Issue Brief

The Need for Drug Safety– The Older Person and Ageism

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Introduction

In 2007 in the United States, more than 50 new medications entered the market, joining some 14,000 previously approved drugs. Before it reaches the consumer, a prescription drug must pass a series of clinical tests to validate its efficacy and safety. Once approved, the drug enters the real world and is prescribed to thousands of people with specific medical histories who take a variety of medications to treat their ailments. It is not uncommon for a drug to interact unfavorably with other medications, and possibly with the nutrients, herbals and dietary supplements the patient may also be ingesting. Finally, unbeknownst to the physician, the patient, and the pharmaceutical company, the drug may be contraindicated for use in a patient with an unrelated disease.

The issue is particularly serious for older people, since they frequently suffer from multiple conditions and take a variety of medications simultaneously. Older Americans consume about 40 percent of all medicines although they constitute a little more than 12 percent of the general population. Careful surveillance, both before and after a drug becomes available, is important in order to avoid the attendant susceptibility to dangerous and potentially deadly drug interactions.

It is surprising that the Food and Drug Administration (FDA) is not required to include older persons in clinical trials that study efficacy and safety. And given the pressure to get medicines on the market as soon as possible, the safety of drugs that have not been carefully tested and that have not stood the test of time is all the more in doubt.

Drug safety has been a concern of the International Longevity Center's since 2002, when we published the issue brief *Clinical Trials and Older Persons: The Need for Greater Representation*. Because medicines in the United States are disproportionately used by older persons, we must conclude that failures in drug safety are due in part to the belief that older persons, having lived their lives, are expendable. This is a manifestation of ageism. In response to the continuing and emerging problems with medications already on the market, even medications that have been available for some years, in 2004 the ILC published *Improving Drug Safety: The Importance of Postmarketing Drug Surveillance*.

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The Need for Drug Safety– The Older Person and Ageism

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Special Vulnerability of Older Persons

Many older patients have complex and chronic conditions that make them vulnerable to the adverse effects of medications that are taken alone or in combination with other drugs. In the United States, older persons carry the majority of the disease burden; in 2005 it was reported that 75 percent took four prescription drugs every day. Persons over 65 are more than twice as likely to be treated in an emergency room and seven times more likely to be hospitalized for adverse drug events than persons under 65.

Even healthy older people manifest different physiological characteristics than do younger adults:

- With the passage of time there is a shift in lean body mass toward fat. Fat soluble drugs such as diazepam (Valium) remain much longer in older bodies.
- Liver enzymes that metabolize and detoxify medications decrease in efficacy.
- Kidney excretion may not function as well. Drugs may remain in an older body longer than anticipated.
- Absorption of drugs in the gastrointestinal tract is slow.

Potential Risks of Approved Drugs

A safe drug does not mean that the drug is totally risk-free. All drugs have risks. *Safety simply means the benefits outweigh the risks*. Illustrative of this point are antiseizure medications that protect against the grave effects of epilepsy but often have untoward side effects.

Both errors in the administration of and adverse reactions to drugs account for more than an estimated 100,000 deaths annually,[1] making prescription drugs among the top ten causes of death in the United States. Considering their enormous value and their contribution to increasing longevity, it is astonishing to realize that medicines also result in thousands of deaths and that protocols are not in place to minimize these occurrences. The following are cases in point:

- **2007:** Dr. Steven Nissen, chairman of cardiovascular medicine in the Cleveland Clinic, announced the results of a meta-analysis of rosiglitazone (Avandia, manufactured by GlaxoSmithKline), a drug to treat type 2 diabetes that had been on the market since 1999. He combined 42 previous studies that compared people who took the drug with those who did not. He reported a 43 percent greater risk of sudden heart attack in the rosiglitazone group than in the control group. But it took a full year after FDA reviewers strongly recommended tough safety warnings for that agency to finally call for a "black box" alert to consumers to be placed on Avandia and on Actos, a similar diabetes drug (manufactured by Takeda Pharmaceuticals in Japan).
- **2005:** Merck Pharmaceuticals was accused of hiding evidence that rofecoxib (Vioxx), an anti-inflammatory medication, doubles the risk of myocardial infarction and stroke. Vioxx had been on the market since 2000.
- **1997:** Dexfenfluramine (Redux) and fenfluramine (Pondimin), weight-reducing drugs, were withdrawn from the market because they caused pulmonary hypertension and heart-valve damage. To date, Wyeth Pharmaceuticals has paid more than $20 billion in damages.

Postmarketing Surveillance

Nature does not always relinquish its secrets as quickly as we would like, and the actions of medications in real world conditions may differ from carefully controlled clinical trials. For example, the most frequent reason a drug is removed from the market is drug-induced liver injury, but to detect possible liver injury requires postmarketing surveillance on up to 30,000 consumers of the medication, whereas on average a drug is approved after studies of only 3,000 patients.

Therefore, once a drug is approved, robust and comprehensive efforts must be put in place that go far beyond the current method of postmarketing surveillance.

Current postmarketing surveillance

The pharmaceutical company that brings a drug to the marketplace is not usually eager to monitor its safety and efficacy after it has been approved for use. In 2007, pharmaceutical companies conducted only 7 percent of the studies they had promised. Understandably, it is asking a lot of a company to voluntarily fund studies that might result in the removal of its product from the marketplace.

At present the FDA MedWatch program[2] is a voluntary program of limited value that gathers information from the pharmaceutical industry, medical providers, and patients and that reports only slightly more than 10 percent of adverse reactions. Hospitals don't do much better. Only 6 percent of American hospitals use drug computer-entry systems to ensure that patients receive the right medications at the correct dose.

The long-term use of medications is another significant problem that requires postmarketing surveillance. People are living longer, but most clinical trials are conducted only for a limited time. What, for example, will be the long-term effects on muscles of cholesterol-lowering drugs such as statins?[3] Can psychoactive medications, such as the stimulant Ritalin, and antidepressants result in changes in circuitry in the user's brain? We know that childhood cancer survivors who have been treated with chemotherapy and radiation have high rates of heart disease, cancers, infertility, and other problems.

Compassionate use

For humanitarian reasons, everyone supports the rapid release to the marketplace of medicine that may extend or save lives and reduce suffering. It can be heartbreaking to withhold the use of potentially valuable medications until the drug is proven safe and effective. Patient advocates, understandably concerned about the speed of approval of promising new drugs, lobby Congress. One example of a successful effort on behalf of desperately ill patients was by the AIDS community in the 1990s. However, accelerating approval of a drug has its downside, in that the FDA can become too involved with the pharmaceutical industry that it regulates. *The great challenge is to balance speed with safety and efficacy.*

When drug approval is rapid, it is especially important to have effective postmarketing surveillance in place.

Off-label drugs

About 20 percent of all prescriptions are written for treatments of illnesses for which the drug has not been approved and that lack scientific support. This "off-label" usage demands special study. Off label is, in fact, only questionably legal and ethical, and the FDA bars drug detail personnel from promoting off-label treatments. For example, in 2007, Fentora, a powerful pain reliever used in cancer, was linked to several deaths when it was used off label for headache and back pain. Fentora contains fentanyl, which is highly addictive and 80 times more potent than morphine.

Overseas chemical ingredients

The FDA does not have the resources to evaluate the purity of the chemical ingredients that are purchased from overseas and used in drugs by U.S. manufacturers. This very serious oversight requires immediate attention.

Food and Drug Administration (FDA)

Clinical trials

Clinical trials present several problems. Questions of selection, adequate monitoring, and record keeping arise in clinical trials conducted both in the United States and overseas. There are questions of conflict of interest between investigators and pharmaceutical companies. Unconscious bias has been noted in the greater extent to which investigators who are paid by pharmaceutical companies tend to support approval and to overlook problems relating to the drug they are testing. Conflict of interest of FDA advisory committee members is also an issue.

The FDA does not require that older persons be included in clinical trials, although voluntary guidelines support their inclusion in trials of drugs that are primarily for their use.[4] Exclusion of older persons particularly affects women, who make up the largest proportion of this population and have also been underrepresented in clinical trials in the past. The notion that older people cannot tolerate or benefit from new drugs, new medical devices, and diagnostic treatment procedures needs to be set aside. Protecting older persons from the possible dangers of research also "protects" them from any fruitful results.

Just as the FDA does not require the inclusion of older people in clinical trials, neither does it require the inclusion of children or adolescents. Examples of their importance in these trials are unfortunately abundant:

- Clinical trials offer evidence that antidepressants play a role in promoting suicide in adolescents.
- In 2007, the FDA issued an advisory warning to parents about the dangers of giving cough and cold medicines to children under 2 years of age unless instructed by a doctor. (Some experts felt the warning should apply to children under 6.) The ingredients of concern are dextromethorphan (DM), which can cause neurological problems, and pseudoephedrine, which can result in increased blood pressure, arrhythmias, and death.

Phase 3

Phase 3 testing of drugs is the final phase before a drug is approved for entry to the market. The FDA's review time is among the shortest in the world. It is noteworthy that there is a clear deficiency in the phase 3 testing process since 20 percent of drugs do receive black box warnings after approval and 4 percent are withdrawn from the market for safety reasons. Parenthetically, many doctors will not take a drug themselves nor prescribe it to their family until the drug has been on the market for between five to seven years.

Prescription Drug User Fee Act

The Prescription Drug User Fee Act (PDUFA) of 1992 mandates that pharmaceutical companies pay user fees for drug reviews. Since the existence of PDUFA, review time has been cut in half from an average of 30 months to 15 months, which fortunately has not resulted in shorter clinical drug studies. Prior to its renewal in 2007 and in response to increased concern about drug safety, the FDA proposed positive changes to PDUFA. These included the development of a five-year plan to enhance and modernize the drug-safety system, earlier discussions with manufacturers about labeling and postapproval commitments, and the expansion of payment for postapproval safety activities.

While the renewal has to some degree strengthened postmarketing surveillance, to date the FDA has provided inadequate PDUFA funds for postapproval drug safety in general and studies of specific drug safety issues in particular.[5] More than 40 percent of the budget of the FDA division used in new drug review comes from user fees. This law risks the suggestion that the FDA is accountable to the very industry it regulates. Four previous FDA commissioners agree that the FDA should be funded directly through the Treasury, not from user payments.

The Pharmaceutical Industry

It can cost up to $1 billion for a pharmaceutical company to bring a new medication from conception to the marketplace and take up to 15 years, and the time the clock runs from patenting passes rapidly. Pharmaceutical companies necessarily maintain large funds to cover unanticipated liabilities, which may make it worthwhile to gain entry to the markets even when drugs might be of risk. Under favorable circumstances it would be more useful if companies used these funds for research and development. Over time, unexpected secondary beneficial effects of a drug may be discovered, which is also of financial value to companies.

Recommendation

An Institute of Medicine (IOM) report concluded that direct consumer advertising results in greater early use of new drugs and that a moratorium on advertising would be advisable. Describing internal strife in the FDA, its underfunding, poor management, and outdated regulations, the report notes that the FDA safety reviewers are discouraged or punished after uncovering drug dangers. It recommends that newly approved drugs display a black triangle on the label for two years to warn consumers of the uncertainty of drug safety and that the safety of drugs should be reviewed at least every five years.[6]

In our issue brief of 2002 we recommended that postmarketing surveillance systems be run independently of the pharmaceutical industry and that the National Institutes of Health (NIH), alone or in collaboration with the FDA, should plan coordination and carry out the reviewing process. *Given that the NIH has a long and distinguished history in the conduct of clinical trials,*[7] *and in the interests of true independence, we now believe the NIH should do this work alone. An alternative would be the creation of a new structure, independent of both agencies.*

Today, we recommend that a highly competitive system be built, based on peer-reviewed selection of an academic medical center in each of the ten regions of the Department of Health and Human Services. This would provide broad representation, assuring urban, rural, socioeconomic, cultural, gender, and racial and ethnic diversity.

Models for such a system include the Centers for Education and Research on Therapeutics (CERTs), operated by the Agency for Healthcare Research and Quality (AHCRQ). There is also the pioneering effort of the Boston Collaborative Drug Surveillance Program, which has been in operation since 1966 under the leadership of Hershel Jick, at Boston University School of Medicine. A variety of databases are available, such as those maintained by the Veterans Administration and by the insurance industry, health insurers, and HMOs, in particular Kaiser Permanente. Each could be used for special studies and experiments, leading to improvements in the NIH system proposed here.

Ideally, the NIH system would result in creation of a highly qualified interdisciplinary teams of physicians, as well as pharmacists, clinical pharmacologists, pharmacoepidemiologists, medicinal chemists, nurses, computer specialists, and biostatisticians as needed to continually monitor all prescription and over-the-counter drugs, herbals, and dietary supplements that have been identified in both inpatient and outpatient populations in the academic medical center.

Indirectly, it should be possible to carry out head-to-head studies between old and new drugs and to consider lifestyle factors. For example, exercise has been shown to be as effective as metformin against diabetes and as the selective serotonin reuptake inhibitors (SSRIs) against depression.

The central leadership in the NIH would organize this national network and develop standard protocols of study. Systems in place would identify long-term and short-term effects in comprehensive, integrated postmarketing surveillance. The team would be familiar with the mechanisms of action and other features of new drugs and the pathogenesis of the diseases tested and treated. Studies would focus on actual

clinical outcomes, not just surrogates (such as lab tests for blood sugar), however useful the latter are in preliminary studies.

We also recommend that the Dietary Supplement Health and Education Act (DSHEA) of 1994, which allows over-the-counter vitamins, herbal remedies, and other dietary supplements to be sold without premarket safety evaluations, be rescinded. We recommend that these substances be subject to the same drug-testing standards as accomplished by the FDA.

Who will pay?

The proposed postmarketing surveillance system should be financed by taxpayer dollars, representing a significant financial relief and reduction of liability to the pharmaceutical industry. Pharmaceutical companies could also benefit from discovery of unanticipated off-label benefits;[8] hospitals, nursing homes, and health care providers would benefit from the safety data; most of all, patients would benefit from improved quality of care. Such benefits include newborns, who would be spared drug-related birth defects.

Conclusion

The FDA regulates 25 percent of the U.S. economy. This includes responsibilities for much of food safety as well as drug safety. Although in this document I have been critical of some of its actions over the past several years, I must note that the FDA is the best of its kind in the world.

Given the risks to the lives of patients and the expense to the pharmaceutical industry, it is essential that the FDA receive major additional funding, based on federal taxes. To keep up with its funding level of 2003, the FDA should receive a minimum of $2 billion in annual funding. In keeping with most other federal agencies, the FDA should be given subpoena power.

Looking to improve the FDA's ability to monitor drugs, the Enhancing Drug Safety and Innovation Act of 2006, sponsored by senators Edward M. Kennedy and Michael B. Enzi, proposed that the FDA be authorized to use a range of regulatory tools to help assure drug safety, including restrictions that limit direct consumer marketing and requirements for postmarketing studies. Another bill, sponsored by senators Charles Grassley and Christopher J. Dodd, offers somewhat similar proposals. These ideas should be pursued legislatively.

Inasmuch as Medicare is the largest purchaser of drugs in the United States based on taxpayer dollars, it is only appropriate that taxpayers be assured of the quality of both phase 3 and phase 4 reviews. It has been said that documenting a drug's risk and getting it off the market one year sooner would pay for drug surveillance for four years!

Hopefully, the future will be very different. The application of genomics to create personalized medicine will likely lead to niche or boutique approaches by pharmaceutical companies and to fewer adverse drug reactions. In contrast to finding the "one-size-fits-all" $1 billion blockbuster, a better match between specific drugs and the individual's genetic predisposition will be more beneficial overall:

- We recognize that the Food and Drug Administration Revitalization Act could make significant reforms in drug safety, but it is not comprehensive in meeting the requirements of a truly effective system of postmarketing surveillance.
- We believe FDA commissioners should have a tenure of at least six years, in order to overlap the terms of presidential administrations and thus be less subject to politics. No recent FDA commissioner has lasted in the job for more than two years.

There is no ideal solution to the issue of postmarketing surveillance. Epidemiological research, including observational studies and meta-analyses, has its limits. Randomized, double-blind, crossover prospective clinical trials are far more valuable and continue to be the gold standard of phase 3 trial studies. However, they tend to be short and to involve homogeneous populations.

The system I have proposed does more than contribute to drug safety through postmarketing surveillance and should be seen in the context of the real world of medical care. It will create the possibility of longitudinally tracking care, including diagnostic and therapeutic procedures before, during, and after hospital admission. This in turn could become a fine source of clinical research, with a focus on the most common medical conditions. Of course, there are limits to data acquisition. For example, the system still will not pick up drug events in the small solo- and joint-practice offices of many doctors. Nonetheless, it would provide needed information about practices in academic medical centers.

Wider use of the Electronic Medical Record (EMR) would ensure linkage across clinical sites, offering an enormous amount of information concerning pharmacy transactions. Over time the system will include hundreds of thousands of patients, providing a great deal of useful information about helpful and adverse polypharmacy and picking up errors in drug administration. It would identify the roughly 50 percent of patients who fail to respond to drugs that are prescribed for specific diseases. Finally, the use of biomarkers by drug companies will only increase in the future and will be available to the research team.

The recommendation made here to build a new system of postmarketing surveillance will be costly but in the long-term will likely save time, energy, and money, not to mention lengthening and improving the quality of lives.

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Notes

1. J Lazarou, BH Pomeranz, PN Corey, "Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies," *JAMA* 279 (1998):1200–05.

2. See www.fda.gov/medwatch. This system is called the Adverse Event Reporting System (AERS). An adverse event is one resulting in death, a birth defect, disability, or hospitalization.

3. Less clear has been the potential side effects of statins, such as muscle aches and memory problems. A new website has been launched to help change that. The Statin Effects Survey site (www.statineffects.com) was created by University of California-San Diego researchers who are studying the full range of effects—both good and bad. Many purported side effects of statins—muscle aches, thinking problems, and fatigue, among others—are common complaints associated with aging. Statins can cause rhabdomyolysis, which can cause protein spillage in the urine and kidney failure.

4. Food and Drug Administration, "Guideline for the study of drugs likely to be used in the elderly," *Federal Register* 59, no. 102 (1994): 39398–400 (accessed March 15, 2007, at www.fda.gov/cder/guidance/iche7.pdf).

5. S Hennessy and BL Strom, "PDUFA reauthorization—drug safety's golden moment of opportunity?" *N Engl J Me*d 356 (2007):1703–4.

6. Institute of Medicine, *The future of drug safety: promoting and protecting the health of the public* (Washington, DC, 2006).

7. See www.clinicaltrials.gov.

8. Propranolol has been found to be useful against stage fright and perhaps post-traumatic stress disorder.

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The International Longevity Center–USA (ILC–USA) is a not-for-profit, nonpartisan research, education, and policy organization whose mission is to help individuals and societies address longevity and population aging in positive and productive ways, and to highlight older people's productivity and contributions to their families and society as a whole.

The organization is part of a multinational research and education consortium, which includes centers in the United States, Japan, Great Britain, France, the Dominican Republic, India, South Africa, Argentina, the Netherlands, and Israel. These centers work both autonomously and collaboratively to study how greater life expectancy and increased proportions of older people impact nations around the world.

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