Statement of Consumers Union
The Independent, Non-Profit Publisher of *Consumer Reports*[1]
By William Vaughan, Health Policy Analyst

before the
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
September 30, 2010

Mr. Chairman, Members of the Subcommittee:

Thank you for this opportunity to testify on the Dingell-Waxman-Pallone-Stupak draft drug safety legislation that is being circulated.

Consumers Union is the independent, non-profit publisher of *Consumer Reports.* For 73 years, we have been providing the best available scientific information on the safety and efficacy of medicines and other consumer products. We have a free program, BestBuyDrugs.org, which provides consumers with information about the relative value of drugs in about 25 different classes of medicine. Attachment #1 is a sample copy.

We strongly endorse the draft bill

By requiring systems of drug supply safety and quality both abroad and at home, by funding an increase in inspectors, by improving the import system, and increasing penalties, the bill will make fundamental improvements in American drug safety. Basically, the bill will change the current system where the FDA plays chase and catch-up, to a system where suppliers will have to be pro-active on specific safety and quality issues and the FDA will have more resources to verify compliance with reasonable safety requirements.

Urgent Need for Early Action

We hope a way can be found to pass this legislation before the end of the year. We understand how difficult that could be given the time pressures. But every day that we delay in enacting this type of legislation is another day that the American people are vulnerable to deadly medicines or worthless placebo pills. Given the fortunes that can be made by counterfeiting medicines, we are very lucky—every day that passes--that there

[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.

has not been another public health scandal. Unless we act, we are just waiting for another disaster to happen.

The evidence supporting the need for this bill, particularly its international provisions, is overwhelming

For example,

> --Today "up to 40 percent of the drugs we take are imported, and up to 80 percent of the active pharmaceutical ingredients in the drugs we use are from foreign sources."[2]
>
> --"It is becoming increasingly urgent that FDA have accurate, complete, and up-to-date information on the drug products supply chain. The number of drug import lines has grown 119 percent in the six years from 2002 to 2007—from 142,389 to 312,392—and the number of foreign establishments referenced in an original new or generic drug application has grown 159 percent in the seven years from 2002 to 2008—from 779 to 2019."[3]
>
> --A 2007 GAO report put the problem in stark relief: of all foreign plants, at most only seven percent of them are inspected in a year.[4] Of those that are inspected, these inspections are announced to the plant owners in advance, despite FDA policy guidelines requiring that inspections be conducted without prior notification.
>
> --According to an April 2008 *New England Journal of Medicine* article, ". . .the evidence suggests that inspection needs have overwhelmed the agency's capacity;"[5] despite an increased appropriations request, the percent of entries of imported drug will decline between FY 2010 and 2011, from 1.55% to 1.31%.[6]
>
> --"The FDA estimates that there are about 3,250 foreign establishments. If you consider that approximately half of them would be inspected each year if they were held to the same standards as U.S. establishments, that means there are about 1,625 foreign establishments that should be inspected each year. That is almost 1,400 more inspections than were actually conducted in 2007. And, if we reason that foreign establishments would have about the same rate of action items resulting from inspection, we can conservatively estimate that a minimum of 15

---

[2] Dr. Joshua Sharfstein, testifying before this Subcommittee, March 10, 2010.
[3] FY 2011 FDA Budget Justifications, p. 372.
[4] "Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers," GAO-08-224T (Washington, D.C.: Nov. 1, 2007).
[5] Stuart O. Schweitzer, "Trying Times at the FDA – The Challenge of Ensuring the Safety of Imported Pharmaceuticals, *The New England Journal of Medicine*, April 24, 2008, p. 1776.
[6] Op. cit., FY 2011 FDA Budget, p. 119.

> action items—warning letters, import alerts, seizures—for foreign establishments were missed."[7]
>
> --the FDA lacks a wide range of needed authorities to ensure the safety of imported drug and device products.[8]

Some of the more high-profile failures of our drug, device, and cosmetics regulatory system are well known:

> --the import of contaminated heparin, a blood-thinning drug whose active pharmaceutical ingredient (API) was manufactured in China, and which is suspected to have been involved in the deaths of as many as 149 Americans;
>
> --the 2006 recall of 183,000 packages of contact lens solution, manufactured in China, because of bacterial contamination; and
>
> --a June 2007 import alert about toothpaste made in China that contained the very dangerous chemical Diethylene Glycol, which is used in antifreeze and as a solvent.

A September 2004 FDA report on the risk-based method of choosing foreign facilities for inspection indicated that the number of "registered human drug establishments" had increased by more than 400 percent during the previous 25 years, whereas the number of Good Manufacturing Practices inspections conducted dropped by more than 60 percent during that same time period. As FDA itself stated in that report,

> "it is impossible for FDA to achieve uniformly intensive [Current Good Manufacturing Practices] inspectional coverage for all registered drug facilities."[9]

It is very clear that the FDA needs additional resources and clearer legal authorities to do its job protecting Americans against deadly products.

Some Highlights

While we endorse the whole bill, we would especially like to call attention to several sections.

Doing more on clinical trial integrity: First, Section 105 (strengthening the authority to inspect clinical trials, contract research organizations, and investigational review boards) is very important. Having the staff to follow through on biomedical research inspections is even more important.

---

[7] Testimony of Mylan, Inc., before the FDA to discuss generic drug user fees, Rockville, MD, September 17, 2010

[8] Chairman Emeritus Dingell questioning of Dr. Sharfstein, March 10, 2010.

[9] FDA, "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model," p. 4.

There has been a massive shift of clinical trials and biomedical research overseas, to areas where integrity programs may be lacking and where patients and researchers are desperate for money. The stage has been set for corruption of basic clinical trial research. If a drug is approved on the basis of falsified data, not only will patients pay billions for questionably effective medicines, but they may even be in danger of unsafe medicines. Attachment 2 provides documentation of these concerns.

The FDA is to be congratulated for trying to do more to inspect IRBs and research sites.[10] Data from the FDA shows that a fairly high percent of their biomedical site visits result in a voluntary or mandatory correction. In some cases, over half the inspections result in recommendations for changes—some minor, but some serious.[11]

We urge you to consider an amendment to require a specific, higher percentage of BIMO and IRB inspections, especially in those sites with above average risk.

We also hope that the Committee will consider Rep. Barton's HR 3932, a bill to adopt the GAO's recommendations on debarment of researchers found guilty of scientific misconduct and to speed up the debarment process (one case took 11 years, for example). The entire debarment area needs to be reviewed to ensure that the FDA acts in a timely manner against all of those found guilty of violations. In addition, it is not easy to determine if any foreign researchers have been placed on the debarment list, despite the huge increase in overseas research.[12]

Dedicated Foreign Inspectorate (Section 306): A "corps of inspectors dedicated to inspections of foreign drug facilities and establishments" is an excellent idea. As the GAO has pointed out, in the past inspectors have flown in for a few days of pre-announced visits, with very limited time, and relied on local plant employees for translational services—hardly the way to discover a fox in the henhouse.[13] The FDA is to be congratulated for its move to set up foreign field offices with staff that will be increasingly expert. But local offices are expensive, and we need the resources provided by the draft legislation.

In Section 306, page 73, line 12, we urge you to substitute the word "ensure" for the word "allow". The staffing of the Foreign Inspectorate should be at a level that ensures or guarantees that, on a risk adjusted basis, we can inspect foreign drug facilities "at a frequency at least equivalent to the inspection rate of domestic drug facilities and establishments."

Suggestions for Improvements

[10] Drug Industry Daily, "BIMO Inspections Up 10 Percent in 2009…." Sept. 23, 2010.
[11] FDA's HSP/BIMO Initiative Accomplishments—Update, September, 2010.
[12] All of the individuals (for which electronic information is available) listed on the FDA debarment list appear to have been residents of the U.S. We are awaiting a telephone call from the FDA as to where one could go to find a list of foreign researchers who have been debarred and which one should avoid.
[13] GAO-08-224T, "Drug Safety: Preliminary Findings…." Nov. 1, 2007.

To repeat, we strongly endorse the draft and hope it can pass soon, before another heparin-type scandal.

But we also have some suggestions.

First, to build up a "Foreign Inspectorate" and train a strong staff for international work will take time and is expensive. It is important that the talented people recruited to this task have confidence in our long-range support for the program. Therefore, we urge you to make the registration fees established by this draft bill, permanent. Do not include a sunset. The Federal budget situation is so unpredictable in the next few years that a sunset in the summer of 2014 may encounter a legislative situation that would inadvertently kill the measure and leave the FDA no choice but to shut down the international inspections.

Second, and for similar reasons, please do not trigger off the registration fee system if the FDA budget is frozen or even reduced (Discussion draft, page 10, line 7ff). Again, the budget outlook is so uncertain, but the need for the inspectors created by this bill is so great, that ending the program in case of a Federal budget stalemate would be a terrible waste of previous investment and an even more terrible danger to the public health.

Third, we hope that the FDA's efforts to coordinate with (and improve the quality of) other nations' inspection systems can be encouraged as a way to 'leverage' or get more quality inspections than we could ever afford to do ourselves.[14] There may be some "high integrity" nations that conduct high quality inspections on a two-year frequency schedule where we could immediately move to less frequent FDA inspections (e.g., once every 4 years), and instead could use the resources to concentrate on less reliable sites.

For example, I hope we could do more inspections in nations where there are grounds for concern—and fewer inspections in nations which score higher than we do in, for example, Transparency International's Corruption Perceptions Index. It is not fun to talk about, but we rank only 19th in the world in perceived public-sector integrity. In the 2007 GAO report on foreign drug inspection weakness, they listed the number of FDA inspections in ten nations. Six of those nations score better than we do on the perception of integrity! This data is all obviously totally unscientific, but it makes a point. There are some nations where we might rely more on the integrity of their public officials and systems, so that we can concentrate our inspections in other areas. Again, using the GAO's 2007 data, the FDA did 14 inspections in Switzerland, a nation that ranks 5th in government integrity, and 13 inspections in China, a nation that ranks 79th. We know this data is out-of-date, and the FDA is making a huge effort in places like China—but we should be more strategic in our use of resources in other areas of the world.

Technical suggestions

[14] The FDA is to be congratulated for encouraging companies to 'stretch' their overseas supply oversight through consent decrees, coordination with other government agencies, etc. Drug Industry Daily, "FDA, Companies Must Stretch Overseas Supply Oversight," August 20, 2010. Also, the FY 2011 budget request calls for 3 new employees to "partner with foreign authorities to leverage capabilities" (FDA Budget Justification, p. 371).

The registration fees are adjusted for basically US inflation. But the cost of maintaining a foreign inspectorate can change enormously based on foreign costs. For example, the recent Yen appreciation makes operating in Japan difficult. When the Chinese revalue the RMB, the cost of the three FDA offices in China will soar. We urge you to consider special fee adjustments based on inflation plus currency adjustments.

We assume it is the intention of the FDA and the Committee that inspections should be 'unannounced' or with very short notice. While section 104 makes it clear that an unannounced visit cannot be denied, it may be useful to clarify the intention that visits are supposed to be on a surprise basis.

Regarding notification of the FDA by a registered person that a drug may be adulterated and could cause injury or illness (Sec. 106, p. 35, line 5), the language says the notification shall occur "as soon as practicable". To stress the urgency and avoid future arguments about 'practicable', substitute the word 'immediately'?

Regarding effective dates, would it be possible to shorten several of the dates, given how important it is to act on these public health issues. For example, the recall power is effective one year after enactment (p. 39). Could that be six months? The "good importer practices" program takes three years to implement. Would two years be possible?

The importer annual fee is set at $500 (adjusted for inflation). Is that really enough to start up the program and educate about the "good importer practices" program?

Conclusion

Congratulations again on your work on this legislation. We hope it can be enacted as soon as possible.

Attachment 2: Problems of Integrity in Biomedical Research

"[M]ost testing for the US drug industry's late-stage human trails is now done at sites outside the country, where results often can be obtained cheaper and faster…"[15]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.[16] 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.

The quality and integrity (especially the rights of those enrolled in the trials[17]) of the growing number of clinical trials conducted overseas is a huge unknown. Nearly a decade ago, the HHS Inspector General warned of problems. As the OIG noted in 2001[18]:

> "The number of foreign clinical investigators conducting drug research under investigational New Drug Applications increased 16-fold in the past decade. In 1990, 271 of these foreign clinical investigators were in FDA's database. By 1999 the number grew to 4,458. FDA inspections of foreign clinical investigators conducting drug research have also increased dramatically,[19] from just 22 in 1990 to 64 in 1999.
>
> --"The number of countries in which clinical investigators conduct drug research that is tracked by FDA increased from 28 in 1990 to 79 in 1999. Among the countries that have experienced the largest growth in clinical investigators are Russia and other countries in Eastern Europe and Latin America. Sponsors explain this growth by pointing to readily accessible human subjects, potential new markets for approved drugs, and recent international agreements that ease FDA acceptance of foreign research data…
>
> --"FDA cannot assure the same level of human subject protections in foreign trials as domestic ones…
>
> --"Key entities overseeing or studying foreign research have raised concerns about some foreign institutional review boards."

---

[15] "Most Testing for US drug industry's late-stage human trials done outside of 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.

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

[17] See the extensive ethical discussion in Adriana Petryna's When Experiments Travel, Clinical Trials and the Global Search for Human Subjects, Princeton University Press, 2009.

[18] DHHS, OIG, "The Globalization of Clinical Trials, A Growing Challenge in Protecting Human Subjects," OEI-01-00-00190, September 2001.

[19] Note: CU is surprised at the use of the word "dramatically." Yes, inspections tripled, but number of sites went up 16-fold. Clearly, inspections are not keeping pace.

The OIG has just updated the study, and the situation has become much more serious. Setting aside the important issue of genetic difference among various regional populations that may raise questions about the efficacy of a drug in the North American population, there are huge integrity issues. The Inspector General now reports that

> --80 percent of drugs approved for sale in 2008 had trials in foreign countries;
>
> --in 2008 the FDA inspected 1.9% of domestic clinical trials sites but only 0.7% of foreign sites;
>
> --the FDA is often unaware of the foreign sites and thus has no ability to ensure that enrollees in the trials are properly informed and advised.

FDA Appropriations Subcommittee Chair Rosa DeLauro said, the report "highlights a very frightening and appalling situation…By pursuing clinical trials in foreign countries with lower standards and where the FDA lacks oversight, the industry is seeking the path of least resistance toward lower costs and higher profits to the detriment of public health."[20]

The Administration's FY2011 FDA Appropriations request notes the problem:

> 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 numbers 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…[21]

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 increase request will support.

---

[20] Gardiner Harris, "Concern over Foreign Trials for Drugs Sold in U.S.," The New York Times, June 21, 2010.

[21] HHS, FDA Budget, Component P-5, Protecting Human Subjects, FY 2011.