new clinical benefits and options to patients; warnings about adulterated or misbranded foods, drugs and devices that are being withdrawn or recalled from

the market because they may pose serious or life-threatening health risks; and continuing education efforts such as FDA's Office of Women's Health "Use Medicines Wisely" campaign.

**114. What role should guidance documents, policy statements and points to consider play in FDA's implementation of its statutory policy?**

I understand that FDAMA and FDA's Good Guidance Practices, which were published in the Federal Register on February 27, 1997, treat policy statements and points to consider as guidance documents. Guidance documents clarify statutory and regulatory requirements and explain how industry may comply with those requirements. They also provide specific review and enforcement approaches to help ensure that FDA's employees implement the Agency's mandate in an effective, fair, and consistent manner. Guidance documents do not establish legally enforceable rights or responsibilities and are not legally binding on the public or the Agency.

**115. If you were Commissioner, what communications would you allow between the Agency and regulated persons prior to the publication of a guidance document? A regulation?**

If confirmed, I will work diligently to continue to improve the communication between the Agency and the regulated industry. It goes without saying that communications between the Agency and any party prior to publication of a guidance document or regulation must be consistent with the Administrative Procedure Act, the Federal Advisory Committee Act, the Agency's regulations, and the Agency's need to issue guidance documents and regulations in a timely manner. I understand that the Agency's procedures are set forth in its Good Guidance Practices and regulations, which recognizes the importance of full and fair opportunity for discussion.

**116. In your opinion, do you believe the best means of implementing a law is through guidance documents? If so, why? If not, why?**

Issuance of guidance documents is one important tool used by the Agency in implementing its statutory obligations. Guidance documents also serve as an important mechanism for informing industry about the Agency's interpretation of the law. As FDA stated in publishing its Good Guidance Practices, guidance documents can be helpful in clarifying statutory and regulatory requirements. Whether such additional explanation is necessary or important will vary depending on the statutory provision being implemented.

**117. What is your opinion about the FDA's proposed, and recently withdrawn, regulation on preemption that was published in the *Federal Register* in December 12, 1997?**

I was not involved in the decision to withdraw the regulation. But based on what I know, FDA made the right decision to withdraw the rule. I believe the withdrawal will allow the Agency to consult with all affected parties in assessing preemption.

**118. In complying with FDAMA's requirements to devise a plan to, among other things, meet statutory time frames, how would you ensure that FDA complies with the 180 day PMA review and 90 day 510(k) review requirements?**

Under FDAMA, FDA was directed to prepare and publish an Agency Plan designed to bring the Agency into compliance with its obligations under the Act, and to identify such additional authorities, resources or other measures that are necessary to achieve full compliance. As part of this effort, I understand FDA is in the process of meeting with its stakeholders to develop objectives and mechanisms to achieve this goal.

#### Management Issues

**119. Until enactment of FDAMA, FDA operated without a statutorily defined mission statement. In addition to providing your thoughts on the Agency's current mission statement, please describe any revisions or additions that you believe are necessary.**

I concur with the mission statement included in FDAMA, which I understand was part of a several year process that focused on the purpose and performance of this Agency. I do not have specific revisions or additions to the mission statement to suggest at this time.

**120. In terms of resource prioritization, how would you determine FDA's staffing and funding needs with respect to each of the Agency's centers, and the Office of the Commissioner? Please address each category, i.e., CDRH, Office of the Commissioner, separately.**

If I am confirmed, I intend to focus on setting resource priorities among the various organizational entities as well as among various Agency activities. It is difficult to answer this question without the detailed review that I plan to undertake. I would be pleased to share my thoughts on this question with the Committee once I have had the opportunity to assess how existing priorities have been set and any changes that I believe may be necessary to meet the Agency's critical missions.

**121. The Occupational Safety and Health Administration (OSHA) has indicated its intention to promulgate draft rules pertaining to natural rubber latex gloves (which can cause allergies) and unshielded syringes (which can cause accidental needle sticks). Regulation and oversight of each medical device unquestionably falls under the jurisdiction of the FDA, not OSHA. In an effort to eliminate the unnecessary duplication of responsibilities between two agencies, do you believe that in general the FDA should claim exclusive jurisdiction over federal matters that clearly fall within its regulatory boundaries?**

This is a difficult question that I would need to review in more detail. It does seem that FDA's statutory authority to assure that medical devices are safe and effective for their intended use may not include all of the occupational safety and health responsibilities of OSHA. At a minimum, in those cases where the agencies have overlapping responsibility, as in the two examples cited of natural rubber latex gloves and unshielded syringes, the agencies should work together to coordinate their efforts so that government can speak with one voice and not cause confusion for the public or for regulated industry.

**122. With regard to the regulation and oversight of natural rubber latex gloves and unshielded syringes, do you believe that the FDA should assert exclusive jurisdiction on this matter?**

Please see response to number 121 above.

**123. Early this year, the public was confronted with breakthroughs in cloning techniques and the theoretical possibility of cloning a human being. The following questions are with regard to FDA's role in this area and your views:**

**(a) Under what conditions would you consider it acceptable to clone a human being?**

I support federal legislation that would make it illegal for anyone to create a human being through cloning. In banning this particular research, however, we must be very careful not to prohibit important biomedical research that holds the potential cures for serious and life-threatening diseases, including cancer, diabetes and spinal cord injuries. I know that there are different legislative proposals before Congress on this issue, but I have not reviewed them and thus should not comment on them at this time. Any proposal in this area would have to be carefully crafted.

**(b) How would you define a human being in this context?**

A cloned human being would be a person produced through a cellular copy of a pre-existing human being.

**(c) What is your view of the extent of FDA's jurisdiction over the cloning of a human being?**

My understanding is that the Agency has taken the position that it has the authority to regulate the conduct of research to clone a human being. The Agency's view is that such research would involve highly manipulated human tissue, and as such, would be subject to IND requirements. FDA stated that there were a variety of safety questions that would need to be answered before the agency would allow such research to proceed, and that researchers would need to address questions related to informed consent. I look forward to reviewing carefully FDA's policy if I am confirmed by the Senate.

**(d) What approach to the regulation of human germ line engineering should the FDA take?**

I believe FDA's primary role is to evaluate the safety and effectiveness of emerging medical technologies and potential therapies. My understanding is that any research to engineer a human being through manipulation of the human germ line would fall under FDA jurisdiction and would require an IND, including Institutional Review Board (IRB) review and informed consent.

**(e) Do you think FDA has a role in regulating in vitro fertilization? Please explain.**

I am aware that in February 1997 FDA announced a comprehensive plan to regulate tissue and cell based therapies. FDA's approach to regulating these therapies is tier-based according to risk. Reproductive tissues are part of that plan. In addition, FDA has issued a rule that regulates the devices used for in-vitro fertilization, such as media culture dishes as well as instruments used for implantation.

**(f) With regard to a human embryo produced by somatic cell nuclear transfer, FDA has asserted authority to regulate this entity. Would you propose to regulate this entity as a medical device, drug, biologic, combination product, cell, or tissue? Under what authority in the Act would FDA make this decision? Please also answer the immediately preceding two questions with regard to a transgenic embryo.**

I understand that FDA has concluded that it has jurisdiction over somatic cell clones and cloning activities based on the biological products and communicable disease provisions of the PHS Act and the drug and device provisions of the FD&C Act. The specific product classification would depend on a number of factors, including the product application. I would

assume that these statutory authorities also would apply in the transgenic area.

**124. Do you believe that the Agency can meet the performance goals specified in the reauthorized Prescription Drug User Fee Act? If not, why not, and what would you do to ensure that the PDUFA II performance goals are met.**

Yes. The Agency is confident it can meet the PDUFA II performance goals and I am committed to achieving these goals.

**125. What initiatives would you take to further reduce total drug development time?**

I recognize that total drug development time is influenced by a number of factors. FDAMA embodies specific performance goals and procedures as part of the reauthorization of PDUFA II, that are expected to reduce drug development time. These efforts will expedite getting drugs to patients without compromising the safety and effectiveness standards that patients and practitioners clearly expect.

Under PDUFA I, the time from submission of marketing application to completion of review has been reduced substantially. I believe that the key to further reduction of drug development times lies in shortening the period between the filing of an IND and an application, and in improving the quality and reviewability of data in the application. We need to continue to: to improve communications with sponsors regarding FDA requirements and FDA assessment of plans and data during the developmental phase; better target research to identify and address problem areas in drug development and review; and promote international harmonization of requirements for data and documentation.

**126. Do you think Agency personnel should carry out research unrelated to its mission; i.e., basic research? What about mission-directed research, i.e., research that improves the Agency's ability to carry out its regulatory function?**

As I stated in response to an earlier question, research conducted at FDA must be relevant to the mission of the Agency and contribute to the scientific basis for the Agency's decisions. Often FDA research provides data to support regulatory decisions and policies that are not available from any other source. At present, only FDA can conduct research using the large database of information submitted to it by industry one application at a time.

To stay abreast of newly developing technologies and regulatory issues raised by a rapidly changing array of new products, it is important for FDA scientists to be well grounded in a

continuum of research from basic and applied to clinical investigations. A full appreciation of basic research often is necessary to support the critical decisions to approve a new product, retain a previously approved product, or remove a product from the market. Providing opportunities to stay involved in research is also a means to recruit and retain some of the most able regulatory reviewers. Without such scientific talent, the Agency would risk having its decision making compromised.

**127. What will you do to ensure that new initiatives, like food safety and tobacco, do not draw resources away from other FDA priorities?**

My understanding is that the Administration has included specific funds in its budget request to implement the new initiatives in food safety and tobacco without drawing resources away from other FDA programs. If these funds are not available, the Agency's priorities would have to be reassessed within the context of the funding amounts provided. If I am confirmed, I will work with the Administration and the Congress to ensure that sufficient resources are available for full and timely implementation of FDAMA and other key priorities.

**128. Do you support the "waterline" concept for FDA appropriations and user fee collection which is intended to ensure that PDUFA fees are additive to and not a substitute for appropriations to FDA?**

As I indicated in response to a previous question, historically, user fees have succeeded only when they resulted from consensus among Congress, the Agency, industry, and consumers. The original enactment and recent reauthorization of PDUFA, for example, were the product of the collaborative effort among all of these groups. PDUFA includes provisions to ensure that the fees paid by industry fund improvements in the program. I believe such protections were critical to the consensus necessary for PDUFA's enactment.

**(a) Will you actively advocate preservation of the waterline and protect the Agency's budget?**

I would strongly advocate preservation of the Agency's overall budget level, and the notion that PDUFA fees are additive to appropriations.

**129. What will the role be of the new "Chief Scientific Officer" at FDA? How will this position be funded?**

To meet the challenge of the new biology and technological innovations of the 21st century, the Agency needs to be at full strength in its scientific base. It is my understanding that this position was created to address this important issue. If I am confirmed, I am fully committed to reviewing the science needs of the Agency and implementing steps to assure that the strong science remains the basis of the Agency's product review and policy decisionmaking.

**130. If confirmed as FDA Commissioner, what would you do to ensure that the progress made during the International Conference on Harmonization continues?**

I was pleased to note that FDAMA contains provisions in support of harmonization. The International Conference on Harmonization has been very successful in reaching consensus on more than 40 scientific guidelines for technical requirements for drugs. At the same time, the resource commitment is considerable, involving as it does senior level staff from CDER, CBER, and the Office of the Commissioner. I can assure you that, if confirmed, these efforts would have my support. Assuming that required resources remain available, I would expect FDA to continue to contribute to these harmonization efforts.

**131. Do you foresee an eventual harmonization of global regulatory systems to the point that mutual recognition of approvals is possible?**

Historically, nations have approached regulation of food, drugs, cosmetics, and medical devices from a variety of philosophical and statutory bases. Harmonization, or even equivalence, requires a common view of the objectives of regulation. That common vision among nations is closer for some FDA-regulated products than for others. The International Conference on Harmonization (a government and industry consortium among the U.S., Japan, and the EC) is an example of a harmonization exercise that was enabled by a common vision of what safety, quality, and effectiveness means for pharmaceuticals for human use. For medical devices, such a consensus has only begun to evolve. It does not seem likely that U.S. recognition of approvals by other countries will occur in the near future.

**132. Do you support mutual recognition of product approvals? If not, why not?**

First, I fully support FDA's participation in worldwide efforts to harmonize regulatory requirements. There is a great deal we can accomplish to the benefit of public health through harmonization of requirements for product testing and data submissions. As I discussed earlier, however, there are many complex issues and differences among regulatory systems that must be resolved before the mutual recognition of product approvals could be possible.

**133. Many federal agencies engage in formal and informal discussions with regulated industries and consumer groups, including regulatory negotiations ("reg-neg"), prior to publishing proposed regulations in the Federal Register. By contrast, FDA generally conducts only internal discussions before publishing proposed regulations in the Federal Register. Do you intend to adopt the "reg-neg" model, so that proposed regulations are more likely to reflect the consensus of affected constituencies?**

In my view, FDA should be open to having negotiated rulemaking as an appropriate alternative to traditional rulemaking. At the same time, I think that it is important to remember that negotiated rulemaking is but one form of consensual rulemaking. FDA traditionally has solicited public comment from all interested persons, including consumers, academia, health professionals, the regulated industry, and state and local governments. Before and during its rulemaking process, FDA often solicits public comment and provides various forums for such commentary. Public comments are received at public meetings, public workshops, consumer exchange meetings, interagency round tables, industry outreach meetings, and a number of service-oriented forums designed to assist small businesses, including the White House Small Business Forum. These procedures also can result in an open and public regulatory process.

**134. The FDA's ambiguity in funding requests and pattern of reprogramming funds without notice to Congress have raised serious concerns among members of the authorization and appropriations committees. Over the last three fiscal year cycles, the Senate Appropriations Committee instructed the FDA to provide concise budget reporting of the FDA's expenditures, however, gaps in the information reported by the FDA remain. Further, the FDA's practice of reprogramming funds, often times without sufficient reporting to Congress on the intended use of those funds, resulted in the House and Senate directive that FDA provide advance written notification to Congress of such reprogramming actions. One area where both reprogramming of funds and ambiguities in fund uses have occurred is the FDA's tobacco initiative. The Committee notes with interest that in its FY 1998 testimony before the Senate Agriculture Appropriations Subcommittee, the FDA gave no indication that it would ask for an additional \$100 million for its tobacco initiative in FY 1999. Rather, one of the selling points of the FDA's request was the relatively low cost of this activity. In light of the FDA's statement that its close coordination efforts with other federal agencies are "working effectively," what does the tripling of your Agency's funding for this activity pay for in FTEs, administration, state and local contracting, advertising, material purchases, etc.? How do those expenditures compare to budget management under SAMHSA's Synar Regulations, CDC's IMPACT program, and NCI's ASSIST program?**

I have been informed that the proposed increase for tobacco would enable the Agency to (1) enter into enforcement contracts with all 50 states to conduct inspections for retailer compliance, (2)

fund an expanded outreach effort to include state by state advertising directed to retailers that provides information concerning provisions of the FDA rule that affect retailers, and (3) review applications for new tobacco products and further evaluate and begin to implement regulatory controls for cigarettes and smokeless tobacco.

While I do not have similar figures for the other agencies, I have been provided with the following information concerning FTEs for FDA. Twenty-five FTEs are allocated to tobacco activity for FY 1998. Most of the people work on all aspects of the program, however, two are dedicated exclusively to outreach and eight are dedicated to enforcement. Twenty-five additional FTEs are sought for FY 1999.

**135. What impact has the use of executive orders for implementing FDA's tobacco rule had on the FDA's rising costs in this area? Without additional resources, what functions within the Agriculture Appropriations bill have the OMB identified as an offset to this \$66 million increase?**

As I mentioned earlier, while the Administration has issued executive memoranda in the tobacco area, I am not aware that they have been used to implement any aspect of FDA's tobacco rule. Therefore, it would appear that executive orders have had no effect on FDA's budget.

**136. Please supply all external and internal documents referencing the decision of the Agency to refrain from meeting or discussing FDAMA implementation issues prior to public dissemination of guidance documents, regulations, and other issuances designed to implement FDAMA. Does this policy extend to other non-FDAMA issues? What [is] your position with respect to this policy?**

I am unaware of any decision by FDA to refrain from meeting or discussing FDAMA implementation issues prior to public dissemination of guidance documents, regulations, and other issuances designed to implement FDAMA. I have been given to understand the Agency made a decision to rely, to the extent possible, on the processes that it has in place, namely notice and comment rulemaking and Good Guidance Practices. At the same time, it did recognize that there would be times when it would be important to meet with outside groups to hear their views on implementation issues and to discuss drafts of FDAMA documents that were made available to the public at large. Further, the Agency also has established public dockets for written comments related to specific FDAMA provisions and has specifically invited such comment. In addition, I am informed that the Agency already has held a number of public meetings to discuss FDAMA implementation.

**137. The Agency has received comments from industry and others on the guidances and Federal Register notices published to date. What are the Agency's plan's for responding to those comments? Please include anticipated time frames for responding. What is your position on this matter?**

My understanding is that pursuant to the Agency's Good Guidance Practices, the Agency will review all comments submitted on draft guidance documents, but in issuing the final guidance, will not specifically address each and every comment. The Agency will, however, make changes to the guidance document in response to comments, as appropriate. With respect to comments received on regulations, I understand that FDA will, pursuant to its procedures for notice and comment rulemaking, respond, in writing, to comments received on proposed regulations when it issues the final regulation consistent with the statutory deadlines. On balance, I think that FDA's approach is appropriate.

**138. On what grounds, if ever, should FDA overrule or ignore the recommendations of advisory committees on product approvals? If FDA is to overrule advisory committees, should there be a consistent set of policies guiding all Centers on the circumstances under which this is acceptable? Should FDA overrule unanimous or near-unanimous recommendations? If FDA on occasion is to overrule an advisory committee, should this be a rare event? How rare?**

FDA looks to advisory committees to provide expert and unbiased advice to the FDA on pending regulatory matters. Advisory committees are an exceptionally valuable part of the regulatory process. FDA usually follows the advice and recommendations of advisory committees, and I believe that this is appropriate. There are rare circumstances, however, when FDA may not follow the advice of a committee, for example, where additional information has become available, where the committee vote was extremely close, or where the advice of the committee would be inconsistent with laws, regulations, or science.

**139. Today most class II medical devices reach the market through substantial equivalence determinations. Do you believe there are other FDA determinations (other than performance standards) under the law, by which class II devices that are not exempt from premarket notification can reach the marketplace? If yes, what are they? If no, would you as Commissioner seek legislative change to enable FDA to clear class II devices for marketing by a means other than a substantial equivalence determination? Please describe any such proposal?**

If I understand the question correctly, I do not believe current law permits FDA to authorize marketing of non-exempt Class II devices by any means other than a determination of substantial

equivalence. The European community has adopted an approach that generally measures each product against essential criteria of safety and performance, particularly for devices of medium risk.

In FDAMA, Congress recognized the value of using conformance to standards as a basis for evaluating new products. It seems to me, however, that Congress chose not to alter the basic statutory scheme that brings most devices to market through a determination of substantial equivalence. While I have no specific proposal to change this approach, I would be willing to review and consider these issues carefully, if confirmed.

**140. FDAMA included reauthorization of the Prescription Drug User Fee Act. The reauthorization allows a higher percentage of FDA's drug review activities to be funded by industry user fees than did the 1992 law. In your view, should there be a ceiling on the percentage of the Agency's drug review function that is funded by industry? Please explain.**

I believe that the Prescription Drug User Fee Act has been highly beneficial to the drug industry, the public, and to the Agency and, most importantly, has accelerated patient access to new therapies. I believe it is appropriate to continue the current dialogue concerning the extent to which regulatory functions should be paid for by private interests. I do not, however, have in mind a specific percentage of the Agency's drug review function that appropriately could be funded by industry.

*Henney, FDA Commissioner File*

## COURTESY VISIT SCHEDULE FOR DR. JANE E. HENNEY

Updated on July 15, 1998 (5:02pm)

Time	Date	Phone	Contact	Location
	<b>WEDNESDAY, JULY 15</b>			
1:30	Meet in Rich's office	P 690-6786	Irene	416G
2:00	Senator Christopher Dodd (D-CT)	P 224-0342 (Adria)	SCH Adria Deasy STF Stephanie Foster, Jeanne Ireland	444 Russell (Note: w/o Senator Bingaman)
4:00 - 4:30	Senator Tim Hutchinson (R-AR)	P 224-2353 F 228-3973	SCH Heather Larrison STF Kate Hull	245 Dirksen
	<b>THURSDAY, JULY 16</b>			
9:30 am	Meet in Rich's office	690-7627	Irene	416G
10:00	Representative Sherrod Brown (D-OH)	P 225-3401 F 225-2266	SCH Ann-Marie Tirpak STF Kevin Brennan	328 Cannon
11:30	Senator Thad Cochran (R-MS)	P 224-5054 F 224-9450	SCH Doris Wagler STF Becky Davies, James Lofton	326 Russell
1:00	Representative Marcy Kaptur (D-OH)	P 224-4146 F 225-7711	SCH Norma Olsen STF Bobbi Jeancourt	2311 Rayburn
1:45	Representative Joe Skeen (R-NM)	P 225-2365 F 225-9599	SCH Linda Huitt STF Tim Sanders (sbct)	2302 Rayburn
2:30	Senator Ted Stevens (R-AK)	P 224-3004 F 224-2354	SCH Dilyn Henry STF Ryan Richards, Carol White	Capitol Office S-128
3:30	Senator Conrad Burns (R-MT)	P 224-8598	SCH Jackie Shin STF Paul Van Remortel	187 Dirksen
5:55	Flight			

# COURTESY VISIT SCHEDULE FOR DR. JANE E. HENNEY

Updated on July 15, 1998 (4:16pm)

	WEDNESDAY, JULY 22			
11:30	Senator Susan Collins (R-ME)	P 224-2523 F 224-2693	SCH Cynthia Bailey STF Priscilla Hanley	172 Russell
12:30	Senator Mike DeWine (R-OH)	P 224-2315 F 228-0412	SCH Julie Vincent STF Barry Dehlin (224-2962)	140 Russell
3:00	Senator Don Nickles (R-OK)	P 224-5754 F 224-3913	SCH Leslie Strubee STF Scott Whitaker	Capitol Ofc S-208
Time: TBA	Rep. Dingell (D-MI)	P 225-4071 F 226-0371	SCH Debbie Arcaute STF John Ford	2328 Rayburn

*Toly*  
**DRAFT**

## Draft Henney op-ed/WSJ

Mark Twain once quipped that a lie can travel around the world while the truth is still putting on its shoes. Right now, President Clinton's remarkable nominee for Commissioner of the Food and Drug Administration -- Dr. Jane Henney -- is pending before the Senate. The FDA needs her right away. It is crucial to correct any distortions before they get ahead of the facts and delay Dr. Henney's confirmation.

So I must take serious personal and professional exception to Henry Miller's portrait of Dr. Henney in his recent *Wall Street Journal* op-ed, "The Wrong Choice for the FDA." I should know. I served at the FDA with both Dr. Henney and Mr. Miller.

First, the facts: Dr. Henney is a nationally recognized leader in public health, a skilled manager, a dedicated reformer, a natural consensus builder and a respected scientist. As a former FDA Deputy Commissioner, she helped modernize the FDA, cut red tape and built a reputation for working closely with consumers, physicians and industry to protect public health.

It is no wonder Dr. Henney's supporters include so many leading providers and defenders of public health, such as the American Medical Association, the American Cancer Society, and the American Dental Association. Count also several leading industries among her endorsers -- the National Association of Chain Drug Stores, the Nonprescription Drug Manufacturers Association, and Pfizer, Inc. Her supporters also include Margaret Heckler, Otis Bowen and Louis Sullivan, U.S. Secretaries of Health and Human Services under Presidents Bush and Reagan. They should know. Dr. Henney worked for them.

From her record and reputation, Dr. Henney is the perfect choice to lead the FDA. Perhaps that explains why forces that favor a weak FDA have little choice but to ignore or stretch the facts.

Take Miller's criticism of FDA's drug approval process, which he calls "intrusive, damn-the-expenses government." Industry calls it a success. Thanks to better management and an innovative user-fee program that Dr. Henney helped to develop, FDA has cut drug review times in half. FDA now reviews all important new drugs within six months, and all others within 12 months. FDA now approves drugs at a pace comparable to that in other developed countries -- and for some important medicines, more quickly -- but under the highest scientific and safety standards in the world.

Due in part of Dr. Henney's past leadership, these drug review reform efforts are a stellar example of good government. That's why these reforms earned FDA the prestigious "Innovations in American Government Program" award, presented by the Ford Foundation, Harvard University's Kennedy School of Government, and the private Council for Excellence in Government. FDA was one of only 10 government programs honored, and one of only two in the federal government.

Miller's other claims about Dr. Henney simply fall apart under scrutiny. He claims while previously at the FDA she showed "no signs of perceiving the need for reform." But it was Dr. Henney who reorganized FDA's six centers on top of leading the drug review reforms. He charges her with a "politically correct" delay in approving BST, the bovine milk-production hormone. But the timetable was dictated by stringent review by scientists and a panel of outside experts. He also criticizes her for the FDA's 1992 moratorium on silicone breast implants. But she did not join the agency until *after the* decision to impose the moratorium was made.

Finally, I'm simply puzzled by Miller's claim that Dr. Henney was considered "unapproachable and intransigent" by colleagues and industry. Certainly that's not the collegial, cooperative leader I enjoyed working with at the FDA. Apparently, many others have had the same experience as me. The American Academy of Pediatrics calls her a "team player." The American Association of Colleges of Pharmacy says, "our educators have had the fortunate opportunity to work with her." The American Dental Association says its officials and staff "know her to be a thoughtful and fair public official who is willing to hear all sides of an issue before reaching a conclusion." These plaudits go on and on, painting a far more accurate portrait of Dr. Henney and her record than Miller's opinion piece.

There's an old saying in the legal profession: If the facts are against you, argue the law. If the law's against you, argue the facts. If both are against you, pound the table. Henry Miller op-ed doesn't have the facts or the record to back his claims. The Senate should not be distracted by table-pounding.

# DRAFT

## Draft Henney op-ed

When we reach into our medicine cabinets or shop the produce section at the supermarket, Americans don't have to think twice about whether our food and drugs are safe. That's because we can count on the federal Food and Drug Administration.

Of all the services we demand and deserve from government, few are more critical every day than safeguarding food, drugs and medical devices. The ultimate responsibility lies with the FDA Commissioner. And right now, the US Senate has the opportunity to put a terrific new Commissioner on the job, Dr. Jane Henney.

This is a challenging time for the nation's premier health and safety agency. Congress recently passed far-reaching FDA reform legislation that will require great skill and tenacity to implement. Changing medical technologies and more sophisticated and complex drugs and devices require that FDA consistently be at the top of its scientific game. It is more important than ever, for both industry and consumers alike, that we have a permanent FDA Commissioner in place to meet these challenges.

Leading the FDA requires a powerful resume. It takes a nationally recognized leader in public health; a skilled manager; a dedicated reformer; a natural consensus builder; and a respected, experienced scientist. The ideal candidate also needs FDA leadership experience, a record of speeding review of crucial products, and a reputation for working closely with industry to protect the public.

In other words, FDA needs an experienced leader for the 21st Century. Dr. Henney is the perfect choice.

On paper and in life, Dr. Henney has been more than a physician, academic leader and public health administrator. Hailing from an Indiana town of 512, she understands rural American life. After losing a hometown friend to breast cancer, she dedicated years to cancer research and care. Having steered the consolidation of the University of New Mexico health facilities, she knows how to streamline an organization for peak performance. Having served under Presidents Carter, Reagan, Bush and Clinton, Dr. Henney is a dedicated public servant known for making decisions based on good science and good policy. Having served as FDA Deputy Commissioner and helping reform the agency, Dr. Henney is a natural choice to lead the FDA.

Given Dr. Henney's superb qualifications, her confirmation would seem a sure thing. Indeed, many responsible leaders in the drug and medical device industries know that a strong leader like Dr. Henney can help shorten the time it takes to bring products to market without compromising public health and safety. But expect other forces that favor a weak FDA to use her nomination as leverage to undermine crucial FDA responsibilities, including protecting children from tobacco.

Certainly, the Senate confirmation process is an appropriate opportunity for Senators to learn more about a nominee's background and philosophy. But the FDA needs a strong Commissioner right away. The President has appointed a strong nominee

in Dr. Henney. The Senate should move quickly on her confirmation. The health and safety of our children and families are at stake.