



Trials and Errors

Drug testing raises ethical – and efficacy – issues

► **By Ted Brewer**

In March 2006, six men volunteering in a clinical drug trial were rushed to a London hospital with severe headaches, convulsions and bloating. Once in intensive care, two of the volunteers fell into a coma, and all were suffering from multiple organ failure.

Just hours before, they had been given a new test drug designed to treat leukemia, and autoimmune and inflammatory diseases. The German-manufactured drug, code-named TGN1412, had proven to be safe in mice, rats and monkeys, and was therefore eligible to be tested on humans. First-phase human trials are generally very cautious, so the six volunteers had received a dose 500 times lower than that given to the monkeys.

All the volunteers survived, but with severe permanent damage

done to their organs by a drug that, according to the animal tests, should have been harmless. An inquiry into the TGN1412 catastrophe, made by the British Medicines and Healthcare products Regulatory Agency, concluded that the volunteers' severe reactions were not due to a breakdown of established protocols, manufacturing errors or contamination, but simply to the effects of the drug in humans – effects not predicted in the animals.

We know that humans are but a few degrees shy of being genetically the same as mice, rats, chimpanzees and other animals used in research laboratories. How then could people react so adversely to a drug that tested safe in these, our biological kin? Why didn't the animal data predict such severe toxic reactions in humans? Was this

some aberration, and if not, is there some other, more effective way of screening drugs that would not include the use of animals?

These are some of the big questions that now underscore the debate over use of vivisection (testing on animals) to research and develop new drugs. Those still in favor of animal testing maintain that the data from animal models can, and do, give us sufficiently accurate predictions of how humans will react to a particular drug, and that without these models, we would not have the good medications we have today. Those in opposition are countering with another argument, one that incorporates a number of sobering statistics suggesting that the tragedy in London was no aberration, but rather a dramatic version of what's become an all-too-common story.

According to the U.S. Food and Drug Administration, 92 percent of all drugs that pass preclinical testing on animals go on to fail in human clinical trials, either because they are too toxic or not effective. Of the 8 percent of drugs that do pass clinical trials and receive approval from the FDA, half are later withdrawn from the market or relabeled for side effects not identified in animal research. Many of those side effects can be extremely serious, lethal even, as evinced by the Food and Drug Administration's estimate that more than 106,000 hospitalized Americans die each year as a result of adverse reactions to approved drugs (making adverse reaction the fourth leading cause of death in the U.S.). Testifying before the U.S. Senate Committee on Finance, Dr. David Graham of the FDA's Office of Drug Safety said that one drug alone, the blockbuster Vioxx, may have caused as many as 139,000 people to have strokes or heart attacks, of which 30 to 40 percent could very well have died as a result.

Those in the anti-vivisection movement also cite a recent study, published in the *British Medical Journal*, which found that only three of six sampled animal-based drug experiments successfully predicted the outcomes of later human trials. "What this means," says Dr. Theodora Capaldo, president of the 112-year-old New England Anti-vivisection Society (NEAVS), "is that I might as well flip a coin. The results are no more predictive than that."

NEAVS and many other anti-vivisection organizations have seized on the TGN1412 and Vioxx disasters and on recent statistics and studies as glaring examples of what makes animal testing wrong, not just from an ethical standpoint, but from a scientific one as well. "That's the role of the anti-vivisection movement in today's world," Capaldo says, "to tell the other side of the story scientifically."

Lost in translation

Certified in internal medicine, cardiovascular diseases and nuclear cardiology, Dr. John Pippin is one person who has been telling the anti-vivisection side of the story, scientifically, for 20 years. A former faculty member of Harvard Medical School and the Medical College of Virginia, he started his career in cardiology conducting experiments on animals.

"My training in medicine was the same as everybody else's," he told Best Friends. "You are brought along to the point that if you're going to do any kind of research, you view the use of animals as not only fundamental, but essential." Pippin's research involved artificially creating heart attacks in dogs, so that he could later determine the efficacy of nuclear imaging agents in identifying damage to the dogs' hearts.

"The research went as we planned it, but the problem was that

it didn't have any relevance for humans. Once we finished those studies, those same imaging agents went into human studies, and we had to do it all over again, learn it all over again." Pippin looked into the animal-based experiments his fellow researchers were conducting, and saw that they too could not translate their experiments to humans. "I realized," Pippin says, "that the purpose of [animal-based] research, for most people doing it, was to create careers. It would be wonderful if you hit on something that benefited human health, but that wasn't necessary.

"It wasn't for me," he added, "so I not only stopped, I began pointing out that the emperor has no clothes, and I've been trying to do that ever since." Pippin is now senior medical and research adviser for the Physicians Committee for Responsible Medicine (PCRM), an organization of doctors and laypersons fighting for effective and humane medical and research practices.

PCRM is one among thousands of plaintiffs suing Vioxx manufacturer Merck. Backed by Pippin's research findings, PCRM charges that Merck wrongfully relied on animal tests in bringing Vioxx to the market while disregarding and suppressing more applicable human data that indicated the drug was harmful to humans. Pippin thinks that this is the first time a U.S. drug company has been sued for relying on animal test results. (Because of the enormous number of lawsuits brought against Merck over the Vioxx disaster, PCRM does not expect its case to be heard for many months, possibly years.)

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In 2005 Pippin brought those same findings to the FDA and the Institute of Medicine, testifying that the Vioxx and other pharmaceutical-related disasters resulted from a woefully misconceived reliance on what he calls "the animal paradigm." In making his case, Pippin points to the statistics, most of which come from the FDA itself, including the fact that 92 percent of drugs that test safe in animals fail human trials and that half of approved drugs are later recalled or relabeled because of adverse health effects. He also takes into account that 75 percent of the drugs the FDA approves are considered "me-too" drugs, meaning they offer no new therapeutic value in comparison to those already on the market.

From these figures, Pippin concludes that, for every 100 drugs tested safe on animals, we get one drug that is safe, effective and unlike any other. "That's not just the flip of a coin," he says. "That is an abject failure rate, and as much proof as you would ever want that the paradigm is false."

Pippin, Capaldo and many others in the anti-vivisection movement contend that differences in anatomy, physiology, metabolism and toxicity risks are what make translating the effects of drugs from animals to humans an arduous endeavor, possibly even an impossible one. These species differences come into play not just in how drugs affect animals as compared to people, but in how diseases



affect them as well, diseases the test drugs are supposed to cure.

For instance, chimpanzees, who are widely used in AIDS vaccine research, are very close to humans genetically. Nonetheless, the AIDS virus is benign in chimps. Heart attacks and hypertension are other maladies that most non-human animals never suffer, forcing researchers (such as Pippin in the early stages of his career) to recreate some close approximation of the disease in their animal sub-

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— Dr. John Pippin

jects. Conversely, a substance with proven therapeutic value for humans can be poisonous in animals. Penicillin, for example, tested lethal in guinea pigs, and aspirin caused birth defects in all five species it was tested on. Just this year, the FDA refused to approve a diabetes drug called Galvus because it had caused skin lesions in test monkeys. However, the drug has tested safe and effective in human trials that spanned two years and involved 5,500 people.

It’s important to keep in mind the high stakes involved in drug development. It costs anywhere from \$800 million to \$1.7 billion to bring a new drug to market. Considering the miniscule chance that a drug will ever be approved by the FDA and the possibility that it will later be recalled or relabeled as potentially dangerous, it’s no wonder we pay the astronomical price we do for the rare product that squeezes through the FDA approval process.

“In many cases, [drug] developers have no choice but to use tools and concepts of the last century to assess this century’s candidates,” reads a 2004 FDA white paper entitled *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Product*. “As a result,” the report says, “the vast majority of investigational products that enter clinical trials fail.... This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive failures.”

Despite all these expensive failures, the FDA prefers and, in many cases, requires the testing of candidate drugs on at least two species of animals before moving on to human trials. Though the numbers vary, researchers will generally use hundreds of animals to test a single drug. “At the moment, we don’t have a better way of doing it,” Dr. David Jacobson-Kram, FDA associate director of pharmacology and toxicology, told the *Wall Street Journal* in March.

But is this really the case? Could it be that animals, the so-called “tools” of the last century, are hindering and stalling the development of this century’s drugs when other, more reliable non-animal tools are available?

Cosmetics industry put to the test

There was perhaps no more galvanizing moment in the anti-vivisection movement than in 1980, when it was revealed that cosmetics companies were using a particularly cruel method to determine the irritancy of their products. The technique, called the Draize Method, involved injecting those products into the eyes of rabbits. The public uproar triggered by the news of these horribly tormented lab rabbits sent the cosmetics industry into public relations overdrive.

To salvage the industry’s image, the Cosmetic, Toiletry and Fragrance Association offered a \$1 million grant to Johns Hopkins University for the creation of a center that would develop alternative

methods to animal experiments. The university accepted the donation and created the Center for Alternatives to Animal Testing (CAAT), the first of many of its kind now in operation across the U.S. and Europe and in Japan, India and Brazil. Though animal testing in the cosmetics business hasn’t been completely eliminated, the number of animals used in cosmetics testing has plummeted since the 1980s, because of

new methods that CAAT and other centers have developed. Since the creation of CAAT, the search for new alternatives has become a field unto itself, producing a vast array of methods and techniques that significantly reduce and, in many cases, eliminate the use of animals in pharmaceutical research.

In vitro is one method that has replaced animal testing. “When I go to conferences, 90 percent of the talk I hear is about *in vitro*,” says Dr. Alan Goldberg, director and chairman of the board at CAAT since day one. *In vitro* involves experimenting with test-tube cultures of tissues and cells. Other alternative methods include microdosing (giving harmlessly low doses of drugs to humans to gauge the effects in their blood and tissues), computer databases and simulators, sophisticated imaging techniques, genetic assays (chips that can read the slightest genetic effects of a drug), human tissue testing and epidemiological studies (looking at the relationship between people and their environment). Moreover, research is under way to develop specific human proteins as drugs, which would eliminate the perceived relevance of animal testing entirely.

“The public has been in an ethical conundrum, a no-win bind,” Capaldo says. “They don’t want to see animals suffer, but they don’t want to die from deadly diseases either. We’re saying to them, now you have a whole different choice, especially in 2007 with the development of sophisticated alternatives.”

Goldberg believes the alternatives improve scientific vigor. “Alternatives make you ask more refined questions,” he told Best Friends. “So you get better answers and better results, and therefore do better science.”

Though alternatives may be causing a groundswell in today’s laboratories and at conferences, providing researchers with more

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scientifically sound and humane choices, the FDA's overwhelming preference is still animal-derived data. A case in point is the agency's recent decision to reject the candidate drug Galvus, choosing to rely on the monkey data rather than the extensive human data.

In determining which alternative methods of testing to accept, the agency relies primarily on recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which comes under the U.S. Department of Health and Human Services. The mission of ICCVAM, as stated on its website, is to conduct "technical evaluation of new, revised, and alternative test methods with regulatory applicability" and to promote "the scientific validation and regulatory acceptance of test methods that more accurately assess the safety and hazards of chemicals and products and that refine, reduce, or replace animal use."

According to ICCVAM director Dr. William Stokes, the committee has evaluated 146 safety testing alternatives in its 10 years of existence. Since the committee evaluates methods that test the safety of chemicals, cosmetics and drugs, it's not known how many of these 146 methods would be applicable to testing drugs.

Of those 146 alternatives, Stokes says that ICCVAM has recommended 12 alternative methods that have the potential to assess the safety of new drugs. He would not, however, specify how many of those 12 have been accepted by the FDA.

Working with toxicology experts, Pippin reviewed the list of drug-screening alternatives that Stokes provided to Best Friends, and found only four methods on the list that have been accepted by the FDA. Three of those four are currently being applied toward the testing of new drugs. (The fourth, which tests the corrosiveness of chemicals and cosmetics on skin, has little, if any, applicability to drug testing and is therefore of little relevance to the FDA.) Of those three, two are methods that reduce, but don't eliminate, the use of animals. The third uses either mouse or human cells. None

of the three methods are replacements for animal tests.

By comparison, ICCVAM's counterpart in Europe – the European Centre for Validation of Alternative Methods (ECVAM) – has validated and recommended 19 drug-screening alternatives, making it legally mandatory for European drug companies to stop or significantly reduce animal testing whenever those methods apply. (Neither ICCVAM nor the FDA has the authority to issue such a mandate to American drug companies.)

So what criteria does ICCVAM use that makes its number of recommendations so paltry as compared to ECVAM's? Here's one of the nine criteria that ICCVAM lists on its "Validation and Acceptance Criteria" webpage:

"Sufficient data should be provided to permit a comparison of the performance of a proposed substitute test with that of the test it is designed to replace. Performance should be evaluated in relation to existing relevant toxicity testing data, and relevant toxicity information from the species of concern. Reference data from the comparable traditional test method should be available and of acceptable quality."

In other words, ICCVAM calls for data showing how the alternative method stacks up against the "traditional" animal method it is supposed to replace. This sounds reasonable enough – obviously, we want to know if the new method can outperform the old. But there's a hitch in this criterion, one that Pippin and many other anti-vivisectionists say greatly accounts for the dismal number of alternatives that ICCVAM has recommended to the FDA. It's a hitch, they say, that has also unnecessarily perpetuated the use of ineffective and inhumane animal tests in the U.S.

The "species of concern," from which the relevant toxicity data and information is supposed to be derived, refers not just to humans, but also to the animals used in the old methods. In effect, ICCVAM judges the performance of an alternative method not necessarily

How five alternative, better methods were ignored

Bureaucracy rules the day in U.S. regulatory agencies

When considering the alternatives it will recommend to the FDA and other U.S. regulatory agencies, the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) usually depends on the work of its better-funded counterpart in Europe. The European Centre for the Validation of Alternative Methods (ECVAM) receives the government funding ICCVAM does not to conduct the comprehensive studies that prove alternatives work. As the process goes, ECVAM submits the procedures and results of its validation studies to ICCVAM, which then appoints a peer review panel to determine whether or not those studies have satisfied ICCVAM's criteria.

In 2007 one of these peer review panels issued a report that looked at the European validation studies of five alternative, *in-vitro* methods designed to detect potential fever-inducing substances called pyrogens. Validated and recommended by ECVAM, these alternatives replace the rabbit pyrogen test, in which researchers inject a rabbit with an experimental substance to measure how it changes the animal's body temperature. European validation studies found that all five *in-vitro* methods, which are already used in more than 200 laboratories around the world, were far superior to the rabbit test in detecting pyrogens. Even

a background study published by ICCVAM showed that one of these alternative methods scored a detection rate of 96 percent, while the animal test's detection rate was only 58 percent.

Nonetheless, the peer review panel found that the European validation studies did not meet ICCVAM's criteria. The report concluded, "The lack of parallel testing in the *in-vitro* tests and the rabbit pyrogen test, and the resulting lack of concordance data, was considered to be a major limitation of the validation study design. For this reason, the Panel recommended that future studies include parallel testing."

And herein lies the difference between ICCVAM's and ECVAM's criteria. Whereas ECVAM compares the alternative method to the animal method to ensure the alternative performs as well as or better than the animal test (when measured against human data), it does not require parallel tests that show corresponding results between the two. ICCVAM usually does require them. It's this difference, critics say, that has made ICCVAM more of a hindrance than a facilitator to the adoption of proven alternative methods in America.

Incidentally, another "traditional" method against which ICCVAM evaluates alternative methods is the notoriously inhumane and inaccurate Draize Method. While the European Union has passed laws that ban the Draize tests by 2009 and obligate researchers to use alternatives to the method in the meantime, the U.S. has yet to take such steps.

on how well it predicts the human response to a substance, which is based on actual human data, but on how closely it relates to the performance of the animal method, from which the “relevant toxicity data” almost always comes. While the committee does consider all relevant and available data (including human data) before giving its approval, it typically requires that the results of the alternative method correspond to the results of the animal test.

“If an alternative method has only a 50 percent correlation with an inaccurate animal method,” explains Pippin, “it’s likely to be denied validation even if it may have a much higher correlation with known or imputed human results. This criterion virtually insures that the best alternatives, which would of course not correlate well with animal tests, will be denied.”

In numerous evaluations that ICCVAM or its peer review panels have conducted, the animal method has, as a result of this criterion, become a major standard by which the alternative is judged – and almost always rejected. And as we know, this is a standard with an overall 92-percent failure rate in detecting human responses to new drugs.

Pippin says this standard of evaluation was confirmed to him in a meeting with ICCVAM and FDA officials in October 2006. Pointing out the absurd rationale behind this criterion, he argued that it could lead to the approval of alternatives no better than the animal tests they’re supposed to replace. Pippin claims that ICCVAM’s chairman at the time, Leonard Schechtman, responded, “That may be true, but I’m not going to discuss that with you. It’s the best we have, and it’s what we’re going to use.”

Data with destiny

Regardless of the recommendations of ICCVAM, the FDA has made one good step forward by allowing drug companies to submit data from one method ICCVAM has not recommended: microdosing. American drug companies are moving ahead, employing a vast array of proven alternatives, especially *in vitro* methods. Drug developers know that they can get better, faster and cheaper data from these methods than they can from animal tests. But, knowing the kind of data that the FDA prefers, the companies almost always conduct animal tests anyway.

“You’ve got data that are more reliable than the animal data,” says Pippin, “and yet because you think it will make [your drug] more likely to get approved, you’ve killed hundreds or thousands of animals to produce data that are garbage, so you can put it in your application package and send it to the FDA. That’s mind-numbing stuff.”

Capaldo of NEAVS is confident the tide is turning, however. She recalls a time a few years ago when James Foster, the president of Charles River Laboratories, announced to shareholders that the corporation would begin investing in alternatives to animal testing. What made this announcement so shocking is that Charles River is in the business, a multibillion-dollar business at that, of breeding animals and selling them to laboratories.

“That was the best piece of news that I’ve had working in vivisection for the past 25 years,” Capaldo says, “because it means that the industry that got rich on animal use is finally getting that there may be another, more humane meal ticket to being a multibillion-dollar corporation. Once that starts to happen, we’re going to see the kind of advances in biomedical research that we see in all other areas of science.”

It remains to be seen whether or not the FDA and ICCVAM will keep up. 🐾

Get Involved!

How you can encourage alternatives to animal research:

Write or call Food and Drug Administration commissioner Andrew von Eschenbach and demand that the FDA take more initiative in adopting proven alternative methods that replace or reduce the use of animals, and that the FDA do so without waiting for recommendations from ICCVAM. While the FDA says it does not have the authority to mandate the use of proven alternative methods in the research and development of new drugs, the agency can still endorse those alternatives and exercise a preference for them.

Commissioner Andrew von Eschenbach
U.S. Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857-0001
(888) 463-6332

Write or call Secretary of Health and Human Services Mike Leavitt and request that he pressure ICCVAM into taking a more proactive role in replacing animal tests with scientifically sound alternatives. ICCVAM can do this by harmonizing its validation criteria with those of the European Centre for the Validation of Alternative Methods (ECVAM) and by eliminating the validation criterion which judges an alternative method by how well its performance corresponds to that of an animal method.

Secretary Mike Leavitt
U.S. Department of Health and Human Services
200 Independence Avenue S.W., Washington, DC 20201
(877) 696-6775

Contact Rep. Henry Waxman (D-Calif.) and Sen. Charles Grassley (R-Iowa) and voice your support for their efforts to establish greater congressional oversight of the FDA and to increase FDA regulation of the pharmaceutical industry. Tighter congressional oversight would hold the FDA to greater accountability and force it to address its reluctance to adopt alternative methods proven to be more accurate in determining the safety of drugs than animal methods. The FDA has, in recent years, backed away from regulating how new drugs are evaluated. If alternative testing methods are to be used by the industry, the FDA must be in a position to mandate their use.

Representative Henry Waxman
2204 Rayburn House Office Building,
Washington, DC 20515
(202) 225-3976

Senator Charles Grassley
135 Hart Senate Building, Washington, DC 20510
(202) 224-3744

Contact your U.S. representatives and senators and express your concern that animal testing is seriously compromising the safety and impeding the development of new drugs. Because many elected representatives and senators are unaware of the inaccuracy of animal testing and the superiority of alternative methods, it’s up to us to inform them. Also, ask your elected officials to consider legislation that would authorize the FDA to mandate the use of methods that replace or significantly reduce the use of animals in the research and development of new drugs. To find contact information, go to www.usa.gov/Contact/Elected.shtml.