Summary of Recommendations for PDUFA 4 and 5
Consumers Union
April 12, 2010

Ensure openness in PDUFA 5 negotiating process; make minutes of negotiations/discussions public as they occur.

Enact Administration's proposed generic drug and re-inspection user fees and support passage of international-imported drug safety user fee legislation (e.g., HR 759/S 882).

Increase pre-review of DTC ads, including new forms of advertising, require the running of corrective ads, and develop an effective DTC user fee program in PDUFA 5. Create systems to actively electronically involve patients in providing feedback on drug benefits and side effects.

In labeling, quickly implement the 'drug fact box' proposal (per section 3507 of PL 111-148), and improve quality of information on pediatric use of medicines.

Take a leadership role in comparative effectiveness research, not only through the 'drug fact box' proposals, but through aggressive use of the Sentinel database and by testing new drugs against both placebo and 'best practice in the field.'

Increase, dramatically, the level of auditing of clinical trials (for the safety of domestic and international patients participating in the tests) and to ensure honesty in the full reporting of such trials.

Develop a system of eventually making Phase I trial data public, to avoid duplicate testing of potentially dangerous drugs, and to speed the advance of science. Reduce the use of surrogate endpoint and non-inferiority techniques: do more to show drug *superiority*.

Aggressively address any questions of generic drug safety and increase physician and public understanding of the value of generics.

Reduce deaths and injuries by more aggressive reduction of drug name confusion.

Statement of Consumers Union
Independent, non-profit publisher of *Consumer Reports*
by William Vaughan, Health Policy Analyst
to the

US FDA
PDUFA Public Meeting
Docket No. FDA-2010-N-0128

April 12, 2010

Thank you for the opportunity to speak on behalf of Consumers Union, the independent, non-profit publishers of *Consumer Reports*.[1] We are also members of the Patient, Consumer, and Public Health Coalition, many of whom are testifying today.

PDUFA 5 is an opportunity to make historic, dramatic, life-saving advances in the rapid, safe development and use of prescription drugs.

Ensure PDUFA 5 Process is Open

We deeply appreciate Congress's decision in the 2007 PDUFA law to include consumers more clearly in the re-negotiation process. On the first day of that process, we thank the FDA for this public hearing and hope the entire multi-year process will be open and public. The law calls for meetings with industry and,

> "[N]ot less frequently than once every month during negotiations with the regulated industry, the Secretary shall hold discussions with representatives of patient and consumer advocacy groups to continue discussions of their views on the reauthorization…[Sec. 736B(d)(3)]

Before presenting the PDUFA 5 recommendations developed through this process to the Congress on January 15, 2012, the FDA is to make publicly available "minutes of all negotiation meetings [with] the regulated industry." There appears to be nothing in the law to prevent the minutes from being made public *as* the negotiations occur so that the process is truly open.

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[1] Consumers Union of United States, Inc., publisher of Consumer Reports®, is a nonprofit membership organization chartered in 1936 to provide consumers with information, education, and counsel about goods, services, health and personal finance. Consumers Union's publications have a combined paid circulation of approximately 8.3 million. These publications regularly carry articles on Consumers Union's own product testing; on health, product safety, and marketplace economics; and on legislative, judicial, and regulatory actions that affect consumer welfare. Consumers Union's income is solely derived from the sale of Consumer Reports®, its other publications and services, fees, noncommercial contributions and grants. Consumers Union's publications and services carry no outside advertising and receive no commercial support.

To the extent that minutes are taken of the 'discussions with representatives of patient and consumer advocacy groups' and if Consumers Union is involved in the process, we would be happy to see our 'discussions' and the minutes of them open to the public and the press.

It will be difficult for the public to be truly involved in the PDUFA process if we do not really know what the industry is proposing during the process. Therefore, we urge the industry to make the same commitment to openness.

How is PDUFA 4 Doing versus Public Policy Suggestions

The notice for this hearing asked for comments on PDUFA 4 "process enhancements and funding issues, and not focus on policy issues."

That is hard to do. Critiques of current drug development and safety issues naturally point to future public policy changes.

I have a longer statement I'd like to submit for the Record that clearly contains a mix of critiques and future policy suggestions for both the FDA and the Congress.

New User Fees Needed Immediately

Also, our comments assume that Congress will pass user fees requested by the Administration

--to eliminate generic drug approval backlogs;[2]

--to finance re-inspections of those who fail a first inspection; and

--to ensure imported drug safety (a bill such as HR 759/S. 882)[3];

While we would prefer that general Treasury revenues, raised through progressive taxes, be used to fund all FDA activities, the Federal government's long-range budget picture makes it crystal clear that we cannot rely on appropriations for all the FDA's tasks. If these user fee proposals are not enacted quickly, they certainly should be part of any future PDUFA for obvious safety and consumer savings reasons.

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[2] "[T]he additional user fees will result in a complete review and response for an estimated 80 percent of applications within twelve months of receipt…" FDA FY 2011 budget p. 21-22.

> "Five years ago, the FDA typically approved a new generic drug within 16.3 months of the application's filing, according to a report from the agency on Tuesday. But by last year, with limited staff to review an increasing number of applications, approvals for new generic drugs were taking 26.7 months, the report said." New York Times, 2/20/10 "New Generic Drugs Face Longer Waits for Approval."

[3] This last is a Congressional initiative, not requested by the Administration, though recent FDA testimony has clearly indicated the need for the authorities and resources provided by these bills.

Direct-to-Consumer (DTC) Advertising

Obviously, the effort for a voluntary DTC user fee program totally failed, when industry didn't 'sign up.' Not surprising. Why should a company want to pay a user fee for pre-clearance of ads when the chances of being 'caught' with a bad ad appear to be remote and the punishment is usually only a slap on the wrist?

We believe the entire DTC effort needs to be reformed, strengthened, and expanded. Since only about half of a drug's side effects are discovered in its first 7 years on market,[4]
the rush to mass market new drugs is—on its face—dangerous. Far too many ads are misleading[5], confusing, and designed to minimize the impact of warning messages. We are very disappointed that electronic ads still do not give the public a contact point to report adverse events, despite the FDAAA Section 906(b) provision two and a half years ago asking for action on this issue. We understand that the FDA is concerned that such contact data might be distracting or information overload, but if studies should show that such information is not helpful, we hope the FDA will come up with alternatives, such as user fee-funded PSAs.

We congratulate the FDA for some stronger and more frequent administrative actions on ads in the last year[6]**,** and hope they continue through the remainder of PDUFA 4. Yet clearly, more needs to be done. As the FDA FY 2011 budget requests makes clear, in the coming year, only about 30% of TV ads will get a review. If the FDA would require extensive corrective ads when it finds an abuse—as it did in the YAZ contraceptive ads--, the extra cost (and embarrassment) of such ads might make the enactment of a mandatory pre-DTC review user fee system more likely in 2012.[7]

In addition, the FDA is totally outmanned and overwhelmed when it comes to the new types of advertising occurring on the Internet and in social networks. New resources are needed in PDUFA 5 to monitor this new, Wild West of advertising.

Involve patients in safety reporting. As noted, we strongly support empowering consumers, by telling them where and how to report drug adverse events and side effects.

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[4] According to a study by the General Accounting Office (GAO), over 50% of all approved drugs had serious post-approval risks. 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. See US General Accounting Office. FDA Drug Review: Post-approval Risks, 1976-1985. Washington, DC: April 26, 1990. GAO/PEMD 90-15, and Lasser, KE et al. Timing of new black box warnings and withdrawals for prescription medications. JAMA. 2002; 287: 2215-2220.

[5] It would be particularly useful if the images on the screen matched the type of person who might actually use the drug.

[6] For example, see April 5, 2010 Bloomberg News, "Talecris, CSL Warned by FDA Over Competing Drug Ads."

[7] See http://www.ourbodiesourblog.org/blog/2009/02/fda-requires-corrective-ads-on-yaz-contraceptive

The current system is defective in a number of ways, particularly as it relates to patients' experience:

> "…a substantial body of evidence contradicts this assumption [of relying on doctors to accurately report drug adverse events], showing that clinicians systematically downgrade the severity of patients' symptoms, that patients' self-reports frequently capture side effects that clinicians miss, and that clinicians' failure to note these symptoms results in the occurrence of preventable adverse events."[8]

In PDUFA 5, we hope a system might be developed and funded which would enable/require new drugs to actively involve patients in safety reporting. If a new drug type is approved where there is some 'hint' of danger, with the patients' permission, it should be possible to use e-mails, phones, EHRs, and other outreach reminders to see if patients' can help in building (or refuting) the adverse events database. For example, a patient given a class of drug that has had serious side effects in others could be 'pinged' at appropriate periods of time as to whether they are experiencing benefits or problems with the drug. While this idea obviously has design problems (the power of suggestion could lead to many false positives), those could probably be solved.

Waiting for Truth in Labeling

Despite the FDA's repeated public hearings and the clear interest of Congress (Section 3507 of PL 111-148/152), drug package labeling is still confusing, inconsistent, and inadequate.

We support immediate implementation of the type of 'drug fact box' called for in Senator Reed's Section 3507 amendment to the reform legislation and which has long-been advocated by Doctors Lisa Schwartz and Steven Woloshin[9]. As the doctors have written:

> "Physicians and patients should be able to get credible, unbiased information directly from the FDA—not through the filter of industry. For this to happen, the FDA needs to make what its reviewers know more accessible. The FDA should create standardized executive summaries of drug reviews that quantify the benefit and important harms found in the phase III trials. We developed a possible format for presenting these data, called the prescription drug facts box, modeled on the FDA's nutrition facts boxes. We have shown in 2 national randomized trials that most consumers can understand and use the data tables.
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> The summaries should also highlight remaining uncertainties—such as reviewers' concerns about the cardiovascular harms of Vioxx—and routinely mention whenever the FDA requires postmarketing studies…."[10]

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[8]Ethan Basch, MD., "The Missing Voice of Patients in Drug-Safety Reporting," NEJM 362;10, March 11, 2010, p. 865ff.

[9] "The Drug Facts Box," Med Decis Making Online First, published 9/14/07.

> "Much critical information that the FDA has at the time of approval may fail to make its way into the drug label and relevant journal articles….We don't need to wait for new comparative-effectiveness results in order to improve practice. We need to better disseminate what is already known [or, Consumers Union would add, unknown]."[11]

A simple quantitative fact box showing relative efficiency and safety would help sweep away the years of confusion in this area. Ensuring the accurate development of these fact box labels will require user fee resources.

We hope the FDA will follow-up on its recent study of the 'safety and transparency of pediatric drug trials' and do more to ensure that better information is provided for the use of drugs in babies and children.[12] Again, to the extent that the FDA does not have resources to provide this basic protection for children, PDUFA 5 user fees should be provided.

FDA's Role in Comparative Effectiveness Research (CER)

We urge that the FDA take a major role in the development and dissemination of CER. Knowing how well a medicine or device works compared to other treatment options is vitally important to patients—and can also result in enormous savings to consumers and the health care system as people are empowered to move away from ineffective treatments toward effective approaches.

The drug facts box mentioned above would be a major FDA contribution to comparative effectiveness information that consumers can use and will help make the billions of dollars being spent in ARRA and health reform on CE 'meaningful' for the public.

But the FDA can take two other actions that will truly promote CER, safety and effectiveness.

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[10] Woloshin and Schwartz, "Bringing the FDA's Information to Market," Archives of Internal Medicine, Vol 169, No. 23, Nov. 23, 2009. P. 1985ff. Consumers Union notes that labels are generally still the subject of 'negotiation' with the manufacturer, which we do not believe serves the consumer well.

[11] Schwartz, Lisa M, MD and Woloshin, Steven, MD, "Lost in Transmission—FDA Drug Information That Never Reaches Clinicians. NEJM 361; 18, October 29, 2009. Consumers Union would add, "and what is not known."

[12] As the FDA's FY 2011 budget documents report, the "FDA decided to quantify the frequency and type of new safety information arising from studies performed under the auspices of the Pediatric Exclusivity Program, to describe the dissemination of these findings in the peer-reviewed literature and compare this with the FDA review, and to describe their effect on pediatric labeling. Findings: Thirty-three products (26 percent) had pediatric safety information added to the labeling. Of these, 12 products had neuropsychiatric safety findings and 21 had other important safety findings. Only 16 of 33 of these trials (48 percent) were reported in the peer-reviewed literature; however, 7 of 16 focused on findings substantively different from those highlighted in the FDA reviews and labeling changes. Labeling changes for pediatric use demonstrate that pediatric drug studies provide valuable and unique safety data that can guide the use of these drugs in children. Unfortunately, most of these articles are not published, and almost half of the published articles focus their attention away from the crucial safety data. No recommendations were presented in the study.

First, we urge full, aggressive implementation of FDAAA Section 905's "Active Postmarket Risk Identification and Analysis" While this new Sentinel system seems to be on-course, a huge amount of work remains to be done to meet the database goals. The importance of the Sentinel program in identifying drug safety problems has recently been re-confirmed by a new study of the Vioxx disaster.[13] The key to the success of the program will be enthusiastically using Section 905's 100 million de-identified medical record data base to test questions of safety, efficacy, and comparative effectiveness. In PDUFA 5, user fee resources should contribute to ensure that this powerful new research tool is fully used, and not left idle (see especially, our off-label discussion below).[14]

Second, it is past time to transition to a new system in which drugs and medical devices are tested against the currently approved 'best practice' treatment. We recognize this is a complicated scientific and regulatory issue and that the policy will have to develop over time—and it will take increased PDUFA 5 resources. Put simply, the placebo test standard for many drugs today is too low a bar and often does not answer a clinically relevant questions for patients. This is especially the case for therapeutic categories with several comparable drugs. The current standards fail to serve the public health goal of maximizing incentives for the development of truly innovative drugs. The FDA has recently moved in this direction. For example, it required that the anti-clotting drug prasugrel be tested against clopidogrel, the current standard of care. By testing against best practice, the FDA can help promote comparative effectiveness research, arm consumers with the best information, and improve clinical practice:

> "If the FDA label were required to indicate what is and is not known about a product's superiority to other treatments, then clinicians, patients, and payers would be less willing to pay more for a new treatment without proof that it improved health outcomes. In addition, manufacturers would have an incentive to conduct much-needed active-comparator superiority trials."[15]

Even more seriously, lack of comparative effectiveness information permits companies to hype the advantages of a new drug, sometimes with dangerous consequences:

> "In many cases, therapies have been prematurely adopted, outpacing the generation of evidence necessary to define the boundaries in which a drug or device offers clinical benefit. Atypical antipsychotics are the latest example, with rapid adoption and expanding use at least a decade before the relatively recent

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[13] Joseph Ross, MD et al., "Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data," in Archives of Internal Medicine, Vol. 169 (No. 21), Nov. 23,2009

> "Cumulative pooled analysis of all randomized, placebo-controlled trials demonstrates a trend toward increased cardiovascular risk associated with rofecoxib compared with placebo as early as December 2000, the comparison reaching a P value of .05 by June 2001, nearly 3.5 years before the manufacturer's voluntary market withdrawal."

[14] Sentinel data could also make unnecessary the contracting out of vital public health functions, such as determining the effectiveness of antibiotics.

[15] Stafford, Wagner, Lavori, "New, but Not Improved? Incorporating Comparative-Effectiveness Information into FDA Labeling," NEJM, Sept 24, 2009, p. 1230

> consensus about the similar efficacy of typical and atypical agents and the full recognition of the previously underappreciated metabolic and cardiovascular adverse effects of the atypical agents. Enthusiastic adoption of innovations, only later found wanting, has been a recurrent problem, with examples far beyond short-acting calcium channel blockers for hypertension, troglitazone for diabetes, tegaserod for irritable bowel syndrome, and rofecoxib for mild to moderate pain."[16]

As a recent Commentary in JAMA noted,

> "The current FDA standards for approval fail to assess whether newly approved drugs and devices are less efficacious or less well-tolerated than existing alternatives. This raises the possibility that patients may be harmed by receiving a newly approved treatment instead of an alternative with established efficacy and safety.
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> "…revision of the Code of Federal Register [relating to how drugs are tested to prove efficacy] is needed so the FDA can ensure that new but inferior treatments do not replace established treatments. Approval decisions based on trials with both active treatment groups and placebo control groups would also improve clinicians' and the public's understanding of the role of new treatments, reduce the amount of taxpayer-funded comparative effectiveness research needed, and may even reduce health care costs. Collaboratively designed active-comparator clinical trials could help the FDA and industry work together to improve the health of the public."[17]

The FDA should take the lead in developing this kind of comparative effectiveness. The drug and device industries will always try to avoid studies that could put their product at a disadvantage. As a new study has reported

> "In these high-impact general medicine journals, approximately one-third of studies evaluating medications were CE studies. Of these studies a minority compared pharmacologic and non-pharmacologic therapies, few focused on safety or cost, and most were funded by noncommercial funding sources."[18]

It is important to note that appropriate comparative effectiveness research is not a call for more inappropriate non-inferiority trials. The goal of clinical research should be to develop interventions with safety and/or effectiveness benefits for patients, and not merely focus on developing agents that are somewhat less effective and less safe than currently available products. Given the numerous possible biases present in non-

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[16] G. Caleb Alexander, Randall S. Stafford, "Does Comparative Effectiveness Have a Comparative Edge?" JAMA, June 17, 2009, p. 2488.

[17] Alec B. O'Connor, MD, "Building Comparative Efficacy and Tolerability Into the FDA Approval Process," JAMA, March 10, 2010, Vol. 303, No. 10.

[18] Michael Hochman, MD, Danny McCormick, MD, "Characteristics of Published Comparative Effectiveness Studies of Medications," JAMA, Vol. 303, No. 10, March 10, 2010.

inferiority trials, when scientifically justifiable, FDA should require sponsors to study new interventions against best available therapies *and* placebo in three arm trials.[19]

Continued Widespread Failure to Ensure Safe Use of Drugs Due to Massive Off-Label (OL) Promotion

The OL issue must be addressed.

Off-label drug use is legal and often beneficial. But there is growing concern that (1) it's on the rise, (2) it's not always wise, (3) it's getting riskier[20], (4) drug companies often skirt the rules restricting the promotion of off-label uses,[21] (5) consumers aren't as informed as they should be when a doctor prescribes a drug off-label, and (6) inappropriate off-label use adds to wasteful health spending.[22]

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—meaning that risks could outweigh the benefits. In some classes of drugs, off-label use accounts for up to 75% of prescriptions.[23] OL prescriptions for psychiatric drugs had scientific support only 4% of the time, while prescriptions for allergy medicines had scientific support 11% of the time.[24]

The usefulness and therefore the cost of these prescriptions are questionable—and more importantly, may be dangerous. A major new study released last Monday in the Annals of Internal Medicine again raises serious questions about increased deaths in the use of both typical and atypical anti-psychotics in elderly—most of which are prescribed OL.[25]

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[19] The importance of requiring three arm trials can be seen in the recent study of St. John's Wort v. Prozac v. placebo. Lars Bjerkenstedt, et al., "Hypericum extract LI 160 and fluoxetine in mild to moderate depression," Eur Arch Psychiatry Clin Neurosci (2005): 40-47.

[20] It is reported that a draft CMS commissioned study has noted the poor quality of research on 'targeted' OL cancer drugs which Medicare is paying for, and that these research problems show the need for quality comparative research. For example, the study, being done by AHRQ, says

> "At times, the volume of poorly done work was remarkable; for example, with rituxumab for chronic lymphocytic leukemia, despite abstracting 81 reports, we were unable to draw conclusions." [Inside Health Policy, 11/13/09]

[21] See for example, lawsuit involving Lilly's OL marketing of Zyprexa. Case 1:04-mid01596-JBW-FLM Document 1869-2 Filed 09/05/2008. Also, Tampabay.com, "Memos: Results hidden to peddle antipsychotic," May 20, 2009, describing AstraZeneca's promotion of Seroquel and the hiding of unfavorable study results. As another example, see The New York Times, 2/26/09, "Drug Maker Is Accused of Fraud," describing the Justice Department's charge against Forest Laboratories for illegal OL marketing in children, despite a concealed study showing the drugs were not effective in children and might even pose risks to them. Individual sales teams have also been tempted to misrepresent the safety of drugs used OL: see UDOJ press release of 6/18/09, "Pharmaceutical Company Manager Sentenced for Off-Label Marketing."

[22] www.CRBestBuyDrugs.org, "Off-Label" Drug Use, Shopper's Guide to Prescription Drugs Number 6.

[23] Radley, et al. "Off-label Prescribing Among Office-Based Physicians," Archives of Internal Medicine. 2006;166: 1021-1026; and Young, Alison and Adams, Chris. "Off-label Drugs Take Their Toll," Knight Ridder Newspapers, November 2, 2003.

[24] www.CRBestBuyDrugs.org, "'Off-Label' Drug Use, Shopper's Guide to Prescription Drugs, Number 6."

[25] Gianluca Trifiro, MD, PhD, et al., "Association of Community-Acquired Pneumonia With Antipsychotic Drug Use in Elderly Patients," Annals of Internal Medicine, 2010; 152: 418-425, April 5, 2010.

The government appears to be in a losing game of 'whack-a-mole' with industry---assessing billions of dollars in fines for OL promotion which the companies appear to treat as an annoying cost of business. Image if those billions were spent on actually testing whether an OL use worked or not, and how it compared to other treatments. The recent $2.3 billion in fines just paid by Pfizer could have proven—or disproven—the worth of numerous OL practices.

We urge that now, and certainly in PDUFA 5, a major effort be made stop this terrible waste of resources that can be so dangerous to patients.

We suggest that each year the FDA identify a number (say 10) of the most commonly prescribed OL drugs and through FDAAA authorized studies, randomized clinical trials, and aggressive use of Section 905 databases, determine whether that OL use is reasonably appropriate. While some doctors have been charmed into prescribing these drugs OL (sometimes with the help of lunches and other payola that may now fade away in the light of the new Health Reform law), we believe that once the evidence is clearly available, they will move to making more appropriate prescribing decisions. Under this plan, the government will not be telling doctors how to prescribe—but it will give them hard evidence.

Finally, to help consumers and prescribers, we wish the FDA would *use* the provision in 21CFR201.57(c)(3) to make it clear when there is no evidence of effectiveness or safety in certain uses:

> "(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition."

When Will We Get Honest Reporting of Clinical Trials?

A major part of FDAAA was reform in the registration and reporting of clinical trials. It appears to be too early to tell how well these changes are working—so far it is hard to see big improvements.

But the last two and a half years have brought us many new reports *continuing* to show that the system of trial registration, reporting, and publication is terribly flawed. For example, the Institute of Medicine's 2009 report on conflict of interest lists 8 flagrant examples on one page of their study.[26] The history of scientific dishonesty in the conduct

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Antipsychotics have become the most widely prescribed drugs in the US market (see lastest data from IMS Health).

[26]IOM, Conflict of Interest, Prepublication copy, page 4-8.

and reporting of clinical trials reflects a pervasive and cultural climate problem[27] and adverse events appear to be frequently under-reported.[28] The integrity of the 'journal' system of publication is also suspect.[29] Despite efforts by the International Committee of Medical Journal Editors to require investigators to register their trials prior to participant enrollment as a precondition for publishing the trial's findings in member journals, a recent study shows poor compliance and that 'selective outcome reporting is prevalent.[30] The ClinicalTrials.gov system itself showed significant weaknesses before the enactment of FDAAA and it may be suspected that compliance with the more extensive reporting requirement of FDAAA Title VIII will be problematic unless there is an aggressive system of audit.[31]

Attached is a further list of recent abuses in the system.

The flaws are so pervasive and so serious, and so often unethical, that we fear for the success and integrity of the new program.

It would be naïve in the extreme to think that for-profit companies will ever voluntarily fully disclose trial data that is disadvantageous to them or that some journals that profit from the process will adequately police these trial publications. *Caveat emptor* is not good enough when it comes to the life-and-death but highly technical data from these trials.

Therefore, we urge that now, and through increased revenues from PDUFA 5, a regular and extensive system of sampling and auditing a certain percentage of trials be

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[27]For example, see reports of a prominent Harvard psychiatrist researcher telling a drug company his 'planned' studies would benefit the company. New York Times 3/20/09. See also, The Washington Post, March 18, 2009, "A Silenced Drug Study Creates An Uproar," describing a long cover-up of an unfavorable study on Seroquel

[28]See Editorial in the Archives of Internal Medicine, Vol. 169, No. 19, October 26, 2009, "Adverse Events in Randomized Trials: Neglected, Restricted, Distorted, and Silenced." Reviewing an article by Dr. Isabelle Pitrou et al in the same issue, the Editorial notes: "Much in line with previous evaluations, the [Pitrou] study found that some trials gave absolutely no information on harms, severity was often undefined or vaguely defined, and half the trials reported no information on withdrawal of patients owing to harms. Only 13% reported the reasons why patients withdrew owing to adverse events, information that is of prime clinical relevance."

[29]For example, see the work of Dr. Tom Jefferson, Cochrane Vaccines Field, 2009. As one of his studies finds, "one of the levers for accessing prestige journals is the financial size of your sponsor. Pharma sponsors order many reprints of studies supporting their products, often with in house translations into many languages, they will also purchase publicity space on the journal. Many publishers openly advertise these services on their website."

[30]Sylvain Mathieu, MD, et al., "Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials," JAMA, Sept. 2, 2009 (Vol. 302, No. 9), p. 977.

[31]Joseph S. Ross, et al., "Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis, PLoS Medicine, Sept. 7, 2009, which concludes:

> "Reporting of optional data elements varied and publication rates among completed trials registered within ClinicalTrials.gov were low. Without greater attention to reporting of all data elements, the potential for ClinicalTrials.gov to address selective publication of clinical trials will be limited."

established to obtain integrity in the registration and reporting of trials required under Title VIII of FDAAA.

Failure to Protect Patients in Clinical Trials

International Trials: "[M]ost testing for the US drug industry's late-stage human trials is now done at sites outside the country, where results often can be obtained cheaper and faster…"[32] But it is clear that such foreign testing raises serious quality, effectiveness (genetic variations in some areas of the world raise issues of effectiveness in the US population), and ethical issues.[33] It is time for a major review—perhaps by the Institute of Medicine or an HHS task force—of the issues raised by the 'export' of clinical trial testing and how to ensure quality in those international trials.

On the issue of integrity, we can't even ensure the integrity of data in our own country, how are we going to do it overseas?[34] Especially when the FDA budget for FY 2011 calls for only 750 inspections of over 6,000 FDA-regulated drug manufacturing facilities worldwide.[35] The Administration is to be commended for seeking increased funding in FY 2011 to protect human subjects in clinical trials, but much more needs to be done than the $500,000 budget request will support. As the FDA budget documents explain (Component P-5),

> "To effectively protect human subjects and ensure integrity of clinical trial data, FDA must inspect clinical trials of investigational drugs. These trials are conducted at increasing number of sites, often in countries with very little history of biomedical research and human subject protection. *However, FDA currently inspects less than 1 percent of these sites.* Multiple problems with the conduct of clinical trials have been documented, including criminal behavior that puts human subjects at serious risk. More commonly, drug reviewers encounter data that appears to have been potentially falsified because results appear too uniform across studies. Furthermore, FDA does not have a reliable method of evaluating the risk profile of different clinical investigation site(s)—a critical tool to deploy limited FDA resources in the most effective and efficient way." [Emphasis added][36]

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[32] "Most Testing for US drug industry's late-stage human trials done outside the country, study indicates," Wall Street Journal, February 19, 2009. See "Ethical and Scientific Implications of the Globalization of Clinical Research, by Seth W. Glickman, MD, et al., NEJM, 360;8, February 19, 2009.

[33] See Peter Lurie, MD, Comment in The Lancet (HRG Publication #1732), "US Exceptionalism Comes to Research Ethics," March 26, 2005.

[34] In April 2009, the FDA suspended one testing company's trials after a GAO undercover study showed that patients' rights were not adequately protected. Drug and device trial enrollees should not need to rely on the legislative branch's GAO for protection—the FDA should have an on-going system of surprise (unannounced) audits and visits to clinical trial sites. (FDA News, April 14, 2009)

[35] FDA FY 2011 Budget, p. 105.

[36] In view of the many cases of scientific misconduct, we congratulate FDA for its March, 2010 proposal to strengthen the Regulations requiring rapid reporting of suspected fraudulent data and research activities.

Phase I Trials: In addition to trial integrity, we need to protect patients against repeated experiments on chemicals and processes that have previously failed. As Cleveland Clinic's Dr. Steven Nissen testified before the Senate HELP Committee on November 16, 2006:

> When drugs show serious toxicity in patients, the results are rarely published. Accordingly, other companies subsequently expose patients to closely-related drugs without knowing that their competitors' study of a similar agent showed significant harm. *I am aware of a class of drugs where more than a dozen compounds showed serious toxicity, resulting in termination of development, but without a single publication of results.* In my view, when a patient volunteers to participate in a drug or device study, there is an implicit moral obligation that the patient's participation will benefit medical science. When studies are not published, we learn nothing from the experiment and make the same mistakes over and over again. [Emphasis added]

Companies argue for trial result secrecy for proprietary reasons, but the world does not have enough resources to needlessly repeat failed experiments, when those same resources could be used on a new and different theory. Failed trials are in many ways as important as successful ones. It is Thomas Edison who is supposed to have said, "Results? Why, man I have gotten a lot of results. I know several thousand things that won't work." Since in almost all cases, the cost of the research receives taxpayer subsidies (through the R&D tax credit) or is used to reduce a corporation's taxes (through deductions and loss-carry-forwards), it is only fitting that the public eventually have the benefit of the scientific knowledge that is gained.

The addition of Phase I data can also add to the population base for purposes of compiling meta-analyses and, while the numbers of tested people involved are very small, that data may help point to areas where there may be drug dangers and where more work is needed.

When Phase I trials are repeated—when one company's Phase I trial fails and then is repeated by another researcher—patients are put at risk. To unnecessarily subject individuals to research risks is fundamentally at odds with the NIH's 1979 Belmont Report, which set ethical principles and guidelines for the protection of human subjects of research.[37] In the FDA's FY 2011 budget request (page 404), the case was made for international cooperation in understanding what pediatric trials are underway, on the grounds that babies and children should not be experimented on unnecessarily. As the FDA says

> Pediatric trials are global, due to the incidence and distribution of diseases in the pediatric population. Since children cannot give informed consent to participate, federal agencies have the additional responsibility of ensuring the appropriateness of pediatric product development trials. To assure that children are not exposed to unnecessary, duplicative or poorly designed clinical trials, FDA must be aware of

[37] See http://ohsr.od.nih.gov/guidelines/belmont.html.

> pediatric proposals in Europe and other countries. To fulfill its mission, FDA must collaborate with other countries or regulatory agencies where pediatric trials are being legislated or conducted. This initiative is necessary to maintain collaboration with European colleagues and to expand the frequency, depth and global outreach to include other regulatory agencies who oversee pediatric studies. International scientific communication and collaboration will enhance the safety, ethics and scientific rigor of pediatric trials, thus preventing children from becoming a global commodity for economic gain.

We believe the same argument applies to all patients and consumers. Therefore,

> --it is time to develop a system whereby the FDA can provide guidance to companies designed to prevent this senseless danger and waste of resources, and
>
> --we urge Congress to require the eventual public reporting of Phase I trials, as part of the approval process, or in the case of withdrawn and failed efforts, after a suitable period of time. This information will advance the cause of science, save lives and resources, speed new drug development, and meet a moral obligation: people who subject themselves to an experiment should have the results of that risk contribute to the world of knowledge.

Surrogate End-points and Non-Inferiority: A related issue is our concern about the use of surrogate endpoints that may, in fact, tell little about the real usefulness of a drug, and the use of non-inferiority trials. Patient don't come to the doctor complaining that their cytokine levels are too high or their enzymes are out of whack. Patients want and need therapies that make them feel better, function better, or prolong their lives. Many biomarkers used as surrogate endpoints do not ultimately prove to predict benefit on outcomes that are important to patients. FDA should promote the use of Patient Reported Outcomes (PROs) that directly measure how interventions make them feel, as outlined in FDA's recently finalized guidance on Patient Reported Outcomes (December 2009).

Non-inferiority trials are subject to many forms of bias that make drugs look more similar when in fact they differ substantially in effectiveness or safety. Non-inferiority trials should only be used when interventions have benefits other than improved effectiveness, such as improved safety. Patients and clinicians need to know how drugs differ from each other and what added benefits one intervention has over another, not how much worse one intervention is compared to already available interventions. Some therapeutic areas, like anti-infectives, have allowed inappropriate use of non-inferiority trials for years, resulting in increased adverse events including antimicrobial resistance with unclear benefit for patients. To adequately address unmet medical needs, patients and clinicians need information from properly designed *superiority* trials. FDA should not allow sponsors to hype unproven supposed "benefits" of interventions from inappropriately designed non-inferiority trials.

Aggressively Address Generic Safety

As noted earlier, we support generic user fees without performance goals (let's not repeat the original mistakes of PDUFA) to eliminate the backlog of generic drug applications. We also need more resources to ensure that follow-on biologic (FOBs) applications are processed as rapidly as possible and that we understand the safety of FOBs being rapidly approved by the Europeans. The rapid entry of generics into the marketplace results in huge savings for consumers over time and will repay the cost of the user fees many times over.

But we also urge more resources to educate and assure the public—if the data supports it--that generics have the same quality, safety, and effectiveness of brand name drugs. Polling in 2009 by Consumer Reports finds that about half (47%) of consumers that take prescriptions regularly have some reservations or misconceptions about generics. In recent years, there have been a number of generic drug recalls—a sign that the FDA's inspection system may be working, but also a sign that this is indeed an area that needs inspection and monitoring.[38] In 2009, there were several media stories that generic anti-epilepsy drugs were not as good as brand drugs.[39] Fortunately, the FDA is working with NIH on studies to determine the truth of such charges.[40] We urge the FDA and HHS to do more to educate the public about the savings available from generics and to answer questions about safety. This can be particularly important for those who most need to consider generics: Consumer Reports' National Research Center's polling in January 2009 found that

> "The share of prescriptions accounted for by generics is lowest among some of the groups that could benefit most by cost savings. Generics accounted for the lowest share of total prescriptions among: Those spending more than $50/month on prescriptions, black non-Hispanics, and those under 35 years of age."

Confusion in Drug Names

Each year, according to the Institute of Medicine, thousands of people die or are injured by taking the wrong medicine—and a major cause of these tragic errors is confusion in the naming, labeling, and packaging of drugs. For example, Actor Dennis Quaid has sued over similar-looking packaging that contributed to a hospital giving his twin babies 1000 times the prescribed dose of heparin, a blood thinner. A 2009 Consumers Union review

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[38]For a list of recent recalls, see Mike Cohen et al, ISMP QuarterWatch report (Q3 2008), released May 7, 2009.

[39]See, for example, the concern of FDA's Congressional appropriators who included the following language in the FY 2010 FDA Appropriations Conference Report:

> "The conferees request the FDA report on adverse events and seizures associated with brand and generic anti-epileptic drugs. Specifically, the agency should examine the pharmacokinetic profiles of "A" rated anti-epileptic drugs from different manufacturers of the same therapeutic agent. The Committee directs the FDA to submit a report not later than September 30, 2010, detailing whether the agency believes that any changes to the current bioequivalence testing should be recommended."

[40] FDA Week, "FDA Seeks NIH Study, Industry Data to Counter Public Doubts on Generics," Nov. 6, 2009.

of the IOM's "To Err is Human" ten years after it was issued noted that 'drug name confusion' was still a major problem:

> "While the FDA reviews new drug names for potential confusion, it rarely requires name changes of existing drugs despite high levels of documented confusion among drugs, which can result in dangerous medication errors."

Consumers Union cited primidone, a seizure medication, and prednisone, an anti-inflammatory drug, as an example of different drugs that sound similar. Confusion over the name of these two drugs has been blamed for the death of a California teenager in 2004.

The FDA's FY 2011 budget seems to provide for one new staff person in the 'protecting patients initiative' that involves, among many tasks, reducing drug name confusion (although other staffing resources are undoubtedly included in the budget).[41] Given the level of physical and financial harm caused by medication errors, we hope that PDUFA 5 resources can make this a larger priority, with a goal of reviewing the entire formulary of potent drugs by a date certain.

Conclusion

There are a number of other actions we hope the 112th Congress will take to ensure that the FDA is, indeed, the world's Gold Standard of timely approval of safe drugs, which we will be presenting in other forums.

We thank the FDA for their daily hard work on behalf of the public and for your time today.

[41] FDA FY 2011 Budget, p. 116.

Attachment

Following are some additional recent examples of trial abuse:

--"The makers of antidepressants like Prozac and Paxil never published the results of about a third of the drug trials that they conducted to win government approval, misleading doctors and consumers about the drugs' true effectiveness….In published trials, about 60 percent of people taking the drugs report significant relief from depression, compared with roughly 40 percent of those on placebo pills. But when the less positive, unpublished trials are included, the advantage shrinks: the drugs outperform placebos, but by a modest margin…."[i] "According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive."[ii]

--A 2009 HHS Inspector General report found that the FDA is failing to identify and mitigate the impact of financial conflicts of interest among researchers who conduct clinical trials. "Despite a 1999 regulation that requires a drug or device manufacturer to disclose the financial interests of clinical trial investigators when the company submits an application to market a product, nearly 42% of the 118 applications approved by the FDA in 2007 lacked complete financial information…"[iii]

--"Over the past 12 years, anesthesiologist Scott Reuben revolutionized the way physicians provide pain relief to patients undergoing orthopedic surgery for everything from torn ligaments to worn-out hips. Now, the profession is in shambles after an investigation revealed that at least 21 of Reuben's papers were pure fiction, and that the pain drugs he touted in them may have slowed postoperative healing."[iv]

--"The drug maker Pfizer earlier this decade manipulated the publication of scientific studies to bolster the use of its epilepsy drug Neurontin for other disorders, while suppressing research that did not support those uses, according to experts who reviewed thousands of company documents for plaintiffs in a lawsuit against the company. Pfizer's tactics included delaying the publication of studies that had found no evidence the drug worked for some other disorders, 'spinning' negative data to place it in a more positive light, and bundling negative findings with positive studies to neutralize the results, according to written reports by the experts, who analyzed the documents at the request of the plaintiff's lawyers."[v]

--"Wyeth, the pharmaceutical company, paid ghostwriters to produce medical journal articles favorable to its hormone replacement therapy Prempro, according to Congressional letters seeking more information about the company's involvement in medical ghostwriting. At least one article was published even after a federal study found the drug raised the risk of breast cancer.[vi]

Nearly two years after FDAAA's clinical trials registry reforms, few results have been posted. In the two years, 80,000 studies have been registered, but sponsors have posted results on fewer than 1 percent of them.[vii]

It is clear that industry-funded trials are often distorted: a drug's benefit is often exaggerated, and harmful side effects minimized, under-reported, and otherwise hidden. For example,

> "those [university researchers] with industrial support were more likely than those without it to report that a publication was delayed by six months or more…or that the delay was to inhibit the dissemination of undesired results (5.0 percent versus 1.1 percent….).[viii]

> "A new study in the journal Cancer [reported] among 52 randomized, controlled trials with no conflict of interest, 14% found significantly better survival with the intervention relative to control, 72% found equivalent survival, and 6% significantly favored the control. In 72 similar trials with conflict of interest, 29% found in favor of the intervention, 61% showed no difference, and none reported better survival with the control.[ix]

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[i] "Antidepressant Studies Unpublished," by Benedict Carey, The New York Times, January 17, 2008.
[ii] Turner, Erik, et al., "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy," New England Journal of Medicine, 358;3. January 17, 2008.
[iii] "Report: FDA Exerts Too Little Oversight of Researchers' Conflicts of Interest," Bridget M. Kuehn, JAMA, Vol. 301, No. 7, February 18, 2009. See www.oig.hhs.gov/oei/reports/oei-05-07-00730.pdf.
[iv] SciAm.com News, March 10, 2009, "A Medical Madoff…" by Brendan Borrell.
[v] "Experts Conclude Pfizer Manipulated Studies," by Stephanie Saul, The New York Times, October 8, 2008.
[vi] "Wyeth's Use of Medical Ghostwriters Questioned," The New York Times, December 12, 2008.
[vii] Drug Industry Daily, 9/16/09.
[viii] Zinner, Darren, et al., "Participation of Academic Scientists in Relationships with Industry," Health Affairs, November/December, 2009, p. 1820.
[ix] Merrill Goozner, http://www.gooznews.com, 05/12/2009, "Are Conflicts of Interest in Cancer Clinical Research the Real Problem?" In addition to showing biased results, the data makes a good case for the FDA doing more to inform the public about comparative effectiveness.