Comments of Consumers Union

before the

Food and Drug Administration
Science Board

April 15, 2005

INTRODUCTION

Consumers Union, publisher of *Consumer Reports* magazine, offers the following comments to the Food and Drug Administration's Science Board for consideration during its April 15, 2005 meeting on FDA's pre- and postmarketing safety programs for drugs and biologics.

Consumers Union is a nonprofit membership organization chartered in 1936 to provide consumers with information, education and counsel about goods and services and to advocate for state and federal policies that advance and protect consumers' interests. CU has a long history of advocating for drug safety reform.

In 1933, CU's predecessor organization, Consumers' Research, published the book *100 Million Guinea Pigs: Dangers in Everyday Foods, Drugs, and Cosmetics* and was an early advocate for legislation requiring drug makers to establish the safety of their products prior to enactment of the Food, Drug and Cosmetic Act of 1938.

Consumer Reports magazine, with approximately 4.5 million print subscribers and more than one million subscribers to our online site ConsumerReports.org, regularly carries articles on health-related topics, including federal and state consumer protection laws, policies and programs. *Consumer Reports* ranks 7th nationally among print periodicals for the number of subscriptions.

Consumers Union also publishes its affiliate *Consumer Reports On Health*, a monthly newsletter with 400,000 subscribers, which is devoted to health-related topics, including diet & exercise, safe and effective use of medications, preventative health, and developments in the medical sciences.

In addition to subscription-based services, Consumer Reports also operates the Best Buy Drugs™ Project, a major new public education program that provides unbiased information about the comparative effectiveness and cost-effectiveness of prescription drugs. This web-based service is free to all consumers, and free print materials are also being distributed.

It has become increasingly clear that consumers do not receive an adequate balance of information about the risks and benefits of many prescription drugs, which has led to the inappropriate and harmful use of some medications in recent years. The project goal is to empower doctors and patients in making informed medication decisions guided by unbiased information rather than direct-to-consumer and direct-to-physician advertising that fails to tell the whole story about safety and effectiveness.

DISCLOSURES

Consumers Union's income is solely derived from the sale of *Consumer Reports*, its other publications and from noncommercial contributions, grants and fees. Our publications carry no advertising and receive no commercial support. Consumers Union has no financial interest in or relationship with any commercial entity that would be affected by the topic of this meeting.

OVERVIEW

Our comments to the Science Board regarding pre- and post-approval drug safety issues and proposed reforms focus on core policy issues. These improvements are essential to ensuring that FDA is equipped to strike the appropriate balance between a drug's risks and benefits at the time of approval, conduct proactive postmarket safety surveillance, and take timely action to mitigate unreasonable risks when they arise.

Consumers Union believes legislative action is essential to address the substantial problems in drug safety and oversight that have been highlighted over the last year. While the FDA may make changes that would ameliorate some of the problems, the FDA should establish a priority of working with Congress to develop fundamental reforms that will assure the agency has the authority, tools, and resources necessary to do its job.

The controversies of the past year regarding the safety of non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants have generated significant mainstream media coverage and stimulated an important discussion among policy makers, the public and the medical community about FDA's ability to ensure the safety of drugs it approves.

Rather than outliers in an otherwise sound regulatory system, the safety failures associated with NSAIDs and antidepressants are symptoms of serious structural and regulatory shortcomings at FDA. Before them came the prescription medications Baycol, Duract, Enkaid, Posicor, Redux, and Rezulin, and the over-the-counter

medication phenylpropanolamine. Without significant reform of the pre- and postmarket safety program at FDA, more drugs will surely be added to this list of safety failures.

The Science Board, in its evaluation of the issues before it, should take seriously the troubling findings of the 2003 Department of Health and Human Services Office of the Inspector General survey of FDA drug reviewers. Among them were the following:

- 36% of FDA reviewers surveyed were not at all confident or only somewhat confident that FDA's final decisions adequately address the safety of a drug;
- 30% of reviewers were not at all confident or only somewhat confident that FDA's labeling decisions adequately address key safety concerns;
- 19% of reviewers were not at all confident that CDER adequately monitors the safety of prescription drugs once they are on the market, and an additional 47% were only somewhat confident; and
- 18% of reviewers said they had been pressured to approve or recommend approval of a drug despite their reservations about safety, efficacy or quality.

Consumers Union urges the Board to critically analyze the questions this survey and the above noted safety failures raise and advise FDA on truly meaningful reforms to ensure consumers have access to medications that are not only effective, but are also safe.

COMMENTS AND RECOMMENDATIONS

1. Pre-approval Safety Improvements

A) Routinely require post-market clinical trial commitments: While pre-market clinical trials can successfully demonstrate efficacy, their ability to identify safety questions is significantly impeded by the duration, size, and subjects of the trial. First, the duration of phase III trials is generally insufficient to identify safety concerns arising from longer-term use of a medication. This is a significant shortcoming for those drugs that may be taken over a lifetime for treatment of chronic conditions.

Second, phase III trials rarely have a sufficient number of subjects to detect all the safety issues that may emerge once the drug is on the market and is prescribed to millions of patients. However, safety signals may be identified by phase II and phase III trials that raise potential safety concerns that warrant additional study in postmarket trials.

Third, phase III trials generally include subjects who are healthier and younger than the intended treatment population and who are not taking other medications that might confound trial results. Thus the clinical trial results will not necessarily detect safety concerns that may arise during actual use by older, less healthy patients who take multiple medications.

While Consumers Union does not propose that FDA implement changes to its pre-approval clinical trial requirements (with the exception of 1(B) below), the shortcomings

identified above strongly argue for postmarket study commitments as a condition of approval for all new drugs.

Currently, FDA may require drug sponsors to conduct postmarket study commitments to address unanswered questions on safety, efficacy, drug interactions, pharmacokinetics and other issues, but does so on a limited basis for standard approvals. FDA also currently requires postmarket study commitments under the Pediatric Research Equity Act and for fast-track drugs approved under accelerated processes. Given the shortcomings of preapproval clinical trials in identifying safety concerns and the inadequacy of FDA's passive postmarketing safety monitoring system (see next section), FDA should require sponsors of new drugs to conduct postmarket clinical trials and vigorously enforce compliance. Of existing open postmarket study commitments required at the time of approval, more than two-thirds have not even been initiated.

FDA's April 7 decision requesting withdrawal of Bextra offers an important lesson. In a January 2001 medical review of the drug, following analysis of cardiovascular (CV) risks in short-term coronary bypass surgery trials, reviewers recommended that among other safety issues, cardiovascular risks be further analyzed in additional clinical trials. The final medical review prior to approval later that year also identified CV data as a safety concern. Yet no study commitment regarding CV risks or any other safety concerns were identified in the approval letter. The lack of data on CV safety for long-term use was among the reasons for Bextra's withdrawal.

At a minimum, FDA should require as a condition of approval, postmarket study commitments for new drugs meeting criteria including, but not limited to, the following:

- The drug is approved for treatment of a common condition, which suggests widespread use by the patient population;
- The drug may be used for long-term treatment of chronic conditions and the duration of premarket clinical trials is insufficient to detect safety concerns arising from long-term use;
- The drug is likely to be used off-label despite FDA's approved use; and
- Premarket trials suggest safety concerns, but produce ambiguous results.

B) Require Comparative Trials: Additionally, under current agency practices, except in rare cases, drug sponsors are required only to conduct clinical trials comparing the new drug to placebo rather than to existing treatments for the same condition. Unless there is a perceived marketing advantage of conducting a clinical trial of a drug against both placebo and existing treatments, drug sponsors are reluctant to do so.

While the Food, Drug and Cosmetic Act does not require FDA to determine that new drugs are more effective than existing treatments, it does require them to determine that the drug is safe and effective. As FDA has often noted, its implementation of this statutory requirement relies on balancing risks of a particular drug with its treatment benefits. But FDA's risk/benefit analysis is functionally limited to evaluating the risks of a particular drug against its benefits, rather than those of existing treatments.

As a result, the pre-approval process does not provide FDA with sufficient data to make fully informed contextual risk/benefit determinations. This shortcoming has particular relevance for drug classes known to have safety risks, such as statins for treatment of cholesterol and NSAIDs for pain relief. Clinical trials comparing a new drug to placebo may produce a more favorable risk/benefit profile than if that drug were compared to an older drug for the same condition. In addition, FDA, patients and healthcare providers would benefit from knowing whether a new drug is both *safer* and *more* effective than older drugs for that condition.

Comparative data would likewise provide a scientific basis for allowing or prohibiting comparative claims in consumer and physician promotional materials. For example, Consumers Union is concerned about recent television advertisements promoting naproxen as the "safest" NSAID when direct comparative data is unavailable. This point was underscored by FDA's April 7 announcement regarding its request for additional comparative studies for all NSAIDs.

Consumers Union therefore recommends that clinical trial data submissions for new drugs be tested against both placebo and existing treatments. At a minimum, FDA should require such comparative clinical trials for new drugs in classes with known safety risks. Existing statutory authority is sufficiently broad for FDA to implement such a requirement. Requiring comparison to existing treatments is not unprecedented. Clinical trials of drugs for serious or life-threatening conditions rarely have placebo groups.

Requiring clinical trials to compare a new drug against both placebo and existing treatments allows FDA to make comparative risk/benefit determinations at the time of approval, not years later after patients have been put at risk. If FDA lacks clear authority to require trials against placebo and existing treatments, this board should recommend that the agency seek it.

C) Require Improved Risk Management at Time of Approval: FDA has available to it a wide range of risk management tools to ensure that drugs do not pose unreasonable risks: requirements and limitations for promotional materials and efforts, black box warnings, restrictions on distribution or detailing, labeling requirements, informed consent, data collection requirements of sponsors, educational efforts, and so forth.

FDA should manage risk carefully *at the time of approval*, particularly for new drugs for which safety concerns have been identified or remain unanswered, postmarketing study commitments have been made, or for which boxed warnings have been required. For example, restrictions on promotional efforts, such as those recently agreed to by the sponsors of Palladone and Symlin, should be the rule rather than the exception. Both drugs carry boxed warnings, and the maker of Symlin must conduct a postmarket study. The restrictions on promotion during the first phase of these drugs' market lives offers additional and important risk management.

With more active risk management at the time of approval, FDA would be in the enviable position of lifting risk management restrictions when safety concerns have been addressed rather than imposing them after the patient population has been put at risk. In the meantime, the risk/benefit profile of the drug is more favorable when it is used only by the patients who really need it.

Again, Bextra provides an important lesson. The medical review for the drug during the approval process raised concerns about the excess of cardiovascular events in coronary artery bypass surgery trials for the drug. Reviewers therefore requested subanalysis of trial data to evaluate of the cardiovascular risk of this drug. The request was based on concerns from trial results and on questions raised on CV risks of COX-2s by the Vioxx VIGOR trial—completed prior to the approval of Bextra. However, that subanalysis precluded "robust evaluation" with other comparators because the trials were small. Yet, FDA did not impose use restrictions on the drug while those safety questions were answered. In fact, FDA did not require the label to include a contraindication for treatment following bypass surgery until November 2004.

In the case of Elidel, for which FDA recently issued a public health advisory, questions on carcinogenicity arose in pre-market trials. As part of the approval decision in 2001, the sponsor agreed to additional postmarketing commitments on carcinogenicity. FDA could have imposed risk management greater steps to limit use of the drug until the study commitment had been met.

And in the case of now-withdrawn Vioxx, when cardiovascular risks were suggested by the VIGOR study in 2000, FDA should have imposed risk management measures contraindicating Vioxx for patients at high cardiovascular risk and restricting promotional efforts until safety concerns were addressed. Instead, the drug was widely prescribed, putting millions of patients at risk.

Such early risk management for drugs with unanswered safety questions would go far in ensuring safety before a wider patient population is exposed. FDA has sufficient authority to take such steps now. In addition, proactive risk management provides direct incentives for drug sponsors to meet deadlines for submission of postmarket study commitments that put safety questions to rest.

2) Postmarket Safety Concerns

A) Adverse Event Reporting System is Inadequate: As noted above, pre-market trials provide only the starting point for drug safety surveillance. Under FDA regulations, drug makers are obligated to submit adverse event (AE) reports to FDA within specified time periods according to the nature of the event. Most of the AE reports FDA receive come directly from the drug sponsor, rather than from clinicians. In addition, FDA requires the submission of annual reports including new information, such as data from published studies, summaries of unpublished studies, and other information relating to the drug's safety, efficacy or labeling.

As a result, FDA's postmarket safety surveillance system relies largely on the drug sponsor to monitor the safety of the drug. FDA's Office of Drug Safety, with a staff of just over 100, is responsible for collecting and analyzing adverse event reports. Last year, according to recent FDA testimony, the agency received some 400,000 adverse event reports—a record number.

The weaknesses of this passive safety surveillance system have been widely noted. Among other shortcomings, adverse event reporting, though better-equipped to identify rare side effects, is far less able to detect common adverse events such as cardiovascular events. It also relies largely on drug sponsors to report adverse events.

In the December 1, 2004 *Journal of the American Medical Association* article "Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions," by Bruce Psaty et. al., the authors note, "…When serious adverse effects … appear after marketing, defects in the safety-surveillance system can, depending on the response of the pharmaceutical company, pose a threat to the health of the public."

B) Office of Drug Safety Lacks Authority & Resources: FDA's Office of Drug Safety (ODS) is responsible for postmarket safety surveillance. In addition to monitoring and evaluating adverse event reports, ODS also takes initiative when safety uncertainties arise to propose and implement observational and pharmacoepidemiologic studies, as it did in the case of Vioxx and Celebrex. The Office's lack of resources (with a budget under $30 million annually) limit its ability to initiate new, independent epidemiologic studies that flag important safety risks that AE reports may not detect.

ODS is also responsible for evaluating and monitoring published research of approved drugs. We note, however, that published research suffers from publication bias—the reluctance of investigators to seek publication of negative results. As a result, the medical literature, while of some value, is an inadequate source of unbiased drug safety information.

In addition, ODS does not have authority to impose risk management measures, manage or oversee the drug advisory committees that make safety recommendations, or to require any additional clinical studies. It serves as a consultative body to the Office of New Drugs (OND) which is empowered to determine what corrective action, if any, will be requested from the manufacturer.

Still, ODS reviewers have played pivotal roles in flagging serious safety concerns that have led to the withdrawal of unsafe drugs. With greater resources, independence and authority, ODS could play a more effective and active role in ensuring the safety of the prescription drugs that two-thirds of adults take.

C) Internal Conflicts of Interest: Last year's troubling reports about pressures facing reviewers within the Office of Drug Safety to withdraw safety recommendations from

their evaluations or to change their findings raise troubling questions about the power imbalance between the ODS and OND. As noted above, OND retains decision making authority on risk management. Moreover, resources devoted to new drug approvals dwarf those devoted to postmarket safety by nearly ten-to-one. As a result, OND and drug approval dominates the Center for Drug Evaluation and Research at the expense of postmarket safety.

Consumers Union challenges the wisdom of empowering the division that approves a new drug with the authority assess and take action on postmarket safety concerns. Under this rubric, the FDA staff that approved a drug are tasked with identifying what could be considered shortcomings with their initial approval decision. It presents an inherent conflict of interest.

Though we are heartened by FDA's recommended withdrawal of Bextra and its inclusion of a class-wide warning in package inserts and medication guides for all prescription NSAIDs, the action was long overdue. We question whether FDA would have taken these and other risk management steps in the absence of Congressional oversight and widespread public disclosure of the Agency's failure to address the serious safety concerns raised by ODS staff in 2004. Indeed, just weeks before Merck voluntarily removed Vioxx from the market, OND approved the drug for pediatric use. Though the drug's CV risks may have been irrelevant to the pediatric label change, the approval does not signal a drug approval division that took Vioxx's risks seriously or intended to take any risk management steps.

D) Lack of Authority to Enforce Postmarket Study Commitments & Mandate Phase IV Clinical Trials After Approval: A critical supplement to AE reports and epidemiologic studies are phase IV controlled clinical trials designed to evaluate long-term safety.

Yet, once a drug is approved, in order to secure commitments for additional postmarket clinical studies to address safety concerns, FDA must negotiate with the drug sponsors to do so. The agency does not have the authority to mandate such studies once a drug is approved. In FDA's recent announcement that Pfizer will conduct a long-term study to address the safety of the drug, the agency notes that it has "asked Pfizer to take the actions"—a carefully worded statement that makes clear the agency's inability to require the steps of the drug maker.

In the same announcement, after noting the lack of long-term clinical trials for most NSAIDs, FDA states that it will "encourage additional long-term controlled clinical trials of non-selective NSAIDS to further evaluate the potential for increased CV risk." It must "encourage," because it cannot require such studies.

Moreover, the agency lacks authority to require compliance with postmarket study commitments made at the time of approval. Unlike its enforcement powers for food and medical devices, FDA does not have the ability to impose civil monetary penalties for compliance violations. The only penalty it can impose on intransigent drug sponsors is

withdrawal, injunction or seizure—enforcement tools the agency uses only as a last resort and has reportedly never used to enforce compliance with postmarket study commitments.

E) Lack of Authority to Mandate Label Changes: As with postmarket study commitments, FDA lacks authority to mandate label changes and other risk management steps such as those requested in FDA's recent announcement on NSAIDs. FDA requested boxed warnings, medication guides and other risk communication measures. After such requests, FDA must negotiate label and other language associated with patient and clinician communications.

The process for the label changes requested of Merck for the COX-2 Vioxx, finalized in April 2002, is instructive. The agency and the drug sponsor Merck spent nearly seven months in negotiations over the label language.

As with postmarket study commitments, the agency has no enforcement tools other than seizure, injunction or withdrawal to enforce compliance with their requests.

F) Recommendation: Establish an Independent Office of Drug Safety with sufficient authority and autonomy to ensure postmarket safety:

To address these serious postmarket safety shortcomings, we make the following recommendations.

FDA should support Congressional efforts to provide ODS with independence from the Center for Drug Evaluation and Research (CDER), which also oversees new drug approvals by the Office of New Drugs. Under this proposal, just as ODS plays a consultative role to OND during the drug approval process, OND would play a consultative role to ODS in postmarket safety surveillance. After consultations with OND reviewers, ODS would have authority for postmarket risk management.

An independent drug safety office would require the following:

- Independence from the Center for Drug Evaluation and Research;
- Authority to make postmarket safety determinations independent of CDER and OND;
- A mandate to be consulted in new drug approval decisions;
- Authority to require of drug sponsors, at any time after approval, postmarket clinical trials or other safety studies;
- Authority to require risk management steps, including label changes, risk communication and patient/clinician education measures, promotional and advertising restrictions, distribution or use restrictions, among others;
- Authority to enforce study commitments and risk management actions by imposing civil penalties for noncompliance.

- The authority and mandate to work with other federal agencies and private partners to develop an infrastructure to improve the quality of epidemiologic studies through large linked healthcare databases.

In addition, the independent office of drug safety should also be provided with sufficient resources to transform the passive safety surveillance system into an effective, proactive program. Such a program would include: comprehensive AE report monitoring; improvement of the AE reporting system; aggressive oversight, implementation and enforcement of postmarket study commitments; and more frequent use of comprehensive and scientifically valid independent pharmacoepidemiologic studies to flag safety risks.

3. FDA-proposed Reforms Are Inadequate

Consumers Union cautions that FDA's proposed drug safety program improvements, though welcome, fail to address FDA's underlying structural and regulatory shortcomings that prevent it from protecting the public from unreasonably risky drugs.

November 5, 2004: 5-Step Plan. On November 5, 2004, Acting Commissioner Crawford announced a five step plan to "strengthen the safety program for marketed drugs." Many of the proposals included activities that FDA had long been conducting. The plan included:

- *Sponsoring an Institute of Medicine Study of the Drug Safety System.* Though an IOM study evaluating safety issues may be helpful, it is not a substitute for adopting meaningful safety reforms. FDA has reported that the study would not begin for another six months—10 months after the Acting Commissioner announced the 5-step plan. Media reports suggest the study will take up to 17 months to complete.
- *Formalizing a program for adjudicating "differences of professional opinion."* This consists of an ad hoc panel of FDA staff not involved in approval decisions to review materials presented by disputing parties and make a recommendation to the Director of the Center for Drug Evaluation and Research (CDER). Petitions for review by the panel can be denied if CDER thinks there is not a significant health impact. CDER officials have been at the center of controversy surrounding the conflicts between OND and ODS.
- *Hiring a director for the Office of Drug Safety*. Providing leadership for the office responsible for the post-market safety of thousands of approved drugs should be a presumed priority for FDA, not a component of a "reform plan."
- *Conducting drug safety/risk management consultations with advisory committees.* This proposal does not appear to reflect substantive change. It would merely provide for an ongoing role for already formed and active advisory committees to discuss safety and risk management issues. Committee recommendations are not binding.

- *Publish Risk Management Guidances for pharmaceutical industry.* Drafts of the non-binding guidances were originally published in May 2004 and were just finalized in March 2005. They largely reflect a continuation of a prior practice, not a response to the crisis of 2004.

Independent Drug Safety Oversight Board: On February 15, 2005, FDA announced the formation of a hastily conceived "Independent Drug Safety Oversight Board" and new "communications" initiatives that would speed information to patients and doctors about safety concerns. The proposal is flawed for several reasons:

- The Board has no regulatory authority and serves in only an advisory capacity;
- The Board is a part-time entity serving ad hoc; it cannot provide the active safety surveillance role lacking at FDA nor resolve ongoing conflicts of interest.
- The Board's makeup is unclear, but no proposal offered to date has proposed inclusion of consumer or patient representatives.
- The Board will be chaired by the deputy director of the Center for Drug Evaluation and Research. CDER officials have been responsible for the conflicts between those who approve drugs in OND and safety reviewers in ODS.
- The increased and more timely patient and doctor communications about safety risks, though an improvement over FDA's past approach favoring caution over education, does not resolve the core shortcomings that prevent the agency from proactively identifying those public health risks.

CONCLUSION

Consumers Union thanks the Science Board for its consideration of our comments and for addressing this important and timely issue.

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