Statement of Jim Guest, President and CEO
Consumers Union, the independent non-profit publisher of Consumer Reports
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before the
Senate Committee on Health, Education, Labor and Pensions
on S. 3807, the Enhancing Drug Safety and Innovation Act of 2006

Mr. Chairman and Members of the Committee:

Thank you for inviting Consumers Union, the non-profit publisher of *Consumer Reports*, to testify. I request that our full statement appear in the Record.

For 70 years Consumers Union has provided consumers with independent, unbiased information on vital public health issues. In the wake of the Vioxx and Paxil disasters, for example, where tens of thousands of Americans needlessly suffered, we've educated our more than 7 million subscribers, our more than 20 million readers, many hundreds of thousands of our citizen activists, on the need for stronger state and Federal drug safety laws. They seek action.

We applaud you, Mr. Chairman and Senator Kennedy, on S. 3807, a good first step toward meeting this need. It would bring greater balance to the process, save countless lives, and help restore public trust in our nation's drug safety system. Further, it does not impede another shared goal – rapid approval of safe, effective medications, particularly life-saving drugs.

We believe the Committee would miss a great opportunity for protecting consumer safety, however, if you don't strengthen the bill in several key areas:

- assuring quicker publication of the results of more clinical drug trials;
- enhancing the FDA's power to protect public health;
- restoring the science-based culture and morale of the FDA ;
- garnering more resources, especially for post-approval safety and information technology; and
- reforming the generic and biogeneric laws to bring lower-cost medicines to patients.

We will elaborate on each of these issues below, noting how the proposed bill addresses them, what the Institute of Medicine (IOM) and other research groups have concluded, and where Consumers Union recommends strengthening the bill.

1. Disclosure of clinical trials

Background:

There are several major issues in the clinical trial area: the registration and disclosure of trials and studies, and the scientific integrity and reasonable patient safety of those trials.

Registration and Disclosure: The registration and public disclosure of clinical trials and other studies is key to determining the safety of drugs. Transparency of study results is necessary to understand the true safety and efficacy of drugs, to identify further research efforts and to ensure appropriate safety warnings. Too often, pharmaceutical companies distort, manipulate and conceal results from clinical studies in order to guarantee the approval of their drug. Today, there is an enormous bias toward reporting favorable results and the hiding or minimizing of lackluster and negative results. As one analyst has written:

> "Another problem with the existing system is that non-publication of negative trials and non-reporting of negative outcomes, coupled with redundant publication of positive findings, has led to systematic publication bias, which can undermine the reliability of medical evidence."[1]

Two such examples are Vioxx and Paxil. Vioxx was removed from the market in 2004 after clinical trials revealed an increased risk of heart attack and stroke for those taking the drug.[2] According to testimony from Dr. Sandra Kweder, deputy director of the FDA's Office of New Drugs (OND), these trial results were not made available to the FDA prior to Merck's voluntary withdrawal of the drug.[3] Similarly, GlaxoSmithKline, maker of Paxil, concealed results from clinical trials linking the drug to an increased risk in suicidality among adolescents, as proven by New York Attorney General Eliot Spitzer's successful complaint against GlaxoSmithKline.[4] These trials also revealed that the drug was actually less effective than placebos among adolescents.[5]

These abuses have not ceased. As recently as September 29, 2006, the FDA released a Public Health Advisory that Bayer, maker of Trasylol, failed to inform the FDA Advisory Committee (which had convened eight days earlier on September 21, 2006 to discuss Trasylol) of a new study that revealed an increased risk of death, serious kidney damage, congestive heart failure and stroke.[6] The FDA began conducting a review of Trasylol in January, 2006, after two published research articles reported serious risks associated with use of the drug.[7] [8] Such research misconduct has contributed to injuries and deaths by consumers who use these potentially dangerous drugs, and USA Today reports that the pharmaceutical industry faced more product liability lawsuits than any other industry last year.[9]

Abuses in the registration and reporting of clinical trial and study results highlight the need for increased transparency. Such transparency would enable the scientific

community to better assess the true safety and efficacy of drugs. The World Health Organization (WHO) has taken steps to standardize trial registration and reporting through the International Clinical Trial Registry Platform (ICTRP), identifying a 20-item minimal dataset for all clinical trials, which includes target sample size and primary and secondary outcomes.[10] Many medical journals have formally supported these steps taken by the WHO and will now consider the publication of the results of a clinical trial only if it has been registered before the enrollment of the first patient.[11] The Journal of the American Medical Association is responding even more aggressively to ensure accuracy in data analysis by requiring all submissions of clinical trial results funded by industry to hire an independent statistician to analyze the data.[12] A coalition of over 100 health care stakeholders have signed the Ottawa Statement, making a moral case for full disclosure:

> "When members of the public agree to participate in trials, it is on the understanding that they are contributing to the global body of health-related knowledge. It is thus unethical to conduct human research without ensuring that valid descriptions of the study and its findings are publicly available."[13]

Lack of oversight and reasonable patient safety in clinical trials: The need for registration of clinical trials (at all phases) became even clearer after this spring's Phase 1 TGN1412 trial in which 6 healthy UK volunteers suffered catastrophic multi-organ failure after taking the drug. Many argue that these events could have been avoided had trial information been available for public review.[14] Although pharmaceutical companies argue that disclosing such sensitive information would allow competitors to conduct similar trials of their own, the WHO and many others in the field find that these concerns are not sufficient to delay disclosure.[15] Given the extraordinarily aggressive patenting of all aspects of a new drug, we do not believe that these public registrations will cause proprietary commercial losses. Disclosure of the TGN1412 trial would have allowed experts to determine if the trial was generally appropriate and if the procedures that were followed were sound.[16]

The research community must take more responsibility in protecting human volunteers, yet recent reports indicate that the FDA is about to loosen regulations in this area. Senator Charles Grassley, in a letter to the HHS Office of Inspector General (OIG), asserts that clinical trial subjects are not always adequately warned of potential risks, and are sometimes endangered and harmed as a direct result of participating in such trials.[17] Bloomberg News investigative reporting has found that safety oversight of clinical trials is often left in the hand of pharmaceutical companies and their contractors and that the quality of these experiments is often suspect and certainly dangerous to the participants.[18] The consequences are clear: the Center for Drug Evaluation and Research (CDER) recommended official action against 6% of the 319 clinical investigators it inspected in 2006 for non-compliance of regulations.[19] CDER requested voluntary corrections for an additional 42% of clinical investigators whose deviations from the regulations were considered to be "minor." Senator Grassley asserts that a fundamental concern regarding the participation of human subjects is the "lack of protections and respect for research participants who place their health and their lives in the hands of

clinical investigators and the entities that are expected to monitor and oversee the studies."[20]

In addition to the lack of safety for individuals enrolled in some trials, there is the safety problem created by fraud in the falsification of data used to justify a drug's approval. In the recent case of Ketek, the FDA found multiple instances of fraud in the company's clinical trial of about 24,000 patients, some cases of which the maker Sanofi already knew about yet failed to notify the agency.[21]

In light of the various abuses that may potentially occur while conducting clinical trials, the FDA must do more to ensure scientific integrity and patient safety in clinical trials. We comment on this problem further in the "Additional FDA Resources Needed" section.

Discussion of solutions in S. 3807 and further recommendations:

S. 3807 addresses the issues regarding transparency in research by establishing (1) a Clinical Trial Registry Database and (2) a Clinical Trial Results Database, both of which would be made public. These databases conform to the WHO ICTRP described in the previous section. If they are seeking journal publication, sponsors may take up to two years after they determine the trial is ended to report Phase 3 and Phase 4 trials to the public.

Consumers Union strongly supports the establishment of the Clinical Trial Registry Database and the Clinical Trial Results Database, but recommends that sponsors be required to report results, including the results of Phase 2 trials, within one (1) year, and that results from trials of drugs revealing safety concerns be reported publicly as soon as trials are completed. This recommendation follows that of the Institute of Medicine (IOM), which requests that trials be registered 'in a timely manner.'[22] Given the history of manipulation and concealment of results by pharmaceutical companies, a stricter deadline than two years for reporting results seems appropriate.

While the proposed legislation requires the registration of the results of Phase 3 and 4 trials, it does not require the registration of the results of Phase 2 trials unless the Government Accountability Office (GAO) specifically recommends registration, which would then be implemented through a further rule-making process. The Institute of Medicine report recommends that, at a minimum, all Phase 2-4 trials be registered, including a posting of a 'structured field summary of the efficacy and safety results of the studies.'[23] Furthermore, trial registration will do nothing to diminish publication bias and misreporting if only trials that have been completed and reveal favorable results are reported and published.[24] In order to really address the problem of selective reporting – which is clearly an issue given recent history – all clinical trials should be registered.

In addition, some argue that even Phase 1 trials can gather data on efficacy in addition to safety, and therefore should also be subject to registration.[25] The data found in

a Phase 1 trial can contribute to meta-analyses of adverse events and is used by successful safety projects such as RADAR.[26] Finally, there is a strong moral argument for such registration: fellow human beings have volunteered to serve basically as guinea pigs to test the basics of a new drug idea. If there is any adverse side effect from such tests, it seems immoral not to report such results and not to warn other companies who may stumble down the same research pathway. There may be little merit in the concern that a company will lose 'proprietary' data. A company's proprietary and commercial interests are undoubtedly protected by the aggressive patenting that occurs in the drug industry. The safety of human test subjects should come first.

Consumers Union supports the public disclosure of as much scientific data as possible. S. 3807 should be amended to change the GAO study of whether Phase 2 trial results should be disclosed. We believe that Phase 2 disclosure should be a given. Instead, the GAO study should concentrate on whether all or some of Phase 1 trials should be disclosed at the point when a final decision is made on the drug subject to the trial (i.e., it is approved, or withdrawn).

Consumers Union also urges that the legislation extend the registry to gradually include all studies completed since at least 1996, and hopefully earlier. For example, each year over the next five years, two years of pre-enactment of S. 3807 trial results could be publicly posted. It would be a great service to the world's scientific community to have in one place an expanded, Internet available library of these past trials.

In order to address the potential of trial abuses and falsifications, the proposed bill calls for the FDA to 'sample' clinical trials to ensure that the descriptions of results are "non-promotional, and are not false or misleading in any particular…" **In light of past abuses, Consumers Union recommends that pharmaceutical companies that neglect to provide relevant results or falsify results should be subject to FDA Civil Monetary Penalties (CMPs). In the "Additional FDA Resources Needed" section, we urge that a higher percentage of trial and study papers be audited for scientific integrity and honesty.**

Finally, S. 3807 pre-empts State laws that require clinical trial registration. Because of lack of action at the Federal level, Consumers Union has been a driving force behind these state debates and laws. **We accept the idea of pre-emption, but only if there is a strong Federal law. If the type of changes we recommend above are not included, we oppose State pre-emption.** The States should be able to do more to protect the safety of their citizens.

2. FDA power to ensure safety

The IOM report highlights the fact that PDUFA has done a great deal to ensure speed in the drug approval process – perhaps at the neglect of safety. The report notes that although the PDUFA laws have established performance goals relating to review speed, there are no performance goals relating to safety.[27] Thus the FDA assigns priority to specific drug approval performance goals, and in turn (as the recent history of withdrawals suggests), lacks resources to act aggressively on safety issues which have no such performance goals.

S. 3807 provides exciting new powers, resources, and enforcement tools for the FDA to improve postmarket approval safety. But in light of recent history, we urge even stronger actions. The following five (5) subsections offer recommendations on how to give the FDA clearer additional authority to ensure safety without in any way slowing the approval of life-saving medicines:

A. Effective use of adverse event reports
B. Post-approval management
C. Direct-To-Consumer (DTC) advertising
D. Off-label use
E. Enforcement

A. **Effective use of adverse event reports**

Background:

An estimated 700,000 people required emergency department attention due to Adverse Drug Reactions (ADRs) in 2004 and 2005.[28] ADRs are responsible for as many as 100,000 deaths annually.[29] Although these numbers indicate that ADRs are an enormous problem, no effective mechanisms for reporting and analyzing potentially serious ADRs exist today.[30] Spontaneous reporting systems such as MEDWATCH, while sometimes useful, are incapable of reliably or quickly detecting many long-range ADRs.[31]

Discussion of solutions in S. 3807 and further recommendations:

S. 3807 establishes a key principle: that drug safety issues do not stop with the approval of the drug. Instead a drug must be looked at over its 'life cycle'--drugs need to be monitored and studied over many years. The bill establishes a system of Risk Evaluation and Mitigation Strategies (REMS). In addition, in Title II it creates the Reagan-Udall Institue, in consultation with the National Institutes of Health (NIH) and other research programs, to explore ways to improve adverse event reporting and analysis and improve the science of drug development and safety.

The IOM report specifically calls for an improved Adverse Event Reporting System (AERS), and asks that the Center for Drug Evaluation and Research (CDER) conduct a scientific review of AERS to identify and implement improvements, and, "systematically implement statistical-surveillance methods on a regular and routine basis

for the automated generation of new safety signals."[32] While spontaneous reporting methods, such as MEDWATCH, may contribute to AERS, these methods are not the only tool to track and evaluate ADRs. **Consumers Union recommends the incorporation of a temporary demo whereby the FDA devotes resources (including user fees) to support NIH funding of a program like the Research on Adverse Drug Events and Reports (RADAR) project in which medical scientists <u>proactively</u> search ADRs for patterns.**[33] The RADAR project is funded entirely by peer-reviewed grants from the NIH, the Veterans Administration (VA), and the American Cancer Society (ACS). Summary safety information from the project is synthesized into reports for medical journals, revised package inserts, and "Dear Doctor" letters. The information is presented to physicians, the FDA and relevant sponsors. The RADAR project may provide important answers as to how more ADRs can be reported and evaluated in a meaningful way.

Today, it is estimated that only 1 to 10 percent of all adverse events are reported. But with the coming age of health information technology and personal health records (PHRs) where patients can be electronically warned of dangers and asked to report reactions to new drugs, we will soon have access to a huge amount of new data. The FDA is to be commended for contracting with a number of large patient encounter databases. The use of these large databases can eventually permit the FDA to detect patterns of ADRs that are invisible when only smaller populations are examined. But it is not yet clear when and how they will be able to use the extraordinarily rich data that will be available from Medicare Parts A, B and D. **We urge the Committee to lay the groundwork in S. 3807 for FDA to use the Medicare databases and PHR systems to establish a truly effective AERS that will be able to detect many more kinds of drug interactions.** Further, such a system will help us compare drug effectiveness to determine which medicines and courses of treatment are most effective in fighting life's diseases. Of course, using large data bases to aggressively search out adverse drug events will take significant new resources (which we discuss below).

B. Post-approval management

Background:

As noted in the previous subsection, ADRs pose serious safety concerns. According to a study by the General Accounting Office (GAO), over 50% of all approved drugs had serious post-approval risks.[34] These ADRs are often detected years after the drug has been on the market. One study indicates that only 50% of ADRs are discovered within 7 years after approval.[35] This delay in detecting drugs with serious risks is apparent in the withdrawal process as well; one report documents the median time on the market before a drug is withdrawn to be 5.4 years.[36]

These figures highlight the importance of post-marketing surveillance, but in the current system the FDA focuses almost exclusively on pre-approval indicators. This strategy has proven to be inadequate and dangerous. Although pre-approval trials may assess efficacy, they cannot assess safety due to the fact that they are conducted in small,

selected populations (often disproportionately males who are younger and healthier than the population which will actually use the drug) for very limited periods of time. In general, Phase 1 trials are conducted on several dozen healthy humans to determine safe dosages and generally evaluate safety. Phase 2 trials are conducted on a slightly larger population—perhaps several hundred people--to test effectiveness and further evaluate safety. Phase 3 trials are conducted on large populations of several thousand to confirm effectiveness, monitor side effects, and gather additional information that will allow the drug to be used safely. An abbreviated trial may be conducted for as little as six months. Finally, Phase 4 trials are conducted after a drug has been marketed to evaluate long-term safety. FDA regulations allow for the approval of a drug with evidence from a single clinical trial.[37] Clearly, clinical trials are simply incapable of portraying an accurate picture of how a drug will behave in the general population or the older patient population over many years. Thus, the need for reviewing drugs once they are on the market is essential.[38] [39]

Although the FDA has the authority to recommend Phase 4 post-approval studies, sponsors of drugs often fail to complete such studies. For example, Sanofi-Aventis failed to complete a post-approval study on the arthritis drug, Arava, after the FDA questioned its long-term safety at the time of its approval in 1998.[40] Arava has been on the market for 8 years and fatal liver complications have been reported in those using the drug.[41] Bloomberg News reports that 860 post-approval studies requested by the FDA have yet to be completed, 260 of which are on drugs that were approved at least 5 years ago.[42] It appears that many of these trials have not even been started and the commitments given to the FDA are often ignored.

Not only is there a problem with getting companies to fulfill their postmarket study commitments, but lack of FDA resources has led to poor enforcement of this program. In June 2006 the HHS Inspector General reported that:

> FDA cannot readily identify whether or how timely postmarketing study commitments are progressing toward completion. About one-third of ASRs [Annual Status Reports on these studies] were missing or incomplete,… ASRs contain information of limited utility…FDA lacks an effective management information system for monitoring postmarketing study commitments…. Monitoring postmarketing study commitments is not a top priority at FDA…Our analysis showed that FDA validated only 30 percent of ASRs submitted in fiscal year 2004….

The OIG called on FDA to instruct companies to provide 'additional, meaningful information in their ASRs, improve the management information system for monitoring postmarketing study commitments so that it provides timely, accurate, and useful information, and ensure that postmarketing study commitments are being monitored and that ASRs are being validated.'[43]

Discussion of solutions in S. 3807 and further recommendations:

This year's GAO report on the FDA comments on the agency's inability to ensure the completion of post-approval studies, asserting that "FDA needs greater authority to require such studies."[44] The report goes on to further document cases where the FDA has been unable to negotiate with sponsors to ensure that post-approval studies are conducted. Since sponsors voluntarily agree to conduct such studies, the FDA has no authority to ensure their completion.

As part of REMS, S. 3807 gives the FDA authority to require safety trials and tools to enforce the requirement. Consumers Union strongly supports this provision: it is one of the most important in the bill.

In addition, required REMS call for 3 years of review, and additional review may be required "at a frequency determined by the Secretary for subsequent years." The IOM repeatedly highlights the need to perform post-marketing surveillance throughout the entire life cycle of a drug. In particular, the IOM recommends that the evaluation of a new drug's total safety profile occur after 5 years. **Consumers Union strongly supports the IOM's recommendation and asks that the review time cycle for a drug be increased from S. 3807's 3 years to 5 years. This review should be institutionalized, and not left to the total discretion of the Commissioner.** Given the history of ADRs and drug withdrawals that occur many years after a drug is first on the market, this kind of extended post-marketing surveillance is necessary. **Because of the history of problems detected many years and even decades after a drug's approval, we also support the institutionalization of another focused review of the literature, ADERs, etc., at some later interval, perhaps at the 10th or 15th year a drug has been on the market.**

With respect to industry conducted post approval safety studies, HHS OIG recommended that the FDA instruct sponsors to provide "additional, meaningful information" in their annual status reports in order to determine how timely post-marketing study commitments are progressing toward completion.[45] According the OIG, the FDA disagreed with this recommendation, stating that the implementation of such a recommendation would require additional regulations. The OIG concludes that the FDA cannot identify the progress of post-marketing study commitments, and that regulatory changes may need to be enacted in order to address these issues. Consumers Union supports the OIG's recommendation that sponsors include progress reports on post-approval safety issues in their annual status reports. S. 3807's annual REMS review process is a major step in this direction.

C. Direct-To-Consumer (DTC) advertising

Background:

Although full safety risks are often unknown for years after approval, pharmaceutical companies invest a great deal of money in the immediate promotion of approved drugs, including billions of dollars in Direct-To-Consumer (DTC) advertising. We have seen, too many times, the devastating effects of such DTC advertising. At least one study has commented on how DTC advertising contributed to the overuse and misuse of Vioxx by both consumers and physicians, which led to an unnecessary increase in the number of people at risk of heart attack and stroke.[46] In addition to the safety concerns, DTC advertising of Vioxx increased costs to consumers and health plans alike, which were paying significantly more for a new drug that added little or no benefit.[47]

Some defend the use of DTC advertising, asserting that it promotes patient-physician dialogue and increases awareness of diseases and treatments. One study shows, however, that these ads are rarely educational; while many advertisements gave the name of the drug and the condition being treated, very few provide any additional health information on alternative treatment of the condition.[48] The study reports that out of a possible 11 educational codes (specific educational points), the average number of codes present in advertisements was 3.2. Despite the lack of truly educational information in DTC advertising, consumers tend to believe the pharmaceutical industry's message that only the safest and most effective drugs appear in advertisements.[49] This is particularly dangerous given the fact that the goal of this advertising is to sell a costly product that can potentially have serious safety risks. Consumers Union believes that if we need to increase awareness or dialogue about certain medical problems, the industry could contribute to scientifically-based Public Service Announcements approved or managed by an impartial, expert group, such as the FDA, CDC, or NIH.[50]

Discussion of solutions in S. 3807 and further recommendations:

As a part of REMS, the proposed bill gives the FDA authority to require the pre-clearance of advertisement to ensure disclosure of a serious risk listed in the labeling of the drug. In light of the promotional nature of DTC advertising and the long history of abuses in DTC advertising, and given that such advertising strongly influences consumers, **Consumers Union recommends a requirement that ALL advertisements be pre-cleared by the FDA for accuracy and honesty, including the growing use of ads in the Internet and other non-traditional sites.**

In addition, the FDA may impose a two (2) year moratorium on DTC advertising for drugs showing more serious safety concerns. Given the amount of influence this type of advertising has on consumers, and given the potential serious ADRs that may occur years after approval, **Consumers Union recommends a moratorium on DTC advertising of three or more years for all new drugs. The history of ADRs and withdrawals shows that drugs cannot be assumed safe after just two years. Adding a possible third year to the moratorium authorities in S. 3807 would be prudent and constitutional.[51]**

D. Off-label use

Background:

The FDA currently approves drugs for specific indications based on scientific evidence and clinical trials. Off-label uses of these drugs (in which physicians prescribe medicines for indications other than the ones for which a drug is approved) lack the same kind of scientific scrutiny. In an analysis of 160 commonly prescribed drugs from 2001, off-label uses accounted for 21% of overall use, and most uses had little or no scientific support for such use.[52] In some classes of drugs, off-label use accounts for up to 75% of prescriptions.[53]

Often, drug companies inappropriately and illegally influence doctors to prescribe medications for off-label uses. In the case of gabapentin, pharmaceutical company Parke-Davis used teleconferences, consultant meetings, selective research, as well as other tactics to encourage doctors to use the drug for off-label uses.[54]

Despite the high occurrence of off-label uses, the scientific efficacy of such drugs for unapproved indications is not established.[55] [56] Many off-label uses are often helpful and probably have little adverse consequences, but since off-label uses are not subject to FDA approval, it is difficult to determine what scientific evidence exists to prove clinical effectiveness. Off-label use of prescription drugs also generally raises concerns regarding potential risks to patients as well as issues about the reimbursement and coverage of these drugs.[57] Adverse drug events may also occur more commonly in off-label settings than in on-label settings, since clinical trial information is often unavailable.[58] The Wall Street Journal recently reported on the off-label use of Actiq, a potent narcotic that is indicated for use in cancer patients who experience intense pain.[59] According to the article, Actiq is 80 times as potent as morphine and is in a group of drugs that has the highest risk of fatal overdose. In fact, 47 deaths due to overdose were associated with the use of Actiq. Despite the safety risks, data suggest that 80% of patients use the drug not for cancer pain, but for off-label uses such as headache and back pain.

Discussion of solutions in S. 3807 and further recommendations:

S. 3807 is silent on the issue of off-label use. Given the potential for off-label uses to create serious safety problems, **Consumers Union recommends that the FDA develop a program to scientifically study drugs widely used in off-label settings.** We are not advocating a ban on such use. We are simply asking that some scientific study be brought to this area, so that the labels on these drugs may be expanded and improved in the cases where the scientific evidence is supportive.

E. Enforcement

Background:

As described above, the FDA has limited authority to effectively enforce post-approval safety. As this year's GAO report highlights, the "FDA has little leverage to ensure that these [commitments for post-approval safety] studies are carried out…by imposing administrative penalties."[60] The IOM also reports that lack of clear regulatory authority is a serious problem at the FDA.

In addition to the lack of clear authority in some areas, there is the issue of failing to use existisng authorities. Rep. Henry Waxman has reported that the level of enforcement actions has been declining and the recommendations of FDA field staff for corrective actions are often disregarded:

> "Internal agency documents show that in at least 138 cases over the last five years involving drugs and biological products, FDA failed to take enforcement actions despite receiving recommendations from agency field inspectors describing violations of FDA requirements."

The House Government Reform Committee report noted a 50 percent decline in warning letters in recent years.[61]

Discussion of solutions in S. 3807 and further recommendations:

In addition to existing authorities (some of which like drug withdrawals or seizures are so serious and disruptive they are not creditable and almost never used), the bill allows the FDA to issue Civil Monetary Penalties (CMPs) of between $15,000 to $250,000. CMPs may not add up to more than $1,000,000 for all violations "in a single proceeding." While this CMP authority is a major improvement, given the large profits that pharmaceutical companies can enjoy every day a drug is on the market, **Consumers Union recommends that CMP authority be increased to more than $1,000,000, especially when companies are repeated offenders**

S. 3807 also gives the FDA more authority to order changes in drug labels and to control the dispensing of drugs so to ensure that particularly vulnerable populations (such as pregnant women) are better protected from unnecessarily dangerous forms of treatment. **Consumers Union strongly endorses these labeling and dispensing provisions in S. 3807.** As the Office of New Drugs Director Dr. John Jenkins said,

> "There's no doubt that there are situations where we internally feel frustrated that the discussions about label changes are taking longer than we would like. Remember that labeling is the primary way we have to communicate to practitioners and health providers about the safety and effectiveness of the drug. So everything keys off the labeling."[62]

The language in S. 3807 should prevent a recurrence of the 22 months of FDA-Merck 'negotiating' on the Vioxx label while millions of patients continued to take an unnecessarily dangerous drug.

3. Resources at the FDA

Background:

The FDA needs more resources if it is to truly be the world's Gold Standard in prescription drug approval and safety.

We agree with the IOM report that the FDA suffers from serious resource limitations. The IOM notes that although user-fees have greatly increased the resources for new drug review, FDA's other functions – such as post-approval drug safety monitoring – are seriously under funded. As the IOM notes, PDUFA not only sets performance goals, but also tightly restricts CDER's use of its funds: "each round of PDUFA negotiations has led to more demands on CDER and continued restrictions on CDER's flexibility."[63]

The lack of resources for safety is appalling. The public would be truly shocked if they realized how huge the FDA's jurisdiction is and how little the agency can really manage to do with its limited budget. Unfortunately, the public is periodically reminded of those limitations by outbursts of fatalities—such as the recent E. coli spinach deaths.

According to the 2006 GAO report on post-market drug safety, the FDA has currently allocated $1.1 million per year for its contracts with researchers outside of FDA to conduct post-approval studies. Yet the GAO also reports that just one clinical trial designed to study long-term drug safety could cost between $3 million and $7 million.[64] The IOM report also highlights the need for increased resources to support new staff devoted to post-market safety work. PDUFA funding has supported the surge of new drug review staff, whereas ODS has not experienced such a dramatic increase in staff: between 1996 and 2004, new drug review staff increased by 125% (from 600-1320) but ODS staff increased by only 75% (from 52 to 90).[65] While the drug companies flood the airwaves and Internet with ads, the FDA is only able to review about 24 percent of these for accuracy.[66] And while generic drugs can save consumers billions of dollars, this fall there is a backlog of 394 generic drugs awaiting approval because of FDA bottlenecks.[67]

The IOM highlights the need for resources to support Information Technology (IT) at the FDA, and concluded that CDER's IT systems are antiquated. Consumers Union staff has been told that half the FDA's computer systems are so old that they will no longer be served by vendors after this year. It is worth quoting at length Dr. Scott Gottlieb, writing before his appointment to the FDA:

> "Although it is impossible to calculate exactly how much the agency's review programs spend on IT-related infrastructure (because it is embedded in many different programs), consider that total spending on IT-related activities at the FDA was cut $29.1 million in 2004 from what the agency had requested so that the FDA could find savings to stay inside its congressional budget allocation.

That exceeds the entire $23.8 million budget of the FDA's Office of Drug Safety for 2004."

"All of this leaves little doubt that even the most basic IT improvements have been slow in coming, hobbled by a lack of budget and vision. As a result, information is made available to the FDA slowly and takes even longer to analyze by the FDA's trained personnel. Subtle side effects—especially medical problems that occur naturally in a large population or as a consequence of the condition that a drug aims to treat (the side effects at issue with Vioxx and the SSRIs met these criteria) could be easily dismissed as normal or "background" events as a result of inadequate sample sizes and the inability to easily aggregate and analyze population-based data on actual drug use.[68]

Yet IT resources are essential for making post market surveillance work, improving AERS, and—in the long run—making comparative effectiveness analyses that will save the Nation tens of billions of dollars by identifying what courses of treatment work and don't work. In addition to modern systems, the FDA needs the resources to develop electronic data submission formats; today, all too many applications are submitted as expensive-to-process reams of paper, because the FDA says it doesn't have the resources to develop regulations for electronic submission formats.

Discussion of S. 3807 and further recommendations:

S. 3807 allows PDUFA user-fees to be available for REMS work to improve post-approval safety. Many are concerned, however, that the FDA is too closely tied with the industries it regulates. User-fees may contribute to the pharmaceutical industry's "capture" of the FDA.[69] The IOM recommends that Congress approve a substantial increase in both funds and personnel for FDA safety activities in order to counteract PDUFA's restrictions on how the FDA can use its funds. The IOM discusses the ideal option of general Treasury revenues to adequately fund the FDA. Importantly, however, the IOM notes that if user-fees are required, Congress should greatly reduce current restrictions on how the FDA can use those funds.

Consumers Union strongly supports the IOM's recommendations for more resources with no 'strings attached.' This could be achieved, as Rep. Maurice Hinchey's bill (HR 2090) does, by depositing user fees into the Treasury, then entitling the FDA to an amount of money from the Treausry equal to the amount currently raised by user fees, but freeing the agency from detailed restrictions on how such monies are spent. As noted in section 5 below, freeing the FDA from dependence on the industry is probably the single major thing we can do to improve the morale and culture within the FDA on behalf of consumers.

Another option would be to increase user fees to deal with a huge backlog of safety issues. Consumers Union echoes the IOM's words that regardless of the funding source, "the functioning of a drug safety system that assesses a drug's risks and benefits

throughout its lifecycle is too important a public health need to continue to be under funded."[70]

If a user fee system is continued, we urge that **S. 3807's section 104 be strengthened to spell out adequate levels of resources and performance goals for safety. Just as the industry has goals for rapid drug approvals, consumers and patients should have goals for rapid resolution of safety concerns.**

Attachment #1 is a list of the kind of safety goals that should be funded, ideally by the general Treasury, but if the user fee program is continued, then by user fees. This list is illustrative. Of course, your Committee would need to provide details on the exact performance levels and the realistic rate of increase in safety quality after consultation with the FDA, OMB, and after studying the President's FY 2008 budget and the FDA's actual safety budget deficiencies in the middle of FY 2007.

While all these safety standards are important, we particularly appreciate S. 3807's study of the FDA's IT needs. But another IT study, without funding, is meaningless. We urge you to give a priority to funding these crucial IT building blocks.

4. Advisory Committees (ACs) at the FDA

Background:

Advisory committee meetings are a very important resource for the FDA. Such meetings are public and provide an opportunity for the agency's scientific experts, consumer advocates, and industry representatives to contribute to the regulatory process. Recently, however, there have been serious concerns about the process.

Although AC meetings provide a valuable contribution to the FDA's efforts to regulate drugs, the frequency with which they convene has been declining. The OIG reported that the number of AC meetings decreased from 40 in 1998 to 23 in 2001.[71] The OIG also reported that FDA managers believed that they had little time to hold these meetings. In addition, only 21% (5/24) of approved New Molecular Entities (NMEs) were preceded by an advisory committee meeting. NMEs are drugs that contain an active ingredient that has never before been approved, and may be more likely to carry safety risks.[72]

In addition to the recent reduction of meetings, important information regarding drug safety is sometimes purposefully excluded. For example, a senior epidemiologist at the FDA, Dr. Andrew Mosholder's concerns that Paxil increased suicidal behavior in children were dismissed by higher FDA authorities.[73] Dr. Mosholder was not allowed to present his analysis at the February 2004 joint meeting of the Psychopharmacologic Drugs Advisory and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee because it was believed to be too preliminary.[74] In later interviews with the GAO, the Directors of CDER and the Office of New Drugs (OND) said that in retrospect

they felt it was a mistake for the FDA to have restricted Dr. Mosholder from presenting his safety information.[75]

The GAO report on post-market drug safety notes that the role of the Office of Drug Safety (ODS) in AC meetings is unclear. The report cites another case (in addition to the one above) in which ODS staff was not allowed to present their analysis: the OND did not allow the ODS to present their review of Arava at the Arthritis Advisory committee meeting in March 2003 because the OND division believed that ODS's review lacked scientific merit. ODS found the use of Arava to be associated with acute liver failure. GAO reports that after the meeting, ODS epidemiologists and safety evaluators requested clarification of ODS's role in advisory committee hearings, but that there was no written response to this request.

Although certain FDA experts have been refused permission to testify at AC meetings, many outside scientific experts are free to participate in such meetings despite having outstanding conflicts of interest. For example, at the February 2005 joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the safety of cyclooxygenase-2 (COX-2) inhibitors, 10 of the 32 voting panel members had financial associations with the manufacturers of these drugs (such as consulting fees or research support).[76] All 10 members were issued general waivers that allowed them to participate in the meeting. Twenty-eight out of the 30 votes cast by these 10 members favored marketing of Bextra, Celebrex and Vioxx, whereas only 37 out of the 66 votes cast by the remaining 22 members favored marketing of these drugs.[77] If the 10 panel members with conflicts of interest had not participated in the meeting, the committee would have voted to remove Bextra from the market, and to keep Vioxx from returning to the market (Merck voluntarily withdrew Vioxx from the market in 2004). Instead, due to the inclusion of the votes from the 10 conflicted panel members, the committee voted to keep these drugs on the market. The FDA consequently announced that it had asked Pfizer to voluntarily withdraw Bextra from the market, which it did in April 2005, two months after the advisory committee meeting.

Discussion of S. 3807 and further recommendations:

Frequency of Meetings: Title IV of S. 3807 recommends a series of clarifying efforts to reduce or disclose conflicts of interest. The IOM recommends that FDA advisory committees review all NMEs either prior to approval or soon after approval. The IOM notes that although it might be impossible to convene AC meetings for all NMEs prior to approval, the FDA should have the authority to require such meetings after approval. Since advisory committees provide valuable scientific expertise, it is important that the FDA capitalize on such a resource. **Consumers Union supports the IOM's recommendation that all NMEs be reviewed by FDA advisory committees and be part of the REMS process.**

ODS involvement in ACs: In addition to encouraging participation of outside scientific experts through AC meetings, it is important that FDA's own scientific experts also be heard. ODS staff has recommended that as a matter of policy, they present post-

market safety data at these meetings.[78] **Consumers Union recommends that ODS always have the right to testify before ACs. If ODS chooses not to testify, Consumers Union strongly recommends that ACs be granted the authority to request such testimony or a statement from ODS that they have no safety concerns to raise.**

The IOM highlights the fact that the FDA must undergo cultural changes if post approval safety is to be improved. Consumers Union encourages language in S. 3807 that would speak to this issue and assure the right of FDA scientists to dissent or provide 'additional views' to the majority view. The right to dissent must be especially acknowledged at AC meetings.

Also, a recent report by the National Resource Center for Women and Families[79] shows that while ACs often raise safety questions, they very seldom reject a drug. There appears to be a clear bias toward approval and a suppression of safety concerns (which is another reasons to seek more conflict-free experts). The study also shows that even when an AC rejects a drug, the FDA frequently ignores the recommendation. We believe that if the FDA overrules an AC recommendation, it should provide a detailed public statement of why it disagrees and why it believes the science supports the FDA's disregard of the expert outside panel.

Ending Conflict of Interest: AC meetings must be conducted in such a way that scientific integrity is promoted. Recent history suggests that committee members are given voting rights despite significant financial associations with the pharmaceutical companies affected by the committee's review. The New England Journal of Medicine reports that, according to Dr. J. J. Wood, the chair of the joint meeting that reviewed the COX-2 inhibitors, the FDA made a "judgment error" when it decided to issue a general waiver and not to disclose specific information regarding the conflicts of interests of committee members.[80] The IOM recommends that a "substantial majority" (and suggests 60%) of the members of each advisory committee be "free of significant financial involvement" with the pharmaceutical companies that would be affected by the committee's review. In addition, the IOM recommends that the FDA issue waivers to committee members "very sparingly."

Consumers Unions recommends that no advisory committee meeting be convened unless a substantial majority of the committee is free of significant financial involvement. We think it is important for restoring public confidence in the agency and creating a culture of the highest public service that no less than 90%, and ideally 100%, of advisory committee members be free of conflict.

The public has lost confidence in the FDA. The Wall Street Journal reported on a May 24, 2006 WSJ Online/Harris Interactive poll that 58% of the public feels the FDA does a fair or poor job on ensuring the safety and efficacy of new drugs, and 80% said they are somewhat or very concerned about the agency's ability to make 'independent' decisions. Clearly, this is a time to bend over backwards to ensure integrity and public interest in all aspects of the FDA, including the integrity of its Advisory Committees.

It is argued that the best experts in a field are those who have been working with drug companies on the research and development of specific drugs and that it would be impossible to staff conflict-of-interest-free committees with qualified experts. We argue that when one looks at the recent FDA's reports to the Congress on advisory committees, it is clear there is no one person at the FDA charged with coordinating the recruitment of advisors to all the various FDA Centers. **We urge the Congress to support a major outreach effort by the FDA to find non-conflicted advisory committee members.** Until one actively recruits, how can one know that AC's that would inspire public confidence cannot be created?

5. Improving culture and morale at FDA

Background:

Some of the conflict of interest problems that plague FDA's advisory committees appear to affect other aspects of life at the FDA as well. The fact that many career FDA scientific staff members believe their voices are silenced speaks of larger, extremely serious troubles relating to culture and morale at the agency.

In August 2006, the Union of Concerned Scientists (UCS) and Public Employees for Environmental Responsibility (PPER) released their survey of FDA staff. The findings echoed those reported by the Office of Inspector General (OIG) in 2003.[81] For example, in response to the question: "Have you ever been pressured to approve or recommend approval for an NDA despite reservations about the safety, efficacy, or quality of the drug?" 41 respondents out of 217 Center for Drug Evaluation and Research (CDER) staff (nearly 19%) answered "yes."[82] These types of responses raise concerns regarding the extent to which these experts are capable of practicing their right to dissent on issues of drug safety.

These poll findings support the IOM report's finding that the organizational culture at the FDA is partially responsible for the marginalization of dissenting voices.[83] The IOM says that the polarization between the pre-marketing and post-marketing review staff contributes to a negative culture at the FDA. This polarization is evidenced in advisory committee meetings as described in the previous section, where the OND has prohibited the ODS from presenting pertinent safety information. In addition, the resource gap resulting from the introduction of user fees has further divided the two offices and increased tension.[84] The IOM notes that ODS staff have been considered marginal players compared with OND staff, and that the ODS is perceived to have a lower status compared to the OND. According to the IOM, various concerns relating to culture at the FDA have resulted in a "persisting problem with retention, turnover, and morale in CDER."[85] Key relevant staff members are sometimes excluded from discussion and decision-making about the agency and the work they perform daily.

Discussion of solutions in S. 3807 and further recommendations:

In order to address the culture and morale challenges facing the FDA, it is imperative that the agency establish a climate of open scientific debate. **Consumers Union recommends institutionalizing a system of public staff dissent and additional views on all new drug applications, accompanied by 'whistleblower' type staff protections**. Representative Ed Markey (D-MA) has a bill (HR 5922) with whistleblower language.

Just as Congress or the Courts have institutionalized a system where Members can and are expected to offer additional or dissenting views, we believe a similar, institutionalized system within the FDA would improve culture and morale, and contribute to a healthier scientific debate. Some say that this kind of dissent would confuse the public, make practitioners uncertain about whether a drug was good or not, and make people too cautious to use new, important new drugs. We believe that consumer empowerment is good, and that by making it clear where the scientific questions and uncertainty are, it will help researchers around the world concentrate on answering those questions as quickly as possible. The public would understand that while a majority of the FDA found a drug to be effective and safe, dangers were not swept under the rug as part of some pro-drug company conspiracy. The public will support dissent and debate—suppression of dissent will destroy confidence in the system.

6. Speeding approval of generics and biogenerics

Background:

Health care costs continue to surge at double or triple the rate of general inflation, in part due to the high cost and rate of inflation of brand-name prescription drugs. Generic and biogeneric drugs, can dampen health inflation by providing equally safe and effective medicine at a far lower price—often prices only 70 percent or less of the brand name drug. Generics and biogenerics save consumers billions of dollars. For example, according to one study by the Pharmaceutical Care Management Association (PCMA), generic drugs could save consumers over $23 billion over the next five years if optimal use is made of the 14 generic drugs scheduled to enter the market during this time.[86] These savings could also significantly help reduce Medicare and Medicaid costs, since many of these 14 generic drugs are commonly used by senior citizens.

Despite the enormous savings available from generics, the FDA has been unable to ensure that these drugs are approved for the market in a timely manner. In a memo to Consumers Union this autumn, the FDA reported that an unduplicated count of pending generic applications showed a backlog of 394 drugs pending more than 180 days—drugs which could help lower costs to consumers if they were approved. An article in the Washington Post [87] explains that part of the problem is the lack of staff to review these applications: the Office of Generic Drugs only has 200 employees. This is in stark contrast with the OND, which has more than 2500 employees to review about 150 (admittedly more complex) applications.

There is no clear law providing for the development of generic versions of more complex molecular biologic medicines. These new products are the most expensive medicines on the market—some costing as much as $100,000 to $250,000 for a course of treatment. Some criticize the notion that biogenerics could bring cost-saving benefits, saying that these drugs are far more complex than other drugs because they are made from living organisms, and therefore cannot be copied as easily, as inexpensively, or as safely as other drugs.[88] Nevertheless, the European Medicines Agency is creating a framework for biogenerics to be approved.[89] Consumers Union joins most other observers in believing that biogenerics could provide some savings and can be provided safely, thus helping some of our most severely ill patients.[90] The law should be clarified to allow us to do what the Europeans are doing: bringing some relief to consumers.

In addition to backlogs in the approval of generics and legal uncertainty and stalemate on the issue of biogenerics, there are a series of legal loopholes in the law that have allowed drug companies, often in collusion with generic companies themselves, to block the entry of lower-cost generics—sometimes for years. These loopholes range from abuse of the pediatric exclusivity provision to payment arrangements to keep a generic from entering the market. In recent years, the use of phony citizens petitions has cost consumers millions of dollars by delaying the entry of generics. According to the FDA, only 3 of 42 petitions answered between 2001 and 2005 raised issues that merited changes in the agency's policies about a drug. For example, Flonase, a commonly used prescription allergy medication, went off patent in May 2004. But GlaxoSmithKline stretched its monopoly window by almost two years with petitions and a legal challenge to the use of generics.[91]

Discussion of solutions in S. 3807 and further recommendations:

The current legislation is silent on issues surrounding generics and biogenerics.

Consumers Union urges that a major new title be added to S. 3807 to correct the full range of generic and biogeneric problems, or that the Committee address these issues in separate legislation early in 2007.

Specifically, Consumers Union asks that language be added to S. 3807 to:

> **increase funds and staff at the Office of Generic Drugs, and to set goals to ensure that application backlogs do not occur.** Given the significant savings that are associated with the marketing of generic drugs, this language will help moderate rising health care costs.
>
> **establish a path for the approval of biogenerics. We strongly endorse HR 6257, a bill by Rep. Henry Waxman and others, that provides legal direction to the FDA to approve biogenerics.** Consumers Union hopes that Congress, learning from the European Union experience, will soon create a framework for biogenerics to enter the market.

We hope that the Committee will hold hearings on the abuse of the citizen petition and patent and exclusivity laws to keep generics from the market. Senators Kohl and Leahy (S. 3981) and Stabenow and Lott (S. 2300) and Rep. Waxman and others (HR 6022) have bills to close these loopholes that are worth exploring in hearings and adopting as part of FDA reform legislation or as stand-alone proposals.

7. Improving Science at the FDA: The Reagan-Udall Institute

Background:

The FDA's ability to make sound decisions and to regulate the pharmaceutical industry depends on the quality of scientific data that it receives. Recently, many experts have raised concerns regarding the quality of reports submitted to the FDA and the quality of the science used at the FDA. In particular, questions have been raised about non-inferiority trials and the use of surrogate endpoints.

Often, drug company sponsors conducting clinical trials use "surrogate endpoints" rather than final outcomes. These endpoints are relatively easily and quickly obtainable physical markers that are used to reflect what is believed to be a clinically meaningful outcome. Clinically meaningful outcomes are often difficult and costly to obtain directly because they often require very large and long clinical trials. Although the use of surrogate endpoints is sometimes appropriate, this methodology is often abused and clinical trials which use surrogate endpoints often exaggerate the benefits. One recent article in *Health Affairs* reports that this methodology resulted in the overestimation of the benefits of Natrecor, a drug used to treat acute exacerbations of congestive heart failure.[92] The authors of the article note that higher rates of kidney impairment and mortality are found in those using the drug.

The use of the non-inferiority design has also created a great deal of controversy. Non-inferiority trials are intended to show that the effect of a new treatment is not worse than that of a currently marketed treatment. But as FDA experts have pointed out, it is possible over time that the use of non-inferiority trials could lead to the approval of drugs that are actually less effective and/or harmful compared to a placebo. A number of Members of Congress have requested that the GAO investigate the FDA's acceptance of non-inferiority studies, and Rep. Markey's bill, HR 5922, calls for reports on the use of this method of approving drugs.[93] This Congressional concern has been heightened by the FDA's approval of Ketek, which was based on non-inferiority trials. Ketek, which is indicated for pneumonia, throat and sinus infections, and chronic bronchitis, has caused serious liver toxicity in some patients.[94]

Discussion of solutions in S. 3807 and further recommendations:

S. 3807 proposes the establishment of the Reagan-Udall Institute to "modernize medical product development, accelerate innovation, and enhance product safety by initiating, sponsoring, and organizing collaborative and multidisciplinary research." The Institute appears to be part of the Critical Path Initiative to increase the level of FDA's

scientific research and to find faster, cheaper, and more effective ways to develop drugs. It appears that the Institute's responsibilities are in line with some of the science recommendations of the IOM's report.

We strongly support increased high quality scientific work at the FDA, and research on how to solve problems like those that can occur with surrogate endpoints, non-inferiority, and determining the comparative effectiveness of drugs and classes of drugs. Nevertheless, we hope the Committee will hold further hearings on the idea of this Institute. It is not clear why these functions could not be placed within the FDA directly, rather than conducted through a quasi-private institute. It is important that any actions in this area are not just another industry dominated effort to speed the development of drugs without adequate regard to their safety.[95] We commend you for including many references to drug safety in the Reagan-Udall Institute language. But the governing board of the Institute is tilted toward industry and lacks the guarantee of governance by non-conflicted public, consumer board members. The language calls for the acceptance of funds from private entities, which raises the same independence issues as we have seen in PDUFA fees. To repeat, we hope you will spend more time on this issue and refine some of the language to ensure that whatever is done serves the public in a balanced way.

We note that one way to improve science at the FDA is to reduce the level of staff turnover of experienced, trained personnel, which is higher at the FDA than many other Federal science agencies. Improving the FDA's culture and morale, as discussed earlier, and allowing FDA scientists more freedom to publish academically (as provided in Rep. Markey's bill HR 5922) are all keys to creating a better scientific climate.

Conclusion

Finally, I would be remiss not to acknowledge the countless families who have suffered because of our broken drug safety system. They are the reason we are here today. And many of them have worked tirelessly on this issue so others won't have to endure their heartbreak.

Two of these fine people are here today – Eric Swan, whose brother-in-law, Woody Witzak was casually prescribed an antidepressant for insomnia, and five weeks later killed himself. And Mathy Downing, whose daughter, Candace, was put on Zoloft because she was anxious taking tests at school. Ten months later, she took her own life at the age of 12. Neither Eric nor Mathy knew about clinical trial results that indicated increased risk of suicide from these types of antidepressants, SSRIs.

Senators, I deeply appreciate your time, and I thank you for your consideration of these ideas—and for the good work you have begun.

[Footnotes available upon request]

Attachment #1

Proposal for Safety Resources Amendment

Idea for amendment to S. 3807 to ensure adequate resources for needed FDA safety improvements and to set performance goals for the use of such resources. The percentage increases are just illustrative: the exact increases would have to be determined in consultation with the FDA and in light of the FY 2007 appropriations and the President's budget proposals for FY 2008.

On page 34, line 19, insert the following before the quotation mark:

"Such estimate shall provide enough increased revenue to achieve the following safety improvement goals on a phased-in basis between the date of enactment and the end of fiscal year 2012:

(A) ensure the pre-clearance of all electronic media (including Internet) advertisements and informationals[1];
(B) increase by 100 percent (that is, double) the percent of clinical trial data and investigational review board applications audited to ensure the ethical treatment of enrollees, and the experiments integrity and compliance with good scientific practice[2];
(C) ensure the electronic filing of all applications, amendments, petitions, adverse event reports, and other data required by FDCA laws relating to drugs;
(D) investigate all serious adverse event reports within 15 days, and conduct at least XX investigations per year into patterns or clusters of adverse event reports to determine if REMS action should be taken;
(E) increase by 100 percent the inspection of manufacturing (including compounding) facilities for compliance with FDCA laws;
(F) through active outreach and recruitment, develop and maintain a list of potential advisory committee specific experts who have no conflicts of interest and who have indicated a willingness to be appointed to future relevant advisory committee vacancies, and such advisory committee specific list shall equal 50% of the number of individuals serving on each such advisory committee;
(G) between the completion of the strategic plan for information technology provided for by subsection (c) of this section and the year 2012, collect and apply the resources described by subparagraph (4) of such subsection (c) to the implementation of the strategic plan;

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[1] It would be good to define 'advertisements' so as to pick up the many forms of promotions used to promote drugs and frequently to promote off-label use.

[2] It is reported that the FDA is revising regulations allowing drugs used in a Phase 1 trial to be exempt from quality control manufacturing requirements. If this is accurate, there should be some system of sampling a certain percentage of these drugs for purity and safety. See Triangle Business Journal, Nov. 3, 2006, "Triangle scientists reticent about FDA shift."

(H) in addition to the clinical trial registry and results databases established by Title III of this Act for drug applications received after the enactment of this Act, develop over a phased-in four year period ending in 2012 a similar registry of clinical trials and clinical trial results for those trials initiated or completed after 1997 and before the effective date of this Act.

(I) take action, which may include the levying and collection of civil monetary penalties provided under section 502(f)(3) (as added by this Act) against at least 50 percent of the applicants who have failed to complete follow-up safety studies or trials as provided under section 505(o)(4)(D) and (E) (as added by this Act).

Footnotes

[1] "Publishing Clinical Trial Results: The Future Beckons," by Elizabeth Wager, www.plosclinicaltrials.org, Oct., 2006 e31.
[2] Curfman, et al. Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med. 2000;343:1520-8. New England Journal of Medicine. 2005; 353: 2813-2814.
[3] U.S. Congress. Senate. Committee on Finance. Hearing on "FDA, Merck and Vioxx: Putting Patient Safety First?" Testimony of Sandra Kweder, M.D. (November 18, 2004).
[4] People of the State of New York v. GlaxoSmithKline and SmithKline Beecham Corporation.
[5] Ibid.
[6] FDA Public Health Advisory: Aprotinin Injection (marketed as Trasylol). (September 29, 2006).
[7] FDA Public Health Advisory: Aprotinin Injection (marketed as Trasylol). (February 8, 2006).
[8] Mangano DT, Tudor IC, and Dietzel C. The risk associated with aprotinin in cardiac surgery. N Engl J Med. 2006; 354:353-365.
[9] Schmit, Julie. "More drugs get slapped with lawsuits." USA Today. August 23, 2006.
[10] World Health Organization. World Health Organization international clinical trials registry platform: Unique ID assignment. Geneva: World Health Organization; 2005.
[11] DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, et al. Clinical trial registration: A statement from the International Committee of Medical Journal Editors. JAMA. 2004; 292: 1363–1364.
[12] Fontanarosa PB, Flanagin A, DeAngelis CD. Reporting Conflicts of Interest, Financial Aspects of Research, and Role of Sponsors in Funded Studies. JAMA. 2005; 294: 110-111.
[13] Ottawa Statement on Trial Registration, http://ottawagroup.ohri.ca/statement.html.
[14] Kenter MJH and Cohen AF. Establishing risk of human experimentation with drugs: lessons from TGN1412. The Lancet. 2006; 368: 1387-1391.
[15] Establishing transparency to restore trust in clinical trials. The Lancet Neurology. 2006; 5: 551.
[16] Goodyear M. Learning from the TGN1412 trial. BMJ. 2006; 332: 677-678.
[17] Grassley, Charles. Letter to the Department of Health and Human Services Office of Inspector General. November 8, 2005.
[18] Evans, David. "Human guinea pigs pay for lax FDA rules." Bloomberg News. November 6, 2005.
[19] Gidron, Martin. "Six Percent of Clinical Investigators Violated Regulations, FDA Says." Washington Drug Letter. October 2, 2006.
[20] Grassley, Charles. Letter to the Department of Health and Human Services Office of Inspector General. November 8, 2005.
[21] "Designer Labeling," by Ramsey Baghdadi, The RPM Report, November, 2006. It is equally disturbing that the FDA did not disclose this known fraud to the Advisory Committee members who met to review Ketek.
[22] IOM, 2006.
[23] Ibid.
[24] Ibid.
[25] Rennie D. Trial registration; a great idea switches from ignored to irresistible. JAMA. 2004;292:1359-62.
[26] Bennett, C.L., et al., « The Research on Adverse Drug Events and Reports (RADAR) Project, JAMA, May 4, 2005, Vol. 293, No. 17.
[27] Institute of Medicine (IOM), 2006.
[28] Budnitz DS et al. National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events. JAMA. 2006; 296: 1858-1866.
[29] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998; 279: 1200-1204.
[30] Bennet CL, et al. The Research on Adverse Drug Events and Reports (RADAR) Project. JAMA. 2005; 293: 2131-2139.
[31] Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. JAMA. 1999; 281: 824-829.
[32] IOM, 2006.
[33] Bennet CL, et al, 2005.

[34] US General Accounting Office. FDA Drug Review: Post-approval Risks, 1976-1985. Washington, DC: US General Accounting Office; April 26, 1990. GAO/PEMD 90-15.
[35] Lasser, KE et al. Timing of new black box warnings and withdrawals for prescription medications. JAMA. 2002; 287: 2215-2220.
[36] Man, F et al. Evaluation of the characteristics of safety withdrawal of prescription drugs from worldwide pharmaceutical markets – 1960-1999. Drug Information Journal. 2001;
[37] 505(d) Federal Food Drug and Cosmetic Act
[38] IOM, 2006.
[39] Furberg, CD et al. The FDA and Drug Safety: A proposal for sweeping changes. Arch Intern Med. 2006; 169: 1938-1942.
[40] Blum, Justin. "Sanofi, Drugmakers fail on Promise to Study Medicines' Effect." Bloomberg: June 9, 2006.
[41] US Government Accountability Office. FDA Postmarket Drug Safety. Washington, DC: US Government Accountability Office; March, 2006. GAO-06-402.
[42] Blum, 2006.
[43] "FDA's Monitoring of Postmarketing Study Commitments," HHS OEI-01-00390, June, 2006.
[44] GAO-06-402.
[45] Office of Inspector General. FDA's Monitoring of Postmarketing Study Commitments. June, 2006.
[46] Dai C, Stafford RS, Caleb GC. National Trends in Cyclooxygenase-2 Inhibitor Use Since Market Release: Nonselective Diffusion of a Selectively Cost-effective Innovation. Arch Intern Med. 2005; 165: 171 - 177.
[47] Ibid.
[48] Bell RA, Wilkes MS, Kravitz RL. The educational value of consumer-targeted prescription drug print advertising. J Fam Pract 2000;49:1092-1098.
[49] Bell RA, Kravitz RL, Wilkes MS. Direct-to-consumer prescription drug advertising and the public. J Gen Intern Med 1999;14:651-657.
[50] Wolfe, SM. Direct-to-Consumer Advertising — Education or Emotion Promotion? N Engl J Med. 2002; 346: 1424.

[51] "The Court has developed a four-pronged test to measure the validity of restraints upon commercial expression. Under the first prong of the test as originally formulated, certain commercial speech is not entitled to protection; the informational function of advertising is the First Amendment concern and if it does not accurately inform the public about lawful activity, it can be suppressed. Second, if the speech is protected, the interest of the government in regulating and limiting it must be assessed. The State must assert a substantial interest to be achieved by restrictions on commercial speech. Third, the restriction cannot be sustained if it provides only ineffective or remote support for the asserted purpose. Instead, the regulation must "directly advance" the governmental interest. The Court resolves this issue with reference to aggregate effects, and does not limit its consideration to effects on the challenging litigant. Fourth, if the governmental interest could be served as well by a more limited restriction on commercial speech, the excessive restriction cannot survive. The Court has rejected the idea that a "least restrictive means" test is required. Instead, what is now required is a "reasonable fit" between means and ends, with the means "narrowly tailored to achieve the desired objective." Central Hudson Gas & Electric Co. v. Public Service Comm'n, 447 U.S. 557 (1980). Quote from http://caselaw.lp.findlaw.com/data/constitution/amendment01/17.html

[52] Radley, et al. Off-label Prescribing Among Office-Based Physicians**.** Archives of Internal Medicine. 2006;166: 1021-1026
[53] Young, Alison and Adams, Chris. "Off-label Drugs Take Their Toll," Knight Ridder Newspapers, November 2, 2003.
[54] Steinman MA, Bero LA, Chren M, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. Annals of Internal Medicine. 2006; 145: 284-93.
[55] Radley, et al. 2006.
[56] Henney, JE. Safeguarding patient welfare: Who's in charge? Annals of Internal Medicine. 2006; 145: 305-307.

[57] Nightingale, SL. Off-label use of prescription drugs. American Family Physician. 2003; 68: 425-427.
[58] Bennet CL et al, 2005.
[59] Carreyrou, John. "Narcotic 'Lollipop' Becomes Big Seller Despite FDA Curbs. Wall Street Journal. November 3, 2006.
[60] GAO, 2006.
[61] FDA Week, November 10, 2006, "Waxman May Investigate FDA on a Broad Range of Issues."
[62] "Designer Labeling," by Ramsey Baghdadi, The RPM Report, November 2006.
[63] IOM, 2006.
[64] GAO-06-402.
[65] FDA. Center for Drug Evaluation and Research-Activities and Level of Effort Devoted to Drug Safety. 2005.
[66] FDA, "White Paper: Prescription Drug User Fee Act (PDUFA)," p. 34. As the FDA says, "In 2004, [FDA] reviewed 142 proposed broadcast ads, with the 4 full-time staff available to perform these reviews. Although FDA review of all materials would ensure alignment with the approved labeling and a fair balance of information on benefits and risks, current FDA resourcing for this work would probably result in delayed reviews if all companies were to submit their ads. Such delays would likely affect companies' ability to meet their marketing timelines, and discourage them from submitting the materials for prior FDA review."
[67] FDA e-mail memo to Consumers Union.
[68] Gottlieb, in "Opening Pandora's Pillbox: Using Modern Information Tools to Improve Drug Safety," *Health Affairs*, July/August 2005, p. 938ff.
[69] IOM, 2006.
[70] IOM, 2006.
[71] Department of Health and Human Services. Office of Inspector General, Report No. OEI-01-01-00590, FDA's Review Process for New Drug Applications: A Management Review 42 (2003).
[72] IOM, 2006.
[73] Ibid.
[74] GAO-06-402.
[75] Ibid. The exclusion of information at advisory committee meetings has been documented with devices as well: the European experience with anti-wrinkle device ArteColl was not part of the discussion at the February 2003 Medical Devices Advisory Committee for ArteFill (same product under a different brand name), despite the fact that the device caused serious disfigurations years after implantation. (Rundle, Rhonda. "Antiwrinkle Shots Spark Debate." The Wall Street Journal D3, October 31, 2006.)
[76] Center for Science in the Public Interest. Conflicts of interest on COX-2 panel. February 25, 2005. (Accessed October 30, 2006, at http://cspinet.org/new/200502251_print.html.)
[77] Harris G, Berenson A. 10 Voters on panel backing pain pills had industry ties. New York Times. February 25, 2005.
[78] GAO-06-402.
[79] NRCWF, "FDA Advisory Committee: Does Approval Mean Safety?" August 28, 2006.
[80] Steinbrook, R. Financial Conflicts of Interest and the Food and Drug Administration's Advisory Committees. N Engl J of Med. 2005; 353: 116-118.
[81] Union of Concerned Scientists (UCS) and Public Employees for Environmental Responsibility (PEER). UCS 2006 Food and Drug Administration Survey Compared to the 2002 Health and Human Services Inspector General Survey.
[82] Ibid.
[83] IOM, 2006.
[84] Ibid.
[85] Ibid.
[86] Pharmaceutical Care Management Association (PCMA). "Potential Savings to Medicare from New Generic Drugs Becoming Available." Accessed November 7, 2006 available at: http://www.pcmanet.org/newsroom/2006/Pr_4_06/Medicare%20Savings%20from%20Generics.pdf.
[87] Kaufman, Marc. "Generic Drugs Hit Backlog at FDA – No New Plans to Expand Review Capabilities," The Washington Post, February 4, 2006.
[88] Pharmaceutical Business Review. "Biogenerics: the battle is only just beginning," January 18, 2006.

[89] Ibid.
[90] Tsao, Amy. "Seeking a Prescription for Biogenerics." Business Week. October 24, 2003.
[91] Consumer Reports, November, 2006, p. 58.
[92] Kesselheim AS, Fischer MA, and Avorn J. The rise and fall of natrecor for congestive heart failure: Implications for drug policy. Health Affairs. 2006; 25: 1095-1102.
[93] Letter to the GAO. 09-06-06 Letter to GAO.pdf
[94] Letter to the GAO, 2006.
[95] There is certainly no evidence that approval times are a problem. The US leads the world in the first introduction of new drugs. In 2006, standard reviews are averaging 12.7 months, half the 25.4 months it took to review applications in 2005. Priority review times in 2006 average 9.4 months, down 16% from 2005 and 33% from 2004. "Designer Labeling," by Ramsey Baghdadi, *The RPM Report*, November, 2006.