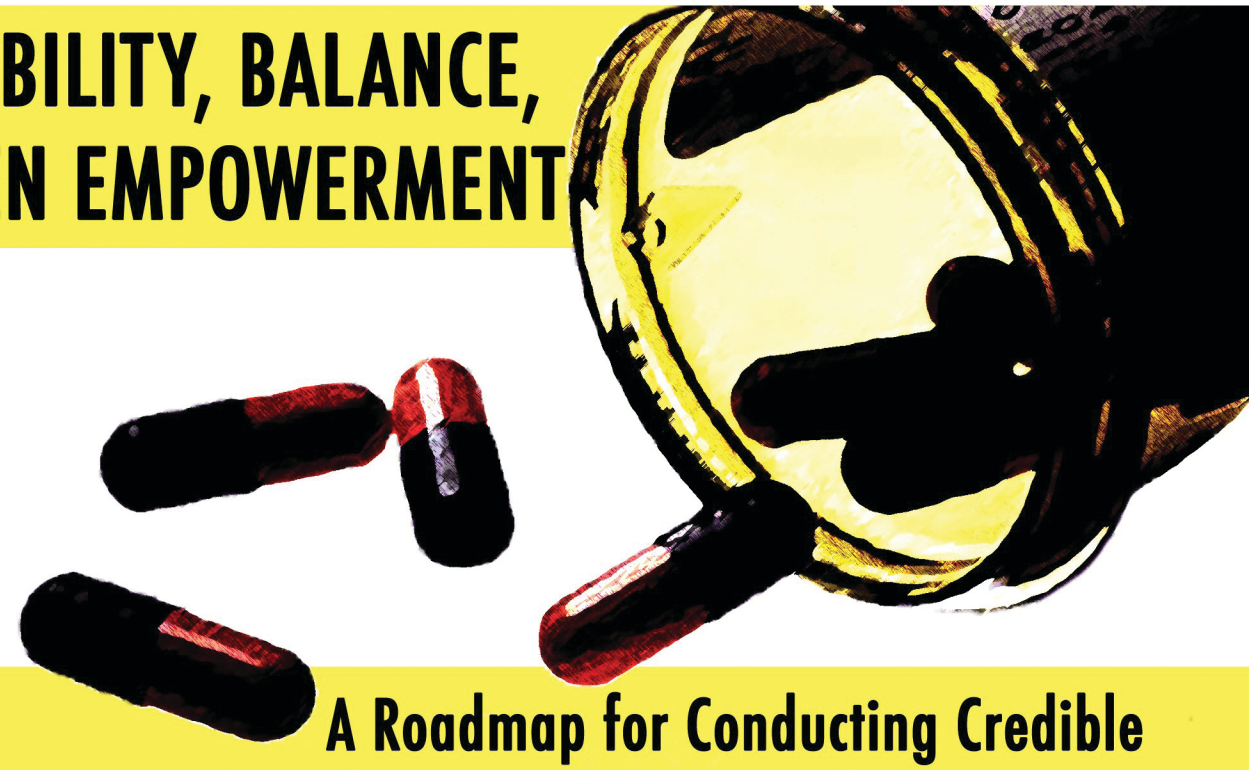
# The ABCs of DRUG SAFETY:

## ACCOUNTABILITY, BALANCE, and CITIZEN EMPOWERMENT



## A Roadmap for Conducting Credible Clinical Drug Trials and Protecting Drug Trial Participants

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www.whistleblower.org

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# About the Government Accountability Project

The Government Accountability Project (GAP) is a not-for-profit organization that is dedicated to the defense of whistleblowers in government and corporations. GAP's mission is to promote corporate and governmental accountability by advancing occupational free speech, defending whistleblowers, and empowering citizen activists. Founded in the wake of the White House scandals of the 1970s, GAP has been on the frontlines exposing corruption and fraud for over 30 years. By defending whistleblowers against retaliation and championing their disclosures, GAP plays a unique and sometimes pivotal role in guarding the public interest. Effective reform of clinical drug trials will require greater openness and accountability, as well as protection for those who speak out about fraud and the abuse of trial participants.

GAP has defended whistleblowers in hundreds of cases that have exposed billons of dollars in waste and fraud. In addition to a long history of work in support of public health and safety whistleblowers, GAP reviews over 400 potential whistleblower cases annually in areas such as transportation safety and security, national security, nuclear safety, international institutions, and corporate accountability. GAP is nonpartisan and receives no government funding. Financial support comes from foundations, individuals, and fees from legal cases. GAP is headquartered in Washington, D.C. For more information, visit GAP's website at: www.whistleblower.org.

# Disclaimer

This White Paper explores the pitfalls in the conduct of clinical trials, particularly as they relate to the safety of trial participants and drug and medical device patients. The information provided is of a general nature and is not offered as legal advice to any individual regarding his or her specific situation. If you are seeking legal advice regarding issues related to the conduct of a clinical trial, please contact GAP, or another legal organization or attorney, regarding your concerns.

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# FOREWORD

The clinical trial is the engine of clinical progress. A new drug may show intriguing evidence of activity in the laboratory, but clinical trials are the true test of whether a new therapy helps people to live longer or better. Clinical trials, when properly performed, provide objective data by which the safety and effectiveness of a new medical product – whether a drug, biologic, device, or other technology – can be judged and compared to that of other agents.

Although Avicenna first described clinical trials in 1025 AD in his *Canon of Medicine*, it was not until the latter half of the 20th century that they came into their own as the gold standard for evaluating new therapies. In 1962, the Food, Drug, and Cosmetic Act was amended to require manufacturers seeking to market a new drug in the United States to provide substantial evidence of safety and efficacy via adequate and well-controlled trials. This event laid a firm scientific foundation for the investigation of proposed therapies in this country and allowed the rapid development, evaluation and refinement of new treatments, as well as the removal of obsolete or even harmful agents that no longer measured up. Without this requirement, the explosive growth in the number of life-saving therapies for cancer, infectious diseases, cardiovascular disorders, and many other serious conditions would never have happened. Although the science of clinical trials continues to evolve, as evidenced by recent interest in defining study populations based on pharmacogenetic markers, the essential components of any clinical trial – a sound design focused on a valid research question; reliable data collection, reporting, and analysis; and protection of clinical trial subjects – remain unchanged.

Unfortunately, in the last decade, the clinical trial framework of design, data, and ethical integrity that spans the gap between scientific hypothesis and proven clinical worth has shown signs of becoming seriously corroded – in some cases, with lethal results. Just as a bridge may collapse if its structure is weakened, clinical trials lose their strength if their core is hollowed out. The litany of recent scandals in clinical trial (mis)conduct, involving products as varied as Vioxx, Ketek, and ProHeart6, has involved missteps by pharmaceutical manufacturers, regulatory agencies, and clinician-investigators. The situation threatens the credibility of the current drug development system in much the same way that subprime mortgages have threatened the financial system.

*The ABCs of Drug Safety: Accountability, Balance, and Citizen Empowerment*, a White Paper from the Government Accountability Project, is a roadmap for rebuilding the clinical trial system. In clear, precise, uncompromising language, this White Paper describes the fractures that have developed in the scientific, legal, and ethical structure of clinical trials, and puts forth a plan for repairing the damage. Based on my experience as a clinician, regulator, and public health physician, the steps outlined here are not only practical and achievable – they're vital to addressing the current problems in clinical trials.

Restoring this system to health will not be easy, and will require hard work – and the courage to change – on the part of the medical product industry, the U.S. Food and Drug Administration, academic medical centers, and health care providers. But simply hoping that the system does not collapse is not an option. *The ABCs of Drug Safety* shows the way to renew the promise of clinical trials to improve our health.

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December 2008

# EXECUTIVE SUMMARY

Drug companies spend $14 billion a year testing new drugs.[1] Many of these drugs are life-savers. But too many are the opposite.

Tens of thousands of Americans have died from taking United States Food and Drug Administration ("FDA") approved drugs. The painkiller Vioxx alone is responsible for upwards of 55,000 American deaths.[2] Many more people have died as study participants in poorly monitored, FDA mandated clinical drug trials. The tragic fact is that most of these deaths were preventable. To borrow a political campaign cliché, we can do better. Much better.

This White Paper focuses on the approval process of new drugs, in particular, the conduct of clinical trials involving human participants. It also examines the systems in place that monitor patient safety once these products are approved.

The manufacture and testing of new drugs is the province of the pharmaceutical industry; regulation of the industry is the job of the FDA. In 2006, the top ten drug manufacturers earned nearly $40 billion in profits.[3] With such vast sums at stake, it comes as no surprise that the drug industry is very focused on expediting the drug approval process.

The FDA is charged by statute with the critical public health and safety duty of regulating prescription and over-the-counter drugs, medical devices, biological products, and certain foods.[4] Together, these products account for roughly 25 percent of all consumer spending in the United States.[5]

How effectively is the FDA discharging its duty? According to Dr. David Graham, a leading FDA scientist, "as currently configured, [the FDA] is incapable of protecting America against another Vioxx. We are virtually defenseless."[6]

Why? In part, the FDA is defenseless because of finances. Federal funding for the FDA has decreased since 1992, forcing the Agency to heavily rely on fees it receives from the very industry it is supposed to regulate. The industry's financial grip over the FDA has undermined both the perception and reality of an arms-length relationship between the regulator and the regulated.

The drug approval process is now a product of closed-door negotiations between the drug companies and the FDA. With the leverage of their user fees, drug companies have successfully pressured the FDA to greatly expedite the timetable for drug approvals, which results in a frequent rush to judgment about a product's safety and efficacy.

The conflicts corroding drug safety, however, run even deeper: They are structural to the FDA and to the conduct of clinical drug trials. A 2003 study found that approximately two-thirds of academic medical centers hold equity interests in companies that sponsor research at these institutions.[7] And this study did not even touch on trials being conducted by for-profit entities on behalf of drug sponsors. Marcia Angell, former editor of the *New England Journal of Medicine* and a senior lecturer at the Harvard Medical School, maintains that all clinical trials should be administered by the National Institutes of Health: "It is self-evidently absurd to look to investor-owned companies for unbiased evaluations of their own products. Yet many academic investigators and their institutions pretend otherwise, and it is convenient and profitable for them to do so."[8]

The law not only promotes conflicted relations between drug sponsors and universities, but between drug sponsors and the contract research organizations (CROs) and Institutional Review Boards meant to ensure the integrity of the trials and the safety of the participants. CROs, which conduct clinical trials to assess a drug's safety and efficacy, sometimes even hold equity positions in the very drug companies at issue. In addition, as the inspector general of the Department of Health and Human Services found in early 2009, in 42 percent of clinical trials, the FDA neither received required forms disclosing doctors' financial conflicts of interests nor did the agency take any action about this noncompliance.[9] Equally as troubling, the law does not currently require governmental oversight of all human clinical trials.

Laws intended to protect patients and clinical trial participants are too often honored in the breach. As Bloomberg Markets reported in a seminal 2005 series, over half the reviews of new drug submissions to the

FDA were handled by a single Institutional Review Board (IRB), Western, whose track record on behalf of patients is anything but reassuring.[10]

Equally troubling, laws aimed to encourage industry and government scientists to speak out about risky drugs and devices have too often failed to provide adequate protection. The failure of these whistleblower protections has fostered an environment in which employees know that disclosing the truth may cost them their job, financial security, and reputation.

This White Paper examines a number of the recent drug controversies and how the various institutional players performed, and too frequently failed to perform, their critical duties. It also discusses legal remedies – and too often the lack of remedies – for persons injured by failures in the system. And, it proposes constructive reforms to empower participants in clinical trials, remove conflicts of interest that undermine patient safety, and bring into balance risk-benefit calculations.

GAP, which represents numerous drug industry and FDA whistleblowers, is uniquely situated to offer this White Paper. Our clients' disclosures of fraud, mismanagement, abuse of authority, corruption, and disregard for public safety inform both the identified pitfalls and our recommended reforms. Complementing whistleblowers' vital disclosures, this White Paper draws on a focused literature review of clinical trial scientific research. We also examined relevant case law, FDA legislative history, and drug safety articles in the media.

The key themes that emerge align with what the White Paper refers to as the ABCs of Drug Safety: Accountability, Balance, and Citizen Empowerment: Accountability at the investigator, institutional review board, government, and industry level; Balance in the assessment of drug risks and benefits; and Citizen Empowerment by strengthening the legal rights of drug trial participants, and whistleblower protections for drug industry and government scientists. In summary, the White Paper advocates:

## Whistleblower Protections

A number of statutory and common law provisions aim to safeguard whistleblowers. These protections, however, are inadequate in scope and remedy. Government agencies and courts also fail to appropriately enforce whistleblower laws. GAP proposes specific provisions to reform these laws and effectively protect drug industry and government whistleblowers.

## Recourse for Injured Patient or Trial Participant

The U.S. Supreme Court held in *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999 (2008), that state court personal injury suits are preempted if FDA approved the faulty medical device. Happily, the Supreme Court in *Wyeth v. Levine* refused to extend preemption to prescription drugs. Had it done so, the effect would have been to wholly immunize device and drug manufacturers for the harm their FDA approved products cause. Congress needs to step in and make clear that these personal injury suits are not preempted.

## Protection for *All* Human Subjects

The federal government only regulates clinical research trials that fall under the Department of Health and Human Services or FDA oversight. Many pre-Phase I, Phase IV, and investigator-initiated trials are thereby exempted, leaving an estimated 40 percent of studies and over five million research participants uncovered each year. GAP supports the National Bioethics Advisory Commission recommendation for a national system of oversight of all human research.

## Reform of Institutional [or Independent] Review Boards ("IRB")

A number of structural, financial, procedural, and regulatory gaps plague the IRB system. Legislative reform is needed to ensure that IRBs operate at arms length from drug sponsors and that IRB members are, themselves, free of compromising industry conflicts.

## Truly Monitor Informed Consent

The current IRB system literally places form over substance: It focuses almost exclusively on the review of consent forms. Yet, the law does not require IRBs to regularly observe consent interviews or the conduct of study protocols. Instead, these critical processes are left to self-regulation by the investigators themselves. GAP proposes pilot projects to determine which processes obtain truly informed consent.

## Comparative Trials/Non-Inferiority Trials

The FDA currently permits the drug industry to prove the efficacy of a new drug by comparing it to a placebo or to a previously approved drug for the same indication. In a placebo trial, the investigational drug is compared to a sugar pill. If the investigational drug proves more effective than the sugar pill, it is declared efficacious, even if it is less effective than existing drugs on the market for the same condition. The public should be informed about the relative effectiveness of various drugs approved by the FDA but, currently, that information is treated as a trade secret.

In trials involving subjects with life-threatening ailments, it would be unconscionable to assign placebo to any trial participants. So the FDA also permits investigational drugs to be tried against previously approved comparator drugs. Although comparative trials seemingly pose a higher bar to approval than placebo trials, drug-makers often prefer them, or rather a species of comparative trials call "non-inferiority trials."

In a non-inferiority trial, an investigational drug may be approved even if it is *less* effective than the comparator drug. Not surprisingly, drug-makers prefer this low bar to approval, especially for common and lucrative conditions, like ear infections. These conditions almost always resolve on their own *before* the drugs are shown to have an actual impact.

GAP recommends that rather than either standard placebo or comparative trials, that new drugs be subjected to three-arm trials in which an investigational drug is tested against both a placebo and a comparator drug.

## Federal Funding

Since 2003, the funding for clinical research has failed to keep pace with inflation or even been cut. Reduced federal funds means clinical trials are eliminated, terminated, limited, or delayed. The climate of funding uncertainty has forced researchers to do more with less, or rely more heavily on industry support. This environment weakens the capacity of clinical centers to discover new treatments and drugs. Fewer patients can access clinical trials and the treatments they may provide. Tight finances also foster conditions that increase the likelihood of unsafe and unethical trials. The dim funding future has pushed out young investigators and discouraged students from entering the field, creating a "lost generation of scientists."

## Conflicts of Interest

The government must proactively assert its regulatory authority to oversee the increasing commercialization of clinical trials. Conflicts of interest are corrosive to the integrity of trials and should be eliminated or minimized as much as possible. Federal, institutional, and commercial policies must help clarify methods for investigators, research partners and participants, and regulators on how to avoid, disclose, recognize, manage, and eliminate conflicts of interest.

Getting clinical trials and drug safety right is literally a life and death matter. We can and must do a lot better, starting with effective whistleblower protections for scientists and other employees, effective legal recourse for trial participants whose consent is less than truly voluntary, and by instituting mechanisms to remove or effectively diminish the corrupting influences of financially conflicted relationships. In other words, we need to re-learn our ABCs: Accountability, Balance, and Citizen Empowerment.

# INTRODUCTION

***A Broken System***

If ever there were a "perfect storm" illuminating systemic failures in the United States' drug approval process, the story of the antibiotic Ketek ("telithromycin") would be it.[11] Every institutional actor – from the drug sponsor, to the clinical trial investigators, to the Institutional Review Board ("IRB"), to the FDA – failed to honestly or adequately perform their critical mission.

The stakes, financial and human, were enormous. Drug-maker Aventis (now Sanofi-Aventis) saw Ketek as another blockbuster, like azithromycin. But rather than a lifesaver, Ketek proved to be a killer and has exposed the company to huge liability.

Early studies on Ketek flagged the drug as potentially causing liver failure and other adverse effects. In 2001, as a condition for recommending its approval, an FDA Advisory Committee insisted that Aventis undertake a major clinical trial to determine Ketek's safety. Aventis grudgingly hired Pharmaceutical Product Development, Inc. ("PPD"), the contract research organization ("CRO"), to coordinate what would be known as Study 3014.

At the study site that enrolled the most patients, not one single informed consent was properly completed. The majority of "consent forms" were initialed or dated by someone other than the participant, or the form was blatantly forged. Dr. Anne Kirkman-Campbell, the principal investigator at this site, enrolled patients when her office was closed, her entire staff and family members, and even patients who had no history of the medical condition being studied. "Frankly," Ann Marie Cisneros, a senior clinical research associate for PPD, told the U.S. House and Commerce Subcommittee on Oversight and Investigations, "all Kirkman-Campbell seemed truly interested in was getting more business from Aventis as an investigator."

There's no mystery why she wanted the business: Aventis paid her $400 for each of the 407 patients she enrolled – a tidy $162,800 for Study 3014 alone.

Aventis claimed it never suspected fraud in Study 3014. Yet Cisneros reported on the irregularities at the Kirkman-Campbell site by email and teleconference to both PPD and Aventis. She even phoned Copernicus, the IRB, to report her concerns. Cisneros testified to Congress: "I knew [of the fraud], PPD knew it, and Aventis knew it."[12]

Cisneros has no regrets that Kirkman-Campbell is serving a five-year prison sentence for fraud related to Study 3014. But she balks at the court's finding that Aventis was an unwitting victim of Kirkman-Campbell. Cisneros testified to Congress that she learned from a trusted PPD colleague that the Aventis project manager had "coached Dr. Kirkman-Campbell on how to explain away some of the site irregularities." Rather than being alarmed or displeased by what it found at Kirkman-Campbell's site, Aventis hired her as an investigator for a second study and flew her to San Diego to learn how to market Ketek to other physicians.

Why didn't PPD forcefully intervene with Aventis and the FDA to expose the fraud? Could the $20 million fee Aventis paid for Study 3014 have distorted PPD's ethical judgment? And, what about the IRB charged with ensuring the study participant's consent forms were voluntary and authentic?

Copernicus, which was also paid by Aventis, was no more scrupulous than its paymaster. Despite Cisneros' phone call alert, the IRB neither audited the Kirkman-Campbell site nor did it report any irregularities to the FDA. For six years, Copernicus maintained it never received the phone call from Cisneros. Only when the company CEO testified under the pain of perjury in 2008 before Congress did she finally acknowledge finding a written record that Cisneros had indeed called. At the Oversight hearing, the Subcommittee Chairman was palpably outraged. "Why do you exist?" Representative Bart Stupak (D-MI) asked Copernicus' Sharon Hill Price.

This was neither the first hearing on Ketek nor is it the only drug that has prompted Congressional scrutiny for regulatory failure and needless loss of American lives. The Congressman's outrage is understandable: His high school aged son, Bart Jr., committed suicide while taking the acne drug, Accutane –

another suspect drug that nonetheless cleared the drug approval process and is associated with hundreds of suicides.

Hence, Rep. Stupak was little surprised to learn that the Kirkman-Campbell site was not an anomaly. The second largest Study 3014 site was enrolling ineligible patients, its lab tests were incomplete, and it failed to maintain accountable logs or report adverse drug reactions. The physician in charge of the third-largest site was on probation for gross medical negligence. His medical license was yanked shortly after the study closed (when he was arrested on drug and weapon charges). In fact, *every* Study 3014 site ultimately inspected by the FDA had compliance problems.

Study 3014 may be an extreme illustration but it points to a clinical trial system that is rife with inherent conflicts of interest. Where the CRO conducting the trial and the IRB charged with protecting the patients are selected by and paid by the drug sponsor, there is not even the pretense of an arms-length relationship.

The Ketek debacle is certainly disheartening but it is not altogether unexpected. Profit drives the decisions of private companies, not public health. The public relies on the government to serve as our backstop and watchdog. But the FDA shares the blame for the Ketek disaster.

The Agency knew that Study 3014 was unreliable. Nevertheless, FDA senior management chose not to inform the 2003 FDA Advisory Committee on Ketek about the Kirkman-Campbell criminal investigation and data irregularities in the study. Kept in the dark by the FDA, this Advisory Committee recommended approval and the Agency soon thereafter put its stamp of approval on Ketek. As Senator Charles Grassley (R-IA) observed, "It looks like the FDA caught the drug company red handed and let them get away with it."

In truth, FDA scientists had tried to do the right thing about Ketek. The problem was the Agency's top management pressured its own safety officer, Dr. David Ross, to change his negative review of the drug and threatened to fire him if he spoke out publicly about the drug's dangers. After he "voluntarily" left the Agency, Dr. Ross warned Congress that the FDA's fiscal reliance on industry user fees has fostered a "culture of approval" at the Agency. He noted: "[Ketek] was not a drug that anybody thought was necessary in terms of public health. But, it was important to the company financially."

By December 2006, when the FDA bowed to adverse media reports and Congressional scrutiny and held a third Advisory Committee on Ketek, 53 cases of liver failure had already been associated with the drug. This time, armed with more information, the Advisory Committee recommended stripping Ketek of two out of three approved uses, and it advised putting a black-box warning on the label for the lone remaining approved use. Two months later, on the day before a House Energy and Commerce Oversight hearing on Ketek, the FDA announced it would largely follow the Advisory Committee's recommendations.

### *The Gold Standard?*

The FDA purports to be the world's "gold standard" for ensuring drug safety, even as public confidence in the Agency has been in freefall in recent years. As already noted, the Ketek fiasco was hardly unique.

Of course, all drugs have risks.[13] So too do clinical trials. Determining the appropriate risk-to-benefit ratio for an individual, let alone the American public, is a complex but critical undertaking. The public relies on the FDA to ensure the integrity of the drug and medical device[14] trials, protect the subjects who serve as human guinea pigs for new pharmaceutical products, and, ultimately, vet the safety and efficacy of the drugs before they enter into the stream of commerce.

The FDA does not regulate the practice of medicine nor does the FDA itself ordinarily test pharmaceutical drugs. Rather, the FDA reviews the results of laboratory, animal, and human clinical testing conducted by a drug-maker to determine if a new drug is safe and effective in treating specific ailments or conditions ("indications"). If the new drug is determined both safe and effective for a particular indication, FDA approves the drug for that limited use. Once on the market for any indication, however, a licensed physician may prescribe an FDA approved drug "off-label" for anything, even indications never considered by FDA.

Monitoring the safety of off-label uses is even more difficult than for approved indications. A pharmaceutical company is legally obligated to report to FDA any adverse events it learns of that a patient experiences while taking a drug. Yet doctors—whose ears are much closer to the ground—are under no such

reporting compulsion, even for off-label prescriptions. As a result, the post-market monitoring and reporting of adverse drug events is notoriously unreliable.

The stated goal of the FDA drug approval and monitoring process is to ensure that patients receive drugs that are effective and safe in a timely way. How well the FDA balances benefits and risks of a new drug may well be a question of life and death. Sometimes, faster may be better: Reforms in the 1990s that facilitated expedited approvals for Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome ("HIV/AIDS") drugs helped save lives.[15]

Most drugs, however, are not for the treatment of life-threatening conditions. In fact, many of the most profitable drugs are for the treatment of relatively benign, even self-resolving conditions. In such a circumstance, where the benefit of the drug is relatively minor, the level of acceptable risk related to the drug should be commensurately lower, or virtually non-existent.

The FDA's record in ensuring a proper risk-benefit ratio, unfortunately, falls well below a "gold standard".[16] A recent report found that new drugs are twice as likely to cause harm as provide added benefit.[17] Not exactly the ideal balance of risks and benefits. As Dr. Rosemary Johann-Liang, then Deputy Director of the FDA's Division of Drug Risk Evaluation, observed about the safety profile of Ketek, a garden variety antibiotic approved by FDA: "How does one justify balancing the risk of fatal liver failure against one day less of ear pain?"[18]

***GAP's Goals***

This White Paper aims to describe the pitfalls in the American drug approval system, in particular human drug trials. We examine a number of the recent drug controversies and how the various institutional players performed or failed to perform their critical duties. The paper discusses legal remedies for persons injured by failures in the system and concludes by proposing constructive reforms to empower participants in clinical trials, remove conflicts of interest that undermine patient safety, and bring into balance risk-benefit calculations.

GAP, which represents many drug industry and FDA whistleblowers, is uniquely situated to offer this White Paper. Our clients' disclosures of fraud, mismanagement, abuse of authority, corruption, and disregard for public safety inform both the identified pitfalls and our recommended reforms. Complementing their vital disclosures, this White Paper draws on a focused literature review of clinical trial scientific research and case law, FDA legislative history, and drug safety articles in the media.

The key themes that emerge align with what the White Paper refers to as the ABCs of Drug Safety: Accountability, Balance, and Citizen Empowerment: Accountability at the investigator, institutional review board, government, and industry level; Balance in the assessment of drug risks and benefits; and Citizen Empowerment by strengthening the legal rights of drug trial participants, and whistleblower protections for drug industry and government scientists.

# TRIAL TRAGEDIES

We begin with the human toll exacted by a broken drug safety system, in particular, in the conduct of human clinical trials. The deaths of these individuals, many of whom were young and otherwise healthy, are beyond unconscionable. Compounding these tragedies is that little has yet changed. Instead, piece-meal solutions and fragmented remedies leave in place an unreliable and frequently ineffectual system to protect research study participants and, ultimately, patients.[19] Our goal with this section is to show how the current legal regime evolved in response to tragedies.

Appendix 1 offers a more expansive listing of drug safety and clinical trial failings, reviews the key civil law court cases that apply to research participation, and documents an evolution from basic personal injury tort claims to alleged violations of the Belmont Report and the False Claims Act. This is by no means an exhaustive or analytical review of clinical trial case law.[20] Our aim is to provide a quick glance at the state of the law regarding the conduct of clinical trials in order to frame legislative reform proposals.

The diversity of causes of actions offers plaintiffs a variety of ways to frame claims. The universe of defendants in research-related cases is also expansive. Plaintiffs have sought to hold drug sponsors, researchers, contract research organizations, and IRBs accountable.

The standard of proof demanded by courts in research cases *may* be greater than in the therapeutic treatment context. It is difficult to assess this standard since the vast majority of cases have either settled before trial or courts have yet to address the issues.[21] The cases tend to illustrate that a plaintiff who shows clear negligence or a definite and egregious violation of the law will prevail.

## A. Background on Clinical Trials

A clinical research study aims to develop new treatments and medications for diseases and conditions. Before a drug or therapy can be approved for general use, clinical investigations must first examine: (1) how the treatment works; (2) how effective it is (compared to a placebo or a comparator drug); and (3) what potential risks and benefits may exist. Study investigators recruit study participants using certain inclusion and exclusion criteria, such as age, gender, the type and stage of disease, previous treatment history, and other medical conditions.

All participants must go through the informed consent process. When properly implemented, informed consent is an ongoing process that empowers the clinical trial participant to understand what the benefits and risks are of participating in the study. The process is intended to afford an opportunity for the participant to decide whether or not she wants to participate or terminate her participation at any time.

Participation in a clinical trial involves benefits and risks as Appendix 2 illustrates. Clinical trials occur at multiple medical venues, including hospitals, academic centers, and clinics. Some trials are merely diagnostic while others offer treatment.[22] As Appendix 3 depicts, there are four different trial phases. The number of participants range from 20 to the thousands. If a drug is approved, the FDA's post-marketing surveillance system, Medwatch, is then charged with monitoring the drug's safety.[23]

## B. The Development & Current State of International & Federal Research Laws

The ethical and legal codes that apply to clinical trials are similar to those in medical practice. Appendix 4 lists some of the key historical events in the progression of these codes. Prior to the condemnation of Nazi "medicine" at the Nuremburg trials, the U.S. government played only a minor role in regulating research.[24] On an international level, clinical practitioners are, at a minimum, meant to adhere to the universal standards set forth in the Nuremberg Code, the Declaration of Helsinki, and the Council of International Organization of Medical Science ("CIOMS")/World Health Organization ("WHO").[25] Other international guidelines set forth common standards on good clinical practice ("GCP").[26] Appendix 5 describes key

components of these standards. In addition, Appendices 5-7 list the specific laws that govern clinical trials in the U.S., which historically have accounted for the majority of clinical trials conducted globally. Appendix 7 compares and contrasts FDA and HHS Human Subject Protection Regulations, illustrating some inconsistencies between regulations of human participant research. Despite the notion of universal standards, the pertinent local, health, economic, cultural, and technological circumstances influence the application of the standards in a given research setting. Appendix 8 provides further elaboration on the main ethical requirements extracted from these codes: collaborative partnership, social value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for human subjects.

## C. Tragedies & Abuses at Clinical Trials: Some Leading Examples

***The Thalidomide Experience, late 1950s & early 1960s***

Thalidomide was prescribed overseas to women to treat a variety of symptoms associated with pregnancy. Patients in international studies were not informed that the drug was under investigation. Inadequate international trials and animal testing were conducted to assess the drug's safety, particularly in pregnant women. The drug caused severe deformities in over 10,000 infants worldwide. Seventeen American infants were affected. These infants were predominantly born to military families stationed abroad.

**Disclosure:** Dr. Frances Oldham Kelsey, Ph.D., M.D., blocked FDA approval of Thalidomide. She insisted that the drug manufacturer prove the drug's safety with well-designed, scientifically rigorous studies, and account for any complaints before FDA would accept its application for a marketing license. Dr. Kelsey endured months of threats to her professional reputation and position and complaints to her superiors. Dr. Barbara Moulton also alerted Congress and the public to the dangers of Thalidomide. Dr. Moulton resigned her job at the FDA and blew the whistle on the Agency's questionable industry interactions.

**Legislative Response**: Kefauver-Harris Amendments to Food, Drug, and Cosmetic Act required investigators to obtain informed consent from potential subjects before administering investigational medications. Laws were also passed requiring safety tests during pregnancy before a drug could receive FDA approval. Thalidomide was not prescribed for decades.

***Tuskegee Syphilis Study, 1932 - 1972***

The U.S. Public Health Service ("PHS") conducted an experiment in Alabama on 399 African-American men in the late stages of syphilis. None of the men was told he had syphilis. Rather, they were informed they were being treated for "bad blood." The study goal was to observe racial differences in syphilis. The participants were poor and their promised compensation was free medical care. Participants were given low doses of one of the available syphilis drugs at the time, and then only aspirin. Deliberate efforts were made to keep them from penicillin, the first real cure, when the drug was discovered in the 1940s. These experiments were continued by the government despite the Henderson Act, which requires testing and treatment for venereal disease, and the Declaration of Helsinki, which mandates informed consent. In total, 28 men died directly of syphilis and 100 died of related complications. Forty of their wives were infected and 19 of their children had congenital syphilis.

**Disclosure**: Peter Buxtun, a former PHS venereal disease interviewer, provided study information to a reporter, who published a story in the *Washington Star* on July 25, 1972. PHS denied the allegations, but soon thereafter ended the experiment.

**Legislative and Regulatory Responses**: The National Research Act of 1974 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission produced the Belmont Report, codified at Title 45, Part 46 of the Code of Federal Regulations, that outlines federal legal requirements for the protection of human research subjects.

***James Gelsinger, 1999***

James Gelsinger died on September 17, 1999 while a patient with liver disease at the University of Pennsylvania. Gelsinger was participating in a University of Pennsylvania Human Gene Therapy Institute human gene-therapy Phase I study to treat enzyme disorders. He developed a massive immune-response to an adenovirus vector. Dr. James Wilson, a study investigator, held a 30 percent equity stake in the company that owned the rights to license the drug that he was testing in this study. The University also held equity in the company.

**Regulatory and Institutional Responses**: The FDA shut down studies at the University of Pennsylvania and other universities, and restricted research at even more universities.[27] Certain institutions also responded by stopping or limiting research. The National Institute of Health ("NIH") and the FDA undertook initiatives to increase both the scrutiny of research protocols and the dialogue regarding bioethical issues and research methodology among scientists. Furthermore, FDA launched random inspections of over 70 trials. President Clinton initiated efforts to develop policies and initiatives on financial conflicts of interest.

***Seattle's Fred Hutchinson Cancer Research Center, 1981-1993***

In 2001, a media investigation brought to light at least 20 cancer patients who prematurely died from causes directly attributable to an experimental treatment while participating in clinical trials at Seattle's Fred Hutchinson Cancer Research Center. Patients were not informed of their doctors' financial conflicts of interests. Information about the risks involved and the alternatives available were not disclosed.

**Disclosure**: Doctors tried to raise concerns and complained about the trials, but were ignored by their institutional administrator, along with state and federal investigators.

**Regulatory Response**: Research at the center was halted. Reforms included those listed under *Gelsinge*r.

***Ellen Roche, 2001*[28]**

Ellen Roche, a healthy 24-year-old research subject in a Phase I John Hopkins University study on hexamethonium, died from respiratory failure after breathing in a chemical that was designed to help scientists study the effects of asthma. Despite research showing the study compound could be unsafe, the investigator failed to come across this evidence. The Informed Consent forms contained language that made it appear that the study compound was benign and a federally approved product. The product did not have FDA approval. The IRB was not immediately informed that Roche developed a cough after breathing in this chemical.

**Regulatory Response**: All projects at Johns Hopkins were suspended. Reforms included those listed under *Gelsinger*. Johns Hopkins settled with Roche's family for an undisclosed amount of money and then began to overhaul its institutional research oversight processes and policies.

***St. John Medical Center in Tulsa, Oklahoma, 2000***[29]

The IRB approved a protocol for a Phase I study of a cancer vaccine. The majority of the patients enrolled in the study had advanced cancer. Ninety-four research participants received the vaccine and 26 participants died during the study. The deaths were not attributed to the vaccine itself. An independent audit by a contract research organization recommended terminating the three-year-study since numerous human research protection violations were found. The University stopped the study, but failed to notify the participants or the FDA of the study's cessation. Indeed, when the Chairman of a medical center panel overseeing the research learned of the study deficiencies, he not only failed to inform his fellow panel members but also whitewashed the experiment in his annual report.

**Disclosure**: A whistleblower alerted federal authorities about her boss, the study investigator.

**Regulatory Response**: The HHS Office of Human Research Protections suspended all federally funded human research at the Tulsa campus in June 2000. The suspension letter noted a number of alleged human subject protection violations relating to the vaccine study including: inadequate procedures for manufacturing and safety testing of the vaccine, failure to adhere to protocol inclusion and exclusion criteria, incomplete informed consent forms, and a failure by the IRB to meet its regulatory obligations. The suspension was lifted in July 2000, based on the University's assurances that it would implement a more rigorous research review process. The University also promised to improve its educational and training programs for researchers and IRB members. A class action was filed and, for the first time, named IRB members individually as defendants. The court, however, dismissed the case holding that the court did not have jurisdiction over the allegations made in the complaint.

***Ketek, 2000*** [30]

The Introduction to this White Paper and Table 1 lay out the marred history of Ketek. The investigator, who enrolled the most patients for Ketek's clinical trial known as Study 3014, was ultimately sentenced to federal prison for fabricating data for this study. Numerous other study sites were plagued with Good Clinical Practice ("GCP") issues and suspect investigators.

Millions of prescriptions for Ketek were written in the U.S. since its approval in 2004. By September 2007, liver failure had occurred in 27 patients after taking Ketek. Twelve of these patients died. Most of these individuals were healthy before taking this antibiotic.

**Disclosure**: Ann Marie Cisneros worked as a research compliance officer at the contract research organization conducting the Phase III trial. She documented numerous deficiencies and concerns during a Ketek site visit and alerted the CEO of the commercial IRB overseeing this study, Copernicus Group, Inc. Copernicus failed to follow up on Cisneros' warning. Multiple FDA officials also expressed concerns about the Ketek trials and the drug's safety (and efficacy). These include Dr. John Powers and Dr. David Ross, FDA physician-regulators who, like Cisneros, sought and received GAP representation. Powers and Ross left the FDA in large measure over its handling of Ketek and the Agency's retaliation against them. Both Dr. Powers and Dr. Ross continue to advocate for FDA reform.

**Regulatory Response**: The FDA approved Ketek in 2004 for acute bacterial sinusitis, chronic bronchitis, and community-acquired pneumonia even though its own reviewers determined the study data was "riddled with fraudulent information" and its own advisory committee expressed safety concerns.

The evidence that the FDA reviewed suggested that Ketek could potentially cause serious liver damage among other harms. The FDA also had knowledge that Aventis knowingly submitted fabricated

study data. In fact, the FDA's Division of Scientific Investigation concluded that none of the results from the Ketek trial could be trusted. Ketek had no special advantages over other antibiotics; yet, the FDA pressured a medical officer to soften his negative review of Ketek. Data was concealed by the Agency from its own Advisory Committee and the public.

To approve the drug, FDA relied on non-inferiority data and the company's "post-market surveillance" in Europe and Latin America. The drug had been prescribed four million times overseas and adverse event reports were minimal. Relying exclusively on other countries' "surveillance" data was unprecedented for the FDA. (The FDA deems randomized clinical trials as far more reliable than spontaneous reports of side effects, especially given the different reporting requirements and reporting cultures abroad.)

In June 2006, facing intense press scrutiny and concurrent Senate and House investigations into deaths associated with Ketek and the FDA regulatory failures, the FDA announced changes to Ketek's labeling. The label stated that in rare circumstances the drug could cause serious liver injury, liver failure, and even death. In December 2006, the FDA held a third FDA Advisory Committee on Ketek. This Committee recommended withdrawing approvals of two of the three previously approved indications, and putting a black-box warning on the label for its remaining use. The FDA announced it would largely follow this recommendation; the announcement came months later, the day before a Congressional hearing on Ketek.

**Table 1: Timeline of Key Ketek Events**

| DATE | EVENT |
|---|---|
| February 2000 | Sanofi-Aventis (then Aventis) first asked the FDA to approve their antibiotic "Ketek." |
| April 2001 | A Federal Advisory Committee recommended that a large safety study be conducted on Ketek before the drug could be approved. |
| June 2001 | FDA declined to approve the drug and requested further drug safety information noting hints that the company's clinical trials indicate the drug may cause liver problems, blurry vision, loss of consciousness, and other possible side effects. |
| July 2001 | Ketek is approved in Europe. |
| October 2001 | Ketek is seen as a potential big seller, so Aventis hired a contractor, Pharmaceutical Product Development, Inc. ("PPD"), as a contract research organization ("CRO"), to coordinate clinical trials. PPD began enrolling patients with respiratory infections in Study 3014 to test Ketek. Study participants (n=24,000) are given either Ketek or Augmentin, a widely used antibiotic. Aventis and PPD, offered doctors $100 cash for each patient they signed up, $150 when the doctors submitted results, and a final $150 after all questions were resolved. Aventis targeted doctor's offices and non-academic institutions to "mimic the real-world conditions in which Ketek would be used." |
| February 2002 | PPD sent Aventis an email regarding potential problems at the Campbell site (*See* October 2003 for further detail). |
| March 2002 | Aventis directed a company statistician to analyze Campbell's study data. The statistician indicated that Campbell's lab results were "consistent" with those of two other top enrollers and a "systematic pattern is unlikely" (a marker for fraud). Campbell, at this point, was "refusing to address any issues via phone" or respond to faxes or FedEx deliveries. FDA was not notified. |
| July 2002 | Aventis submitted the results of Study 3014 to the FDA. This submission included 407 patients from Campbell. Aventis failed to "alert the Agency to any problems" with Campbell's data at this time. If a company suspects fraud, the law requires the company immediately inform the FDA. |
| October 2002 | FDA reviewers found Ketek data riddled with serious and pervasive misconduct. |
| December 2002 | Aventis admitted it knew of "issues" at its largest enroller – but failed to tell the FDA. |

**Table 1, Continued: Timeline of Key Ketek Events**

| DATE | EVENT |
|---|---|
| January 2003 | FDA declined to approve the drug. The Agency requests further information about Study 3014 and the drug's overseas adverse event reports. |
| October 2003 | Ann Campbell, an Alabama physician, pled guilty and was sentenced to 57 months in prison after pleading guilty to mail fraud. Campbell was an investigator conducting a clinical trial on Ketek. By January 2002, she had enrolled 287 patients or about 30 new participants a day. Campbell submitted false data to Aventis related to the number of people in the study. She was also fined $557,251.22 and was given three years supervised release after the prison term was served. The court ordered Campbell to make restitution to Aventis in the amount of $925,774.61. The case was investigated by the FDA's Office of Criminal Investigations and was prosecuted by Assistant U.S. Attorney Herbert H. Henry. |
| April 2004 | FDA approved Ketek despite not relying on Study 3014, depending on the overseas reports and smaller clinical trials. |
| February 2005 | Man died of liver failure in North Carolina after taking Ketek. |
| May 2006 | Gardiner Harris reported in *The New York Times* that Dr. Rosemary Johann-Liang, FDA Deputy Director of the Division of Drug Risk Evaluation, called for Sanofi-Aventis to stop testing Ketek in children, observing "How does one justify balancing the risks of a fatal liver failure against one day less of ear pain? Sanofi-Aventis subsequently announced a "pause" in its pediatric clinical trials. |
| June 2006 | Dr. David Graham, FDA scientist, Vioxx whistleblower, and GAP client, published an article asserting that it was "as if every principle governing the review and approval of new drugs was abandoned or suspended where telithromycin is concerned." |
| June 2006 | Under increasing scrutiny in the media, the FDA announced changes to Ketek's labeling, stating that in rare circumstances the drug could cause serious liver injury, liver failure, and even death. |
| December 2006 | FDA Advisory Committee heard testimony from FDA scientists: Drs. Rosemary Johann-Liang, David Ross, David Graham, and John Powers, as well as GAP's then-Food and Drug Safety Director Mark Cohen. The Advisory Committee votes to withdraw approvals for two of three indications and for a black box warning for the remaining indication. |
| February 2007 | FDA issued decision to follow the advice of its own Advisory Committee, the day before a Congressional hearing on the subject. |
| February 2007 | House Energy and Commerce's Subcommittee on Oversight and Investigations held a Hearing on Ketek. This Hearing featured four GAP clients: Drs. Ross, Powers, and Graham, along with Ann Marie Cisneros. Ms. Cisneros was a contract research associate for PPD, the CRO that monitored clinical Study 3014. Dr. Ross described extensive fraud and irregularities in Study 3014 and efforts by the FDA top management to suppress his disclosures. Ms. Cisneros asserted that Sanofi-Aventis the drug sponsor, PPD the CRO, and The Copernicus Group the for-profit Institutional Review Board were all informed about the serious irregularities in the conduct of Study 3014, but failed to take effective action. |
| February 2008 | House Committee on Energy and Commerce Subcommittee on Oversight and Investigations held an oversight hearing featuring Ketek whistleblowers/GAP clients Cisneros and Dr. Powers, and industry witnesses. The Subcommittee drills representatives of the for-profit IRB overseeing Study 3014 (The Copernicus Group), the CRO responsible for monitoring the study (PPD), and the drug sponsor (Sanofi-Aventis). |

***Paxil, 2004***[31]

The FDA approved Paxil ("paroxetine") in 1992 for treatment of depression in adults. The drug was not approved for children and adolescents. Nonetheless, in 2002, physicians wrote over two million off-label Paxil prescriptions for youngsters, nearly half of which were for mood disorders. They prescribed the drug despite evidence had been accumulating since the mid-1990s that Paxil posed a serious health hazard.

Sufficiently alarmed about Paxil triggering suicides, the British government in June 2003 banned its use for children and adolescents. The BBC TV investigative magazine "Panorama" reported on internal GlaxoSmithKline ("GSK") documents showing the company knew Paxil did not work in children.

Following up the British ban, Dr. Andrew Mosholder, an FDA medical officer and child psychiatrist, began to analyze data involving 4,250 subjects in 22 randomized, placebo-controlled clinical trials involving selective serotonon uptake inhibitor ("SSRI") antidepressants, such as Paxil. Overall, Dr. Mosholder found 108 suicide-related events. Subjects who took the SSRIs had twice the risk of a suicide-related event as those who were given placebos. Dr. Mosholder's findings were buttressed in April 2004 by a study in *Lancet*, which also concluded that clinical trial data revealed problems in prescribing SSRIs like Paxil to children and adolescents.

**Disclosure**: In the 1990s, Donna Howard, a Brown University Psychiatric Department Assistant Administrator, blew the whistle on her Department, which she believed was skewing research data in a randomized trial for the GSK anti-depressant Paxil.

The FDA at first barred Dr. Mosholder from presenting his findings to a public advisory committee meeting on Paxil. Management then informed him he could attend only if he answered questions from an approved script that underrepresented the danger of suicide. Mosholder's research was anonymously disclosed to the *San Francisco Chronicle*, which published the findings. Under intense public scrutiny, the FDA declined approval for unrestricted use of Paxil. The Director of the Office of Drug Safety, Dr. Paul Seligman, continued the investigation, but to determine who at the FDA leaked the report.

Various lawsuits helped prove GSK concealed clinical trial results linking SSRIs to an increased risk of suicide among adolescents.[32] GSK agreed to settle (for $2.5 million) a suit brought by New York Attorney General Eliot Spitzer after it was discovered that GSK actually conducted nine clinical trials on Paxil but only published the results of one. The concealed data showed that Paxil was no more effective than a placebo but could increase the likelihood of suicidal feelings, thoughts, and behaviors as much as three times.

**Regulatory Response**: Following the failed effort to silence Dr. Mosholder's findings, the FDA ordered GSK to place a black-box warning on SSRIs and other antidepressants indicating their risk for potential suicidal thinking in children and adolescents.[33] The FDA also implemented a new public registry system.

Suicides by clinical trial participants and consumers taking Paxil, Accutane, and a number of other drugs ultimately prompted the FDA to require suicide studies in drug trials.[34] Now, makers of drugs to treat obesity, urinary incontinence, epilepsy, smoking cessation, depression, and a number of other conditions are being asked by the FDA to incorporate a comprehensive suicide assessment into their clinical trials.

***More Trial Tragedies***

- ***Willowbrook Hepatitis Studies, 1963-1966***: A New York State institution for "mentally defective persons" deliberately infected children with the hepatitis virus to study the natural

course of the infection. Once the experiment was underway, the school limited admissions to children whose parents agreed to let them participate in the study.[35]

- ***Jewish Chronic Disease Hospital Studies, 1963***: Chronically ill but cancer free patients in New York City were injected with live human cancer cells without their knowledge.[36]

- ***San Antonio Contraception Study, 1969***: Seventy impoverished Mexican-American women who thought they were receiving oral contraceptives were in fact trial participants, and half of them received placebos rather the Pill. A number of unwanted pregnancies resulted.[37]

- ***Tearoom Trade Study, 1960s***: A researcher secretly observed sexual behavior in men and, through false pretenses, obtained their contact information and interviewed them as part of a "marketing research project."[38]

- ***Garry Polsgrove, 2002:*** The Fabre Research Clinic in Houston recruited a homeless Vietnam veteran, Garry Polsgrove, for a trial of clozapine. The trial was funded by Ivax Corporation, the nation's largest manufacturer of generic drugs. Twenty-two days after he entered the clinic, Polsgrove died of myocarditis in the care of an unlicensed clinic assistant. The FDA allowed the clinic to operate for three more years before closing it down.[39]

- ***Jolee Mohr, 2007:*** A 36-year-old woman with rheumatoid arthritis died while participating in a gene-therapy clinical trial. Jolee's rheumatologist told her the trial was her best course of treatment. This rheumatologist was also the trial's principal investigator and was compensated based on the number of participants enrolled in the trial. The for-profit IRB overseeing the study approved a flawed consent form, which buried the risk of death in the middle of a 15-page document.[40]

## D. The Human Toll When Clinical Trials and Post-Market Studies Go Awry: The Case of Vioxx

Vioxx ("rofecoxib") is a member of a class of non-steroidal anti-inflammatory drugs called COX-2 inhibitors. Clinical trials revealed an increased risk of heart attack and stroke for individuals taking Vioxx [41] The FDA nonetheless approved the drug and required only a warning of possible cardiovascular harm on the label. And harm there was: An estimated 88,000 to 139,000 American Vioxx users suffered heart attacks and strokes.[42] The FDA defended its approval by noting that Merck was less than forthcoming about what its studies showed.[43] Merck scientists were aware of the potential heart risks, but made a "marketing decision" to not undertake studies of cardiovascular outcomes.[44]

**Disclosure**: Based on significant heart risks associated with Vioxx and various problems with the drug's safety data, in the spring of 2004, Dr. David Graham, a 20-year veteran FDA scientist called for Merck to withdraw Vioxx, its second most profitable drug, from the market. Dr. Graham later called Vioxx "the single greatest drug safety catastrophe in the history of this country or the history of the world."[45] FDA officials dismissed Dr. Graham's assertions as "irresponsible." The Agency also sought to interfere with Dr. Graham's publication in the *Lancet* of his findings based on Vioxx users in the Kaiser Permanente patient population.

Senator Charles Grassley (R-IA) intervened to ensure the research was not suppressed and scheduled a Congressional hearing. In the weeks before the hearing, FDA officials wielded both a carrot and sticks, repeatedly insisting Dr. Graham's study should not be publicly aired due to alleged scientific misconduct. FDA supervisors even contacted medical journals, characterizing Dr. Graham as a

dangerous demagogue and bully who had to be stopped, urging that they not publish his research. Supervisors then warned Dr. Graham he could be disciplined for releasing the study under his own name, pressuring him to ask the journals to delay publication. They even sought representation from GAP, claiming they were blowing the whistle on the dangerous Dr. Graham. (They knew Dr. Graham was being represented by GAP and, perhaps, hoped to create an ethical conflict for GAP in representing him.) Acting FDA Commissioner Lester Crawford personally extended the carrot, offering Dr. Graham a new position in the Commissioner's office. But Dr. Graham viewed this as a ploy to remove him from the drug safety front lines and put him directly under the Commissioner's thumb. He declined the offer.

Dr. Graham's testimony at the Senate Hearing became front-page news. In addition to Vioxx, when asked by a senator if there were other dangerous drugs on the market, Dr. Graham identified five other suspects: Accutane, Bextra, Crestor, Meridia, and Serevent.

A week after the Hearing, sympathetic insider colleagues and press contacts warned Dr. Graham that the FDA was finalizing plans to immediately exile him from drug safety work. Sen. Grassley, GAP, and the media rallied to his defense, and the FDA retreated. Facing intense scrutiny over efforts to silence Dr. Graham, Acting Commissioner Crawford issued a memo to all staff that they no longer needed prior approval to communicate with Congress and Dr. Graham's supervisors approved publication of his study.

Months later, when the media attention lifted, however, the FDA brass returned to form. Dr. Graham was told that he could not present results from a new study about COX-2 drugs to an FDA Advisory Committee. Once again, Sen. Grassley intervened, and once again, Crawford blinked and let Dr. Graham present his views. Although dominated by industry scientists, the Advisory Committee placed unprecedented safety restrictions on all COX-2 pain relievers and required large warning labels.

**Regulatory Response**: FDA did not mandate that Merck withdraw Vioxx. Merck "voluntarily" withdrew the drug. Various Congressional hearings investigated the approval of Vioxx by the FDA, and the Agency's approval of a number of other drugs with suspect safety profiles. Advocates drew attention to the inherent conflict of interest that arises by having the FDA's Center for Drug Evaluation and Research ("CDER"), which approves a drug as safe and effective, then monitor the drug once it is on the market. This dual role requires that CDER admit, based on post-market evidence, that it erred in approving the drug in the first place.

## E. More Drug Safety Failures Illustrating Post-Market and Adverse Event Reporting Problems

- ***Accutane, 1998***: A number of adverse events, including the death of the son of Rep. Bart Stupak (D-MI) who was taking Accutane to treat his acne, finally sparked the FDA to send a warning letter to Hoffman-LaRoche ("Roche") regarding its misleading advertising and promotional labeling.[46]

  Roche submitted the application for Accutane ("isotretinoin") in July 1981 and the FDA quickly approved the drug in May 1982. From 1982 to 1988, women were only warned that Accutane caused birth defects in animals. No precautions were taken. During this period, over one thousand infants were born without ears, major organs, or portions of their brain. A number of infants were stillborn and others were aborted. In 1988, FDA required stronger warnings and physician mailings on Accutane's risk of birth defects.

  French studies, conducted from 1992-1994, reported in 1997 that users of Accutane suffered severe depression and suicidal ideation. The French equivalent of the FDA ordered a consumer warning. Roche did not inform the FDA. Meanwhile, the FDA issued warning letters to Roche regarding lack of compliance on serious adverse event reporting. Roche blamed computer problems for delaying compliance with the law for up to eight years. Although still uninformed about the French warning requirement, the FDA required changes in Roche

advertising that Accutane "…minimizes negative psychosocial effects such as depression and poor self-image." In July 1998, the FDA learned of the French studies and Roche's failure to notify the FDA.

Finally, in 2000, the Accutane label contained a psychiatric warning: "depression, and rarely suicidal thoughts, suicide attempts, and suicide." The FDA's Dr. Graham called Accutane a 20 year regulatory failure.

- ***Propulsid, 2000***: The FDA approved Propulsid in 1993. Janssen Pharmaceutica, subsidiary of Johnson and Johnson, pulled the gastro esophageal reflex disease drug voluntarily from the market in 2000 after cardiac abnormalities were reported in 340 patients, including over 80 deaths.[47] Although the drug was not approved for use in babies, 11 of the 80 deaths were babies. In 2000, the FDA issued a warning letter to users to get tested to determine if heart damaged had occurred.

- ***Trasylol, 2006***: Made by Bayer, Trayslol was used to control bleeding in one-third of all cardiac bypass operations in America just a few years ago. This widespread use occurred well after red flags were waving about Trasylol. In 2005, a large study by Dr. Dennis Mangano showed widespread kidney failure associated with the drug. Indeed, evidence of renal failure associated with Trasylol first emerged in the 1980s and was confirmed by a study in which 13 out of 20 study participants suffered adverse kidney reactions.

  Bayer withheld from a 2006 FDA Advisory Committee meeting an observational study showing fatalities among hospital patients who took Trasylol. The Committee voted to keep Trasylol on the market. The next week, Alexander Walker, the author of the Bayer study, met with the FDA and blew the whistle on Bayer for failing to disclose the study at the Committee meeting. The FDA then issued a warning to doctors about Trasylol. The Advisory Committee did not meet until the following year to consider the hidden study. FDA eventually determined clotting risks outweighed its benefits and withdrew approval for the drug.

## F. Summary

The preceding examples highlight the propensity of marketing to trump product safety at pharmaceutical companies. They are consistent with the Wharton business school study that asked MBA students whether they would keep the antibiotic Panalba on the market if their company earned one million dollars for each patient who died from the drug. In repeated studies, the students consistently opted to keep Panalba on the market and would even try to intimidate FDA into doing so.[48] The above examples also show that the Wharton students would likely have succeeded: FDA is too often asleep at the regulatory wheel or even complicit in the elevation of drug marketing over safety.

In short the evidence is compelling that: (1) the research oversight system is broken, unaccountable, and out of balance; (2) substantial gaps exist in protecting clinical drug trial subjects, conducting post-market surveillance, and ensuring whistleblower protections; and (3) these gaps cause real harm to people and to the integrity of the medical system.

# UNADDRESSED GAPS IN CLINICAL REFORM

*"Over the past 2 decades, the pharmaceutical industry has gained unprecedented control over the evaluation of its own products. Drug companies now finance most clinical research on prescription drugs, and there is mounting evidence that they often skew the research they sponsor to make their drugs look better and safer."*

– Dr. Marcia Angell, senior lecturer on social medicine at the Harvard Medical School and former editor-in-chief of *The New England Journal of Medicine*[49]

The aim of this White Paper is to shed light on seven areas that, in our view, have been largely unaddressed or inadequately reformed. While these areas do not capture all the gaps in clinical trials and drug safety, they emphasize the three key themes – accountability, balance, and citizen empowerment – that should shape reform at the government, private sector, and institutional levels.

## A. Gaps in Clinical Trials Reform

### 1) Whistleblower Protections

*a) Unaddressed Gap*

Drug companies have an economic stake in, and a documented track record of, covering up dangers their drugs pose to the public. Too often the FDA has been a witting or unwitting accomplice. As the Agency has come to view the industry as its "customer", the FDA has shirked its regulatory duty on behalf of its proper customer – the public. Were it not for employees of conscience in industry who dared to blow the whistle, the toll on public health would be even more astronomical. The law should encourage such whistleblowing rather than punish it.

As far back as 1986, the Administrative Conference of the U.S., a federal advisory agency, issued a compelling study on the need for corporate whistleblower rights, concluding:

*"Where Congress has judged it necessary to regulate an industry so as to ensure the safety of its workplace, products, services, or the environment, it is also appropriate that enforcement of the regulatory scheme be strengthened by providing whistleblower protection for the industry's employees who wish to report statutory violations. Consequently, Congress should consider expanding whistleblower protection to workers in industries who may currently lack such protection."*[50]

The Conference expressly noted the pressing need for whistleblower protection in "*manufacturing and production of food, drugs, medical devices, or consumer products generally*." This was timely advice in 1986 and even more so today.

*b) Caught in the Gap: Whistleblowers*

**i. Whistleblowers are the Public's Eyes and Ears**

Absent legal protection for speaking out, industry employees face the dilemma of remaining silent about safety dangers, waste and fraud, or speaking out and risking professional suicide. Not surprisingly, few choose to run the risk. Nor can FDA's leadership be counted on to ferret out dangers to public health posed by its industry "customer". On the contrary, that burden falls on public-spirited FDA employees who put their careers at risk and blow the whistle

on the wrongdoing against the wishes of their employer. Such conscientious FDA employees also need stronger legal protections for speaking out.

- Drugmaker Merck failed to submit to the FDA various studies showing the dangers of the painkiller Vioxx. The one comparative study Merck submitted reflected a higher heart attack risk with Vioxx. Merck offered the tenuous rationale that the comparator drug was cardio protective and resisted even the modest label changes about Vioxx's dangers that the FDA sought. As Associate Director for Science and Medicine at FDA's Office of Drug Safety, Dr. David Graham conducted an exhaustive study evaluating the impact of Vioxx on the risk of heart attacks, and concluded that high doses sharply increased the risk. The FDA management not only refused to support Dr. Graham, it actively undermined his efforts to publish his study results and publicly defamed him. One senior manager referred to his Vioxx study as a "scientific rumor." Dr. Graham testified before the U.S. Senate Finance Committee in late 2004 that he had been "pressured to change my conclusions and recommendations" by the FDA senior management. Based on his and other studies, the FDA's decision to ignore warning signs about Vioxx may have resulted in as many as 55,000 deaths, according to Dr. Graham. Merck "voluntarily" withdrew the drug from the market in late September 2004 in the face of negative publicity resulting from Dr. Graham's disclosures. (*See* **Trials Tragedies**: *Vioxx*).

- When Dr. David Ross, a lead FDA medical reviewer for the Aventis antibiotic Ketek raised concerns about the drug's safety, he was pressured to muzzle his dissent and ultimately threatened with dismissal. The Agency approved Ketek, Dr. Ross said, "knowing that it could kill people from liver damage and that tens of millions of people would be exposed to it. The drug maker submitted fabricated data on the drug, knowing that Ketek is not better than other antibiotics, may not even work, and had been linked to liver disease and deaths." The FDA partially withdrew its approval for Ketek only after Dr. Ross and other whistleblowers forced the issue before Congress and the media. (*See* **Trials Tragedies**: *Ketek*).

- As Deputy Director of the FDA's Division of Drug Risk Evaluation, Dr. Rosemary Johann-Liang recommended in February 2006 that the diabetes drug Avandia get a "black box" warning for heart problems related to the drug. For doing so, her FDA managers reprimanded her. Not only did FDA not act on her recommendation, they removed her from the review of the drug. "They decided to act like the review never happened," Dr. Johann-Liang told *The New York Times*. Over a year later, an embarrassed FDA ultimately asked for a black box warning after an article in the *New England Journal of Medicine* raised complementary concerns about Avandia increasing the risk of heart attacks in diabetic patients.

- FDA scientist Dr. Andrew Mosholder raised concerns in 2003 that Paxil and several other anti-depressants could lead children and adolescents to become suicidal. When Dr. Mosholder rejected the FDA management's soft warning that these drugs should be taken with "caution", the Agency blocked him from presenting his findings to an FDA Advisory Committee and put him under investigation for leaking the results to the media. Dr. Mosholder's findings were subsequently vindicated. Researchers at Columbia University hired by the FDA confirmed his conclusions – a year later. The effect was that the FDA waited until March 2004 to ask drug companies to include a black box warning about suicide risk for these antidepressants. By the time the FDA acted, dozens of parents had reported that their children had killed themselves while on these drugs.

- The hand-in-glove relationship between drug maker and the highest reaches of the FDA has seldom been as brazen as in the case of FDA veterinarian Victoria Hampshire. Sen. Charles Grassley (R-IA) documented the extraordinary campaign Wyeth Pharmaceuticals undertook to discredit Dr. Hampshire, and the complicity of the highest levels at the FDA.[51] Angered by her findings that its heartworm drug, ProHeart6, was killing hundreds of dogs, Wyeth manufactured misleading evidence against Dr. Hampshire and presented it to the Acting FDA Commissioner in a private meeting. The Agency then removed Dr. Hampshire from the ProHeart6 review with no explanation and launched a criminal investigation of her. The FDA Advisory Committee nevertheless found the evidence that ProHeart6 was a killer compelling and did not recommend its re-approval. Ultimately, the criminal investigation against Dr. Hampshire was dropped with no charges filed, and, she was named Public Health Service Veterinarian of the Year, largely for her diligent work on ProHeart6.

**ii. Drug Industry Whistleblowers Need Legal Protection to Speak Out**

Dr. Aubrey Blumsohn's whistleblower story began in 2002, when he was employed as a senior faculty member at the University of Sheffield in England. His program contracted with Proctor & Gamble ("P&G") to study the effectiveness of P&G's osteoporosis drug, Actonel, in preventing bone fractures and in effecting bone resorption, the rate at which bone is removed. P&G hoped to prove that Actonel was more effective than its leading competitor, Merck's Fosamax, in strengthening bones and preventing fractures in post-menopausal women.

Dr. Blumsohn collected the raw data for the analysis. Since it was a blind study, he needed the randomization codes from P&G to make sense of and analyze the data. Instead, P&G only provided Dr. Blumsohn tabular data it compiled. Aware of the possibility that P&G could have cherry-picked or invented the data it provided, Dr. Blumsohn continued to request the raw data in order to undertake an analysis. Sheffield, feeling economic pressure from P&G, terminated Dr. Blumsohn. Blumsohn sued for wrongful discharge.

P&G, meanwhile, was publishing ghost-written articles and market reports under Dr. Blumsohn's name without his consent or approval. These implied that Actonel was as effective as, and safer than, Fosamax. Dr. Blumsohn blew the whistle on both sides of the Atlantic. With GAP's assistance, he took his concerns to the media and, in the face of mounting negative publicity, P&G issued a far-reaching "Researchers' Bill of Rights." However, P&G continued to resist releasing the randomization codes to Dr. Blumsohn. Sheffield and Dr. Blumsohn reached a confidential settlement of his wrongful discharge action.

Dr. Blumsohn's experience is not unique. Industry's record of compromising the efficient and wide dissemination of unfavorable findings is more than disturbing.[52] The practice of not publishing unfavorable results – or requiring researchers to sign non-disclosure agreements that allow the industry sponsor to veto publication of disadvantageous results – undermines scientific integrity and, ultimately, harms patients.[53] Remarkably, a study of over one hundred industry-sponsored publications on new drug clinical trials found that not even one publication concluded that the rival drug company's product was more effective.[54] This defies statistical credulity.

Another study found that data withholding – beyond pre-patent review – was required by contract in nearly half of the academic-industry relationships.[55] This contract provision was enforced in 56 percent of the contracts.[56] This is consistent with industry suppression of research data in other research realms: tobacco[57], pesticides[58], and the military.[59]

It is an all-too-familiar story now that the marketing imperatives of pharmaceutical companies trump honest science. The antidote to drug companies' spin and deception is truth telling. But, unless and until drug industry – and regulatory – whistleblowers are well protected legally, we should not be surprised that it is only the extraordinary employee who will run the

career risk of speaking out. In the meantime, the public's safety and health are being compromised.

*c) Legal Gaps*

A number of statutory and common law provisions aim to safeguard whistleblowers. These protections, however, are inadequate in scope and remedy. Government agencies and courts also fail to appropriately enforce whistleblower law.

**i. Whistleblower Protection Act ("WPA")**

The WPA, passed in 1989 and amended in 1994, should provide whistleblower protection to government servants, like Drs. Ross, Graham, Johann-Liang, and Hampshire. Sadly, the law has been transformed into a trap for the unwary. The good news is that both chambers of Congress recently revisited the statute and reasserted its protective mission. (At this writing, a final bill is yet to emerge from Senate-House conference.) This is a welcome development as the U.S. Court of Appeals for the Federal Circuit, which holds a monopoly over WPA appeals and the law's interpretation, has cut so deeply into the WPA as to render it dangerous to whistleblowers.

The WPA provides that an employee is protected against retaliation if she discloses: "(i) a violation of any law, rule, or regulation, or (ii) gross mismanagement, a gross waste of funds, an abuse of authority, or a substantial and specific danger to public health or safety."[60] Hence, a government employee who comes forward with a lawful disclosure involving any of the broad types of wrongdoing noted above is expressly protected by the WPA.

Yet, despite this explicit mandate, and the equally unequivocal legislative history of the Act, the Federal Circuit denies the WPA protection in the most common situations in which whistleblower disclosures are made. For example, after the 1994 Amendments to the Whistleblower Protection Act were passed, Representative Frank McCloskey (D-IN) very clearly set forth the Congressional intent in the official record:

*"It is also not possible to further clarify the clear statutory language in §2302(b)(8)(A) that protection for 'any' whistleblowing disclosure evidencing a reasonable belief of specified misconduct truly means 'any'. A protected disclosure may be made as part of an employee's job duties, may concern policy or individual misconduct, and may be oral or written and to any audience inside or outside, without restriction to time, place, motive, or context."*[61]

Notwithstanding Rep. McCloskey, in the Federal Circuit's parallel universe, federal whistleblowers are not protected who make their disclosure to co-workers, supervisors, or others in the chain of command, or to those suspected of wrongdoing. They are not protected if they make the disclosure in the course of performing job duties. And they are not protected if the disclosure challenges illegal or improper policies. The WPA protects an employee who "reasonably believes" her disclosure evidences specified misconduct. The Federal Circuit rewrote this lenient standard to require a showing of "irrefragable" – incontrovertible – proof by the employee to overcome a presumption, nowhere found in the statute, that the government "acts in accordance with the law." This is a burden that can virtually never be met.

Since Congress unanimously *strengthened* the WPA in November 1994, employees have won just two out of 205 cases on the merits before the Federal Circuit. The record is equally shocking at the administrative level: Under the current Chair, appointed by President George W. Bush in 2003, employees have won just two out of 55

cases before the Merit System Protection Board, the final administrative tribunal before an appeal to the Federal Circuit.

In the 2008 reform legislation, both the House and the Senate make clear that "reasonable belief" requires far less than incontrovertible proof and that disclosures made to colleagues and in the course of one's job are protected. The bills also strengthen provisions prohibiting federal agencies from imposing gag orders on their employees or engaging in retaliatory investigations. Under a reformed WPA, *all* federal circuit courts, not just the Federal Circuit, would have jurisdiction to hear and rule on appeals. At this writing, the House and Senate bills have yet to be reconciled.

**ii. Sarbanes-Oxley Act ("SOX")**

In the wake of Enron, WorldCom, and other scandals of the early 2000s, Congress enacted the Sarbanes-Oxley Act ("SOX") to tackle corporate fraud. The Act expressly protects employees who blow the whistle on criminal mail fraud, wire fraud, securities fraud, or bank fraud, any Securities Exchange Commission ("SEC") rule or regulation, or *any Federal law relating to fraud against shareholders*.

SOX, for example, protects a pharmaceutical company employee who discloses that the company made false statements in financial reports to shareholders. But, as interpreted by the courts to date, SOX provides no protection to that same employee who discloses that the company intentionally misled the FDA, physicians, or the public that its product was safe and effective. Hence, had a Merck scientist disclosed that Americans suffered tens of thousands of heart attacks and strokes as a result of taking Vioxx, she would have no protection against retaliation under SOX, even though that very revelation, when voiced by the FDA's Dr. Graham resulted in Merck's stock plummeting $40 billion in value.

This judicial narrowing of SOX is proving counter-productive to not only whistleblowers but the public interest. In the fall of 2000, Wyeth Pharmaceutical entered into a Consent Decree with the Justice Department and the FDA to settle ongoing violations of Good Manufacturing Practices ("GMP"). As the GMP issues were coming to a head, Wyeth hired Mark Livingston as Manager, Training and Continuous Improvement at its Sanford (North Carolina) Vaccine Site.[62] Livingston was promoted to Associate Director of Training and Continuous Improvement in April 2001.

Livingston's principle responsibility was to improve compliance with the GMP Training System at Wyeth Sanford and ensure that adequate training measures were in place for the safe and compliant manufacture of pediatric vaccines, particularly the new infant vaccine, Prevnar. In effect, Livingston was hired by Wyeth to ensure Prevnar's safety.

He discovered several regulatory violations and repeatedly raised concerns about the lack of compliance with regulatory GMP. In particular, Livingston asserted that Wyeth failed to train new employees in critical manufacturing and quality assurance positions fast enough to keep pace with production and sales goals of Prevnar from 1992-2002. According to Livingston, Wyeth repeatedly announced, both internally and publicly, that failure to meet Consent Decree and GMP mandates would negatively affect the company's future. But Wyeth did not act on its own warnings. Instead, Wyeth Sanford management kept the production pipeline flowing despite the lack of compliance, thereby materially misrepresenting the true state of its operations and financial performance.

Livingston spent two years sounding the alarm that the company was concealing its failure to meet GMP mandates. He was fired in December 2002. Shortly thereafter he filed a complaint under the SOX, asserting he was discharged for speaking out about the safety implications for infants, and the huge financial implications for shareholders, of not meeting the GMP mandates. Although he stated that his disclosures implicated fraud against Wyeth shareholders, who stood to lose considerable value were the FDA to penalize the company for

ongoing GMP violations, the Fourth Circuit Court of Appeals held that his disclosures were not protected under SOX because they were not directly related to financial losses.

Such a narrow judicial reading fails to advance SOX's mission of cleaning up corporate conduct. The effect of *Livingston* and similar decisions is rippling through the legal community. An employee of a leading drug and medical device corporation was fired after refusing to implement quality assurance measures that were out of compliance with FDA rules and regulations. He disclosed the company's failure to report to the FDA changes made to an FDA-approved medical device that functionally altered the device. A co-worker who supported the whistleblower and was aware of the company's FDA violations was also fired shortly thereafter. Yet, no private attorney would take their cases because of the narrow scope of protection under SOX.

**iii. Federal False Claims Act ("FCA")**

The federal False Claims Act ("FCA"), first passed in 1863 to crack down on defense contractor fraud against the Union in the Civil War, was amended in 1986 to include a *qui tam* provision and whistleblower protection. The FCA's *qui tam* provision provides that anyone who knows of fraud against the government can sue on the government's behalf and, if successful, share with the government in the recovery. (The percentage of recovery depends upon whether the government decides to prosecute the claim itself.)

The *qui tam* provision has been hugely successful in addressing pharmaceutical company financial fraud against the government. According to the Taxpayers Against Fraud Educational Fund, between 2001 and 2007, Medicare and Medicaid recovered $3.9 billion in 16 actions against the drug industry, with some 180 additional cases yet under seal.

The whistleblower anti-retaliation provision generally requires the plaintiff to show she was engaged in the protected conduct, the employer knew of the disclosures, and the employer discriminated (retaliated) against the employee. The rules vary slightly depending upon the applicable federal circuit.[63] Relief may include reinstatement, twice the amount of back pay owed plus interest, and compensation for any other damages incurred, including litigation costs and attorney fees. However, disclosures about non-compliance with government regulations may not be sufficient to qualify under the FCA's whistleblower provision.

In March 2008, the D.C. Circuit Court of Appeals rejected an FCA whistleblower action by an employee who alleged her employer, the Red Cross, was mishandling blood supplies and that she was discharged for investigating and reporting the mishandling to her supervisors.[64] The district court dismissed the allegation because the blood mishandling was not an attempt to conceal, avoid, or decrease an obligation to provide money or property to the government. The court concluded that an employee's investigation of non-compliance with federal or state regulation is not enough to support a whistleblower claim under the FCA.

**iv. State Statutory Whistleblower Protection Provisions & Common Law or Judicially-Created Remedies**

Eighteen states have enacted legislation protecting employees who blow the whistle on public health and safety hazards. Judicial interpretation of these laws varies considerably even where statutory language is similar. Apart from express whistleblower laws, 44 states and the District of Columbia recognize a judicially-created exception to the generally applicable employment-at-will doctrine. That doctrine holds that, absent a contract to contrary, an employee may be fired at any time without cause. Courts have found exceptions to the doctrine for certain disclosures that protect the public good.

One of the stronger state whistleblower provisions is the New Jersey Conscientious Employee Protection Act ("CEPA"), which protects an employee against retaliation for engaging

in activity prescribed by the statute.[65] This law brought mixed results for Dr. Juan Walterspiel, a U.S. based Pfizer scientist, who blew the whistle on the New Jersey drug giant Pfizer's botched 1996 experiment on Nigerian children.[66]

In March 1996, a severe epidemic of meningococcal meningitis broke out in Nigeria. Pfizer saw a "humanitarian" opportunity to test its experimental broad-spectrum antibiotic Trovan and was encouraged to do so by the Nigerian government (although Nigerian doctors claim the trial was not approved by the hospital ethics committee). The FDA fast-tracked export authorization for Trovan the same day as Pfizer made its request.

Dr. Walterspiel raised concerns to Pfizer before and after the study. He believed the study design was "improper and unsafe." He specifically stated that oral delivery of Trovan was not appropriate for dangerously sick, impoverished children. Some of these children were in critical condition and malnourished – challenging their bodies' ability to absorb the drug when orally administered. Eleven children in the trial died.

Over 30 Nigerian families sued Pfizer in a class action alleging violations of the Nuremberg Code. Their complaint alleged that Pfizer forced sick children into the study and failed to inform them of the experimental nature of the drug or the availability of an alternative treatment. Pfizer admitted that no informed consent forms were signed. Contrary to Pfizer's claim, none of the trial participant parents indicated they gave the "verbal consent." Some of these families did not know they were part of a clinical trial. The FDA did not object to the lack of signed consent forms or the questionable ethics committee approval.

Pfizer's short-term study found that oral Trovan worked as well as an injection form comparator. Although no longer-term studies had been conducted, the FDA approved Trovan for 14 adult indications, until reports of liver damage led the FDA to pull the drug from the market in 1999.

The *Washington Post* published an investigative series on this botched study that helped bring this international dirty secret to light.[67] Then, the late Representatives Tom Lantos (D-CA) and Henry Hyde (R-IL) successfully sponsored a patient-protection amendment to the Export Administration Act, making it more challenging for companies to export experimental medicine for international medical uses.

Dr. Walterspiel settled his CEPA claim out of court. He did not gain reinstatement at Pfizer and was largely blacklisted in the industry for having blown the whistle on the unethical Nigerian trial.

**Summary**

Employees' lack of legal protections for whistleblowing breeds a dangerous silence. The piece-meal protections available inadequately safeguard drug safety whistleblowers nor empower potential employees to blow the whistle. These laws need to be strengthened. More importantly, the federal WPA and SOX Acts need to be reformed to assure protection for government and private sector employees who blow the whistle on threats to public health and safety.

*d) GAP Suggested Reform*

GAP proposes legislation that expressly protects against retaliation any private sector employee of a food, drug, or medical device company, contract research organization, or institutional review board, and contractors of FDA and related State and local government agencies. For proposed legislative language, see Appendix 9.

## 2) Injured Patient or Trial Participant Recourse

*a) Unaddressed Gap*

In its recent *Riegel* decision, the U.S. Supreme Court ruled that state court personal injury suits are preempted if FDA approved the faulty medical device. Although turning on the scope of an express statutory preemption clause in the Medical Device Amendments of 1976. *Riegel* foreshadows possible legal barriers for injured clinical trial participants who sue drug manufacturers. If state court tort suits are preempted by virtue of FDA approval, then participants injured in an FDA *authorized* clinical trial may be the next group to be denied a right to sue.

Preemption of law suits by medical device, drug or clinical trial victims is an egregious violation of the already injured; it is also an affront to credible drug trials and the search for the truth. The key legal device – court-supervised discovery – available to ferret out internal corporate documents revealing whether a company submitted misleading or incomplete data to the FDA will be lost if these suits are preempted.[68]

The rationale for preemption – that the FDA can be relied upon to safeguard the public interest – is belied by the Agency's gross under-funding and resource challenges, and daily revelations of its politically motivated decisions, cozy relationships with industry, and conflicts of interest. It is tragic sophistry for judges to deny injured patients their day in court based on FDA approval.

*b) Caught in the Gap: Research Participants and Patients at Risk*

Granting manufacturers of medical devices and drugs and clinical trial operators, immunity from suit based upon FDA approval undermines the tort system's mission of deterring "unreasonably dangerous actions or omissions", and it pours salt on the wounds of injured patients by denying them judicial redress.[69] The same is true for immunizing industry actors who stand to profit from harm caused in clinical trials. While trial participants may knowingly and voluntarily undertake risks, these risks must be clearly and fully disclosed, and be proportionate to the potential benefit gained. Whether the conduct of a trial satisfies these tests is a question of fact, which is for a court of law to decide.

*c) Legal Gaps*

Historically, FDA product approval and state tort liability operated independently to provide consumers with complementary measures of consumer protection.[70] In her *Riegel* dissent, Justice Ginsberg observed that courts have overwhelmingly held that FDA approval of a new drug application does not preempt state personal injury suits. Indeed, for decades, consumers have brought state tort claims against drug companies over FDA approved drugs.[71] Congress allowed these actions to be brought.[72] If it wanted to preclude such suits, Congress could have enacted legislation clearly expressing its intention to do so.[73] As Justice Ginsburg noted, it is "difficult to believe that Congress would, without comment, remove all means of judicial recourse" for consumers injured by an FDA approved product.[74]

Unlike the medical device statute adjudicated in *Riegel*, the drug statute at issue in *Wyeth* contains no explicit preemption language. However, pro-industry advocates claim that when the FDA approves a drug, the preemption doctrine implicitly bars an injured consumer from claiming the product was inadequately labeled. This misses the fundamentally differing purposes served by the regulatory and civil justice systems. The FDA approval process is intended to make a science-based, policy determination whether the risks of a product outweigh the benefits to Americans as a whole. The availability of a state tort claim ensures that the affected individuals are not sacrificed in the pursuit of the greater good. It also serves as a backstop when a resource strapped and conflict-ridden FDA is too compromised to perform its mission.

There is no basis to deny access to the courts to clinical trial victims. In pre-approval trials, these drugs are yet to receive the imprimatur of the FDA. In ordering post-marketing trials, the FDA is acknowledging that the safety and efficacy of these products is uncertain.

Representatives Henry Waxman (D-CA) and Frank Pallone (D-NJ), along with 62 bi-partisan sponsors, introduced H.R. 6381, The Medical Device Safety Act of 2008.[75] This bill would effectively undo *Riegel* and amend the Federal Food, Drug, and Cosmetic Act ("FDCA") to clearly state that the FDCA would have "no effect on liability under state law – Nothing in this section shall be construed to modify or otherwise affect any action for damages or the liability of any person under the law of any State."[76] This bill makes good sense: Even apart from the unreliability of the FDA as a champion of patient safety, in the age of limited government, the private civil justice system plays a critical role in ensuring that justice is in fact done.

*d) GAP Suggested Reform*

The Supreme Court in *Wyeth* was right to reject preemption in drug cases. Contrary to *Riegel*, companies must be held accountable for the damage their products cause, even if approved by the FDA. A balance must be struck between approving drugs for public use yet allowing recovery for individual damages.

If the *Wyeth* Court had preempted suits in drug cases based on FDA approval, the decision would have been an open invitation to industry to direct even more resources toward dominating the decision-making process at the FDA, at which it has already demonstrated extraordinary effectiveness. Congress must ensure this does not happen. To do otherwise is to give industry a pass to further whittle away patient's rights, including protections for clinical trial participants.

**3) All Humans Subjects Protected**

*a) Unaddressed Gap*

The federal government only regulates clinical trial research that is under HHS or FDA oversight.[77] Several pre-Phase I, Phase IV, and investigator-initiated trials do not fall under the control of either agency.[78] State, local, or institutional research or health laws may provide some trial participant safeguards, but none of these laws or policies effectively protects all human subjects in all research in this country.

If research is eventually submitted as part of a drug application to the FDA, it must comply with federal human subject regulations.[79] But, clinical trials are increasingly conducted abroad, "where oversight is slim and patients plentiful."[80] And, drug companies get the results they want: One review found that 99 percent of controlled trials published in China gave the investigative drug the green light.[81] This challenges credulity. The number of foreign clinical investigators seeking FDA approvals increased 16-fold during the 1990s. San Petersburg (Florida) Times reporter Kris Hundley found that in the past three years, FDA had inspected only eight out of thousands of clinical trial sites in India. Hundley writes: "In the burgeoning clinical trial business, says Amar Jesani, a doctor and medical ethicist in Mumbai, every layer of oversight is compromised by cash, and independent monitoring is nonexistent. He has resigned from supposedly independent ethics committees that rubber-stamp drug companies' proposals and overrule any objections. Said Jesani: 'We're sitting on a time bomb that may explode at any time.'"[82]

Unlike trials in U.S. studies, the FDA does not require animal testing prior to conducting human experiments abroad. The IRB requirement is also waived. Until recently, foreign studies need only have followed the World Medical Association's Declaration of Helsinki, which the *Trovan* case (*see* A.1.c. State Statutory Whistleblower Protection Provisions & Common Law or Judicially-Created Remedies) illustrates is less than an ineffective safeguard. But the FDA recently dropped even the requirement that foreign trials comply with the Helsinki guidelines.[83] Not surprisingly, an HHS report

concluded that "FDA cannot assure the same level of human subject protections in foreign trials as domestic ones."

*b) Caught in the Gap: Research Subjects at Risk*

Each year an estimated 40 percent of research studies, including pre-Phase I, Phase IV, and investigator-initiated trials, conducted in the U.S. are not regulated by the federal government.[84] Over five million Americans participate in these unregulated studies.[85] This gap in federal oversight raises significant public safety issues.[86] Institutions are left with the burden of deciding whether or not to oversee unregulated research, and how extensively, if they decide to oversee this type of research.

*c) Legal Gaps*

Despite enacting the National Animal Welfare Act, which regulates all research conducted on animals, Congress has not yet enacted comparable legislation to protect all human subjects.[87]

*d) GAP Suggested Reform*

GAP supports the National Bioethics Advisory Commission recommendation for a national system of oversight.[88] We also agree with experts and advocates who have lobbied persistently for the passage of a National Human Subjects Protection Act to provide regulatory protection to all research subjects.[89] We suggest that Congress enact legislation to cover all human subject research; alternatively, we encourage states to follow Maryland's lead and enact laws that apply to all human research.[90]

A critical tool that will assist in monitoring all human subject research or at least provide some transparency to current work – regulated or not – being conducted on humans is a more effective clinical trials registry. The current registration system lacks accountability and quality assurance. For example, the exact number of clinical trials currently being conducted worldwide cannot be quantified precisely. (For resources in researching clinical trials, see "Suggested Resources for Researching Clinical Trials, *infra*.) Further, under the current system, a drug company could potentially conduct an unregistered trial and may never report the trial if the results were unsatisfactory. This ability to only register or publish positive results in duplicative, wasteful research, and exposes research participants to dangers that could easily have been avoided with greater transparency.

One suggested solution is to establish a comprehensive registry.[91] Each clinical trial initiated would be required to register and thereby even if study findings were not published, the trial itself would be made public.[92] The registry should describe the main features of the study, such as outcome variables and study duration. Theoretically, this global registry would enable physicians, scientists, and consumers to review both the unsuccessful and successful trials being conducted worldwide.

The Food and Drug Administration Modernization Act required the NIH to establish a registry of clinical trials.[93] Registration on this site, clinicaltrials.gov, is voluntary unless the trial is a federally or privately funded experimental treatment for "serious or life-threatening diseases and conditions." This site is the largest registry in the world and has facilitated an increase in trial registration; yet, it lacks a critical component – results of the trials.[94]

The World Health Organization ("WHO") in 2004 began to assign all randomized controlled trials approved by the WHO Ethics Review Board an International Standard Randomized Controlled Trial Number ("ISRCTN").[95] Prominent medical organizations support this concept of a public, all-inclusive registry.[96] The International Committee of Medical Journal Editors ("ICMJE") requires all clinical trial, including Phase I, to be registered at their inception in an acceptable registry in order to be published in any of their member journals.[97] ICMJE requires that even minimum data and Phase I (early toxicity)[98] be registered, and the site must be publicly accessible at no charge and be managed by a not-for-profit organization.[99] Results are not required. Some pharmaceutical companies have their own registries that contain only their studies, governed by their own registry guidelines, which *may* post

results. The Pharmaceutical Research and Manufacturers of America ("PhRMA") has its own results database called clinicalstudyresults.org, but this site notoriously draws favorable study results.[100]

The variety of registries forces potential research participants to search multiple web sites. The inconsistency in both the kind and the quality of data reported result in potential participants attempting to compare and contrast inadequate and incomplete trial information. Without a results database, quality and timely meta-analyses are unlikely.[101]

Legislation addressing the registry and results database infrastructure is needed. Public financing and monitoring of registration needs to be considered. Similarly, legislative reform should include the publication of all research protocols prior to the initiation of research and public dissemination of the results of all completed trials. Penalties need to attach for non-compliance. Congressional oversight is needed to ensure the FDA enforces registry and results database regulations, particularly in international contexts. The FDA must also strengthen its regulations regarding international studies and partner with foreign governments to ensure the ethical conduct of clinical trials worldwide.

**4) Contract Research Organizations ("CRO")**

*a) Unaddressed Gap*

Clinical research has spread beyond academic centers. Increasingly, industries outsource clinical components to contract research organizations ("CRO"), commercializing traditionally academic endeavors.

According to federal law, a CRO is "a person [or entity] that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g. design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the FDA."[102] CROs initially emerged as highly specialized entities providing biostatistical advice, clinical research associates which monitored investigational sites for regulatory compliance, or regulatory support.[103] Today, CROs offer a range of services, including: developing products, managing clinical trials, processing samples, preparing the FDA New Drug Application ("NDA") or Abbreviated New Drug Application ("ANDA") and related FDA safety reports, recruiting investigators, selecting investigational sites, assisting with patient recruitment, monitoring safety, auditing sites, managing data, and conducting biostatistical analyses.

By performing specialized tasks, CROs enable pharmaceutical manufacturers to outsource certain functions and expenses.[104] Unlike a drug sponsor, a CRO does not have a direct stake in the outcome of the trial. CROs therefore, like academic research centers, are meant to provide the sponsor, the government, and the public an objective view of the drug.

The relationship between a drug sponsor and a CRO, however, is a study in conflicts. CROs are contractors for the drug sponsors. Since sponsors are the CRO's economic lifeline, CROs try hard to please their clients. A CRO that brings a drug sponsor good news about an investigational drug's safety and efficacy is apt to be more greatly appreciated than the CRO that reports bad news, and more likely to be awarded the next contract. Hence, there is considerable economic pressure on the CRO to positively spin its negative findings, or raise them only tepidly, as we saw in the Ketek debacle. The sponsor, after all, is free to shop for a more pliant CRO.

CROs are also for-profit businesses in their own right, aiming to maximize earnings and minimize costs. This may result in the shoddy selection of investigators, the suppression of data, bias in interpreting data, multiple results reports from a single trial, and ghost-authorship.[105] Ghost-authorship is particularly problematic in the private sector where the non-academic writers do not have the tenure process overseeing the quality of their publication record. It is also common for CROs to be investors in the very drug companies whose products they are subjecting to trials, a flagrant conflict of interest that the FDA has winked at.[106]

*b) Caught in the Gap*

CROs are for-profit businesses that organize physician networks to supply patients for clinical trials. As Dr. Marcia Angell pointed out, "Contract research organizations are only too ready to accede to drug company terms because their only clients are drug companies."[107] Moreover, CROs compete with academic medical centers for drug company contracts. Such competitive pressures from CROs tend to drive down the ethical standards of academic institutions as well.

*c) Legal Gap*

A drug sponsor may transfer by written agreement its responsibilities for the conduct of drug trials to CROs, which are then subject to the same legal responsibility as the sponsor. Whatever the legal requirements, there seems either little will or ability to monitor the conduct of trials. An indicator of the extent of FDA scrutiny is Warning Letters issued for significant regulatory violations that require prompt and adequate corrective actions. (Note that these are merely warnings and do not commit the FDA to take enforcement action.) Between 2002 and 2006, FDA issued a total of 36 Warning Letters to CROs over their practices.[108] To put this in perspective, at this writing, the NIH reports that there are 35,632 trials in progress in the US alone – a little more than one-half of the trials worldwide.[109]

*d) GAP Suggested Reform*

The law should subject CROs to greater transparency in clinical trials. Each trial should be registered and clearly indicate which aspects of the trial were conducted by the sponsor, academic center, or the CRO. The FDA should also increase its use of its enforcement tools to oversee all clinical trials, particularly components conducted by the private sector.[110] The FDA should be given subpoena power, enabling it to unearth undisclosed data, such as the various negative Vioxx studies in Merck's files, and make more visible any suppression or bias that may occur at the CRO stages. Of course, actually doing this will require a new direction among FDA leadership.

Contracts between CROs and a drug sponsor may unduly impose the burden on the CRO for financial losses that result if a product approval is delayed. Such contract provisions are contrary to the public interest and should be illegal.

**5) Institutional [or Independent] Review Boards ("IRB")**

> *"The demand for private IRBs isn't hard to understand. In today's research environment, academic IRBs often are overmatched. They're often slow and inefficient, and they are staffed by volunteers who would usually rather be somewhere else. Nor are academic IRBs free from conflicts of interest. Their members are frequently asked to review studies being conducted by their friends and colleagues. And a recent survey of academic IRB members found that nearly half had served as consultants to the drug industry.*
>
> *"But the private IRBs have a direct financial interest in keeping their drug-company clients happy. If one for-profit IRB rejects a study as unethical, the pharmaceutical company sponsoring the study can simply send it somewhere else. Free-marketeers argue that there's a countervailing pressure that should make drug companies welcome strict policing from the IRBs – the possibility that a strict ethics review on the front end could head off a lawsuit on the back end. But in reality, the incentives don't pan out that way. Lawsuits, while on the rise, are still relatively rare. For the companies bankrolling the clinical trials, litigation is a quite-manageable cost of doing business."*
>
> Carl Elliott and Trudo Lemmens[111]

*a) Unaddressed Gap*

Many issues that plague CROs also trouble the effective and credible operations of IRBs, in particular, conflicts of interest and economic pressures from market competition and drug sponsors. Table 2 highlights a cornucopia of unaddressed gaps in and criticisms of IRBs.[112]

**Table 2: Common Institutional or Independent Review Board ("IRB") Criticisms**

| |
|---|
| Structure:<br>• Lack of arms-length relationship between the IRB and study sponsor or investigator.<br>• Current system promotes IRB shopping: If one IRB disapproves a protocol or proves too diligent in protecting subjects, the sponsor can hire another IRB with more elastic ethics.<br>• No effective means for local IRBs to share their similar concerns regarding the same protocol.<br>• Fails to provide an open environment where investigators, who are continually discovering new methods and issues, can come to discuss issues with IRB and seek counsel on past, present, or future ethical dilemmas.<br>• Responsibility for ethical issues too diffused. At any one institution, they may be handled by human resources, a committee on scientific misconduct, departmental committees, college committees, an IRB, conflicts of interest committees, etc. |
| Funding:<br>• Relies on sponsor funding, giving rise to at least the appearance of possible bias.<br>• Too many IRBs have inadequate financial and personnel resources. |
| Members:<br>• IRB members tend to be more sympathetic to doctors than patients. Peers police their peers. Close collegial ties could make members reluctant to criticize studies of their peers or leading scientists at their institution.<br>• Overworked and under-supported members.<br>• Lack community involvement and accountability.<br>• Inadequate training for IRB members on substantive scientific issues, ethical implications, basic IRB operations, and fundamental constitutional due process rights to ensure fair investigations.<br>• No accountability for any significant harm that does occur.<br>• Lack of effective regulatory reform to collect and evaluate adverse events at the local and multi-site level.<br>• Vague definitions and requirements regarding adverse events.<br>• Many major incidences not properly documented or reported to appropriate stakeholders, and not analyzed to track trends at the local or multi-site level.<br>• Time-consuming and inefficient review process that too often tends to be superficial and inconsistent.<br>• Inadequate continuing review.<br>• Too many IRB meetings are held without a quorum, without a community member, or with members that have significant conflicts.<br>• Principal investigators provide IRBs with insufficient information in IRB application.<br>• Ambiguity regarding what is required of IRBs. |

**Table 2, Continued: Common Institutional or Independent Review Board ("IRB") Criticisms**

| |
|---|
| Review Process and Procedures:<br>• Decisions are not transparent and too often illogical.<br>• Excessive focus on Informed Consent forms while inadequate review of protections, such as risk-to-benefit ratios.<br>• Troubling variation in review and operations. |
| Enforcement:<br>• Lacks necessary investigative capacity and any meaningful enforcement powers. |
| Regulatory and Research:<br>• No validated measures to assess IRB performance.<br>• No systematic analysis of IRB performance.<br>• Few regulations to safeguard human subjects against IRBs that inadequately carry out their duties or are subservient to their institution's possibly conflicted and unethical direction.<br>• Research occurring at institutions that are not reviewed by IRBs. |

*b) Caught in the Gaps: Research Participants and Patients at Risk*

The **Trials Tragedies** section at p. 33 highlights examples where an adequate IRB infrastructure and oversight may have prevented death and preserved an institution's ethical reputation.

*c) Legal Gaps*

**i. IRB Basic Legal Obligations**

The IRB's role today was enshrined in law in 1981, when the Department of Health, Education, and Welfare (now HHS) and the FDA issued parallel legal rulings. The HHS regulations apply to all studies the Department funds. The FDA regulations concern all trials for drugs and medical devices that must undergo FDA approval before entering the stream of commerce. Both HHS's and FDA's regulations require all entities conducting such trials on human subjects to sponsor an IRB (*see* Appendices 6 and 7 for further detail on both Agencies' regulations).[113] The intent of American research law is that IRBs monitor clinical trials, as well as other forms of federally funded research, to ensure the safety of both current research subjects and future patients. An IRB is charged with upholding the scientific integrity of the clinical trials.[114] Moreover, an IRB should ensure that human research studies adhere to the ethical guidelines set forth in the Belmont Report (*see* Appendix 5).[115] Specifically, the purpose of an IRB is to protect the subject by: (1) initially examining the research protocol of all federally funded research involving human subjects; (2) monitoring on a continuing basis all funded research involving human subjects; and (3) reporting any serious noncompliance with either the protocol approved for the research or the applicable law and regulations.

Federal law holds an IRB responsible for performing an initial review of the research protocol to ensure that a study: (1) has scientific worth; (2) adequately balances the risks and benefits; (3) selects subjects on an equal basis; (4) provides subjects with documented informed consent forms and no undesirable incentives; (5) has a plan to monitor incoming subject data when there are safety concerns; (6) protects subjects' confidentiality and privacy; and (7) takes special precautions for subjects particularly vulnerable to exploitation.[116] The Health Insurance Portability and Accountability Act ("HIPAA") or specifically the Privacy Rule supplements IRB policies to further safeguard research participants' confidentiality.

**ii. Required Procedures**

The law also requires the IRB to institute written procedures for its: (1) approvals; (2) determinations of which trials require more frequent review and independent verification; (3) strategies for ensuring investigators promptly report to the IRB any changes in their research protocol; and (4) strategies for ensuring that changes during already approved research cannot be made "except where necessary to eliminate apparent immediate hazards to human subjects." In addition, the law demands that any unanticipated problem, any "instance of serious continuing noncompliance" with the IRB, and "any suspension or termination of IRB approval" are to be reported "promptly to the investigator, appropriate institutional officials, and the department or agency head." The law grants authority to the IRB to stop research that does not meet its requirements or has "been associated with unexpected harm to subjects." If an IRB halts a research study, then the law requires that the IRB provide a statement of reasons for its action. A copy of this statement should be given to the investigator, appropriate institutional officials, and the department or agency head.

**iii. Legally Binding Assurances**

An institution must register with the Office of Human Research Protections ("OHRP") in HHS and then provide OHRP a legally binding Federal-Wide Assurance ("FWA") before embarking on any federally-funded, HHS regulated research on human beings.[117] The grantee institution sets forth in signing an assurance that the institution will comply with federal human subject protection policy. The federal government grants three types of assurances: (1) a multiple project assurance of compliance ("MPA"), pertaining to all research conducted at an institution; (2) a single project assurance ("SPA"), covering only one project; or (3) a cooperative project assurance ("CPA"), documenting the commitment of an institution that has an MPA or CPA to human research protection.[118] OHRP can audit any grantee institution that signs an assurance and accepts federal research money. If a grantee institution is found non-compliant, OHRP can and has shut down the institution's research operations.

Aside from audits, the OHRP in HHS has created a self-assessment tool for institutions to evaluate their human subject protection programs. The tool evaluates an IRB's workload, infrastructure, and resources, along with the expertise and educational training of an institution's researchers and IRB members. In addition, OHRP offers site visits to provide specific advice for the institution on how to both improve its protection program and create a continuous quality improvement program. The FDA, however, did not adopt the assurance requirement, reasoning that where IRBs are subject to HHS jurisdiction, adding an FDA assurance requirement would not be justified by the additional administrative burden.[119]

As with CROs, federal monitoring of IRBs is at best spotty. From 2002 through 2006, FDA issued only 30 Warning Letters to IRBs for significant regulatory violations that require prompt and adequate corrective actions.[120]

**iv. Community Component**

The law requires that an IRB have at least five members. These five members should have varying expertise, attitudes, backgrounds, competencies in research regulations, and institutional commitments. Only one of these members, however, must be independent of institutional affiliation. IRBs do not have to operate on consensus; therefore, a dissenting voice on an ethical issue can be easily outvoted by the majority of institutionally affiliated members. The larger the IRB the further diluted the voice is of the one non-institutional member. Since the IRB is self-selecting, an institution can pick a non-institutional member for the IRB that has a strong pro-institutional bias. The selection process is imbalanced and needs to be revisited.

### v. Quasi-Judicial Authority

The IRB's role is quasi-judicial with rule-making and adjudication authority.[121] American universities are largely self-regulating and develop their own "campus common law." For example, an IRB must make factual determinations about the nature of the proposed research, determine what rules and laws are applicable, and then decide whether the proposed research complies with the applicable rules. The IRB may require certain steps to be taken to protect human subjects from harm or violation of their rights.

Nonetheless, the IRB's limited authority and resources constrain its ability to effectively enforce federal regulations and human subject protections. At the same time, the limited oversight of IRBs permits a large degree of discretion and institutional biases to permeate the approval, modification, and rejection of research protocols.

Even more problematic is that there is little done on the record. Sparse documentation is produced regarding rationales for protocol approvals, modifications, or rejections. The FDA does not require public or sponsor access to IRB records; state, local, or institutional policy *may* allow access, as *may* sponsor contractual obligations. IRB related documents are predominantly not subject to the Freedom of Information Act.[122] The meetings often tend to be closed or inadequately advertised so they do not generate consistent and meaningful public attendance.[123] It typically takes a tragedy or complaint to trigger federal government IRB audit, which may result in public access to the IRB documents.[124]

### vi. Conflict of Interest Policy

- **Federal:** Federal conflict of interest regulations apply to federally-funded research or entities that will later seek FDA approval.[125] According to federal regulations, investigators applying for Public Health Service funds must disclose "significant financial interests in companies that might reasonably appear to be affected by the research."[126] Examples include stock and stock options totaling more than $10,000, salary and consultation fees exceeding $10,000 a year, and greater than a five percent ownership in any relevant company of other business entity. Investigators must also disclose the current financial interests of spouses and dependent children."[127]

  The NIH defines "substantial financial interests" as income or equity greater than $10,000 or more than 5 percent ownership of a company. But the existence of a "substantial financial interest" does not necessarily mean, to NIH, that there is a conflict of interest. The Government Accountability Office concluded that NIH has failed to articulate when financial interests should be treated as a potential conflict. Grantee institutions are left with the discretion to determine when such interests "could directly and significantly affect the design, conduct, or reporting of the research."

  The NIH has also not specified how to handle situations in which a university holds an ownership interest in a sponsoring company or collects substantial royalty payments by licensing university-owned patents. Moreover, leaving the sponsor free to shop in the free market for an IRB imposes potentially irresistible competitive economic pressures on institutions to relax their standards to attract clientele. For-profit IRBs have a similar conflict: Impeding a protocol's approval or continuation is not a means of currying the favor of study sponsors. These IRBs depend upon the good will of sponsors and their repeat business. These sorts of economic conflicts compromise the decision-making process and erode public confidence in an IRB's ability to protect human subjects.

  Not surprisingly, enforcement of these vague policies is not occurring.[128] Indeed, the NIH neither maintains reliable statistics on the number of conflicts reported by

grantee institutions nor records of how institutions resolve their reported financial conflicts. The NIH has largely limited its examination to reviewing the conflict of interest policies of grantee institutions; the NIH lacks the staffing to effectively monitor an estimated 3,000 grantee institutions. The NIH only collects "some summary data" from its 27 institutes and centers.[129] Each institute and center issuing an NIH grant must collect conflict reports directly from the grantee institution. Then, each of the 27 institutes and centers has the responsibility and the discretionary power to decide whether or not to inquire further into the reported conflicts.

Enforcement of conflicts rules is no better regarding individuals than it is for institutions. The inspector general for the Department of Health and Human Services found that neither the FDA nor the National Institutes of Health polices financial conflicts of interests involving doctors conducting clinical trials and university professors receiving federal money.[130]

Federal research conflicts rules are relatively lax. Other fields have much stricter policies. For example, a Federal judge is required to recuse herself if "the judge's impartiality might reasonably be questioned" or "if the judge or a family member has an economic interest in the subject matter of the controversy or has any other more than de minimus interest that could be substantially affected by the proceedings.[131] The courts have held that these rules are applicable to quasi-judicial decision makers, such as doctors serving on a medical malpractice review panel.[132] Notwithstanding, scientists are encouraged by law and policy to partner with industry, making conflicts more likely. Although a conflicted scientist may have a critical perspective to contribute, and her views should be solicited, a conflicted scientist should never have voting power.

- **Institutional:** The federal government puts the burden on institutions to "manage, reduce, or eliminate" conflicts and permits considerable institutional discretion.[133] Alternatively, in the absence of policy or in the face of ambiguous policy, grantee institutions are left to police themselves. Oversight of conflicts is generally the responsibility of the grantee institution's IRB.[134] Oversight officials at grantee institutions are charged with managing conflicts appropriately, effectively, and efficiently.[135]

  Several associations of grantee institutions and the institutions themselves have developed conflicts policies that go beyond federal regulations.[136] These include the World Medical Association, the American Medical Association, the Association of American Medical Colleges, the Association of American Universities, and the American Association of University Professors.[137] They adopted their policies in the wake of highly visible, university-based tragedies, and to limit prospective legal liability and financial exposure for harm to research subjects. Although policy differences exist among these organizations, most concur that conflicts should be disclosed to the institution, the sponsors, and the journal editors. Many of these organizations also agree that researchers with significant conflicts should not be engaged in related research at all.[138] In any case, these guidelines lack the force of law or enforceability.

  At the institutional level, substantial variation exists regarding conflicts policies and in conflicts management approaches.[139] Ambiguity as to the kinds of permitted or prohibited relationships is common. The disparate institutional policies may engender competition among academic centers for industry sponsorship that could erode ethical standards.

- **Educational & Training Requirements:** Federal policy requires all federally funded grantee institutions to provide ethical training.[140] The government does not prescribe content or approach, but encourages instruction regarding responsible authorship and

scientific misconduct. Nearly all medical, public health, and nursing schools teach ethics in some format. Several universities incorporate ethics training throughout their curriculum rather than simply offering a single course called "Ethics." Substantial variety in ethical training exists, including: required courses, seminars, ethics grand rounds, elective courses, brown bag lunches, journal clubs, debates, and case studies. Variety also exists in who is teaching ethics. The range includes physicians, medical ethicists, and health care professionals.

*d) GAP Suggested Reform*

The IRB regulations embody key features of an ethical research framework—laws, authority, monitoring, training, discussion, substantive expertise, local involvement, and enforcement. IRBs are required to consider federal, state, and local laws, and institutional rules, and also evaluate the scientific merit and community sensitivity of a project. On paper, this is all good. But as we've seen, reform is needed that maximizes IRBs' strengths and minimize their weaknesses, whether they are local, regional or centralized.[141]

Regardless of what oversight structure emerges in the years to come, the people who make up the system – as subjects and as employees – need to be empowered to enable the system to function best.[142] The IRB needs to be accountable to the federal government, but more importantly, to the public it is charged with protecting. Reforms must aim to remove investigator conflicts of interest, design flaws, fraudulent recruitment, and profit-driven treatment of the subject population as expendable guinea pigs. Tracking adverse events must be a combination of private and public sector oversight. Too much ambiguity exists in who should be receiving adverse event reports, and how these events should be responded to and recorded. Finally, sponsoring universities need to commit adequate resources to their IRBs.

**i. Conflicts of Interest**

Further federal guidance is needed to minimize conflicts of interest.[143] A board established to protect human research subjects should be conflict free and not in the pay of the drug sponsor. No member of a board should profit from a study under review or have any incentive to approve a study protocol.[144] No member should be impeded from halting a non-compliant study out of concern that it would drive away future protocol review business.

Preferably, no member of an IRB should have a financial or employment relationship with the research institution. At a minimum, the conflicts rules that apply to principal investigators should apply to IRB members. Another option is that non-conflicted federal appointees should review research protocols.[145]

Conflicts waivers should only be entertained in the extraordinary circumstance in which it is demonstrable that no non-conflicted experts are available. Such a waiver should be subject to complete and public disclosure.

**ii. Public Access**

Public access to information about human subject experimentation is necessary to bring transparency and accountability to the process. IRBs and IRB members are not surprisingly reticent to open up their processes to scrutiny and possible liability. To overcome this, institutions should indemnify and insure IRB members against good faith errors. At the same time, the federal government should provide safeguards against retaliation to IRB members, staff, and research subjects who blow the whistle on protocol and informed consent violations, and drug safety dangers.

### iii. Education & Training

Too often federal regulation leaves ethical training and accountability to the institution, which then delegates the responsibility to the investigator. Ethics should be a system-wide responsibility with an integrated approach to discussion, accountability, and reform. All members of the research process – government regulators, institutional administrators, IRB members, investigators, student researchers, participants, and the public – should be exposed to the ethical standards for the conduct of research. Education should be a tool to empower all members to be significant contributors to the research process.[146]

**Summary**

IRBs must be fair, impartial, and not financially compromised by the drug sponsor; their members must also be free of conflicts.[147] Reforms need to ensure the oversight role integrates throughout the study protocol and is not just the initial hurdle into unmonitored study. Silence on ethical dilemmas is unacceptable.

## 5) Informed Consent

*a) Unaddressed Gap*

The current IRB system focuses almost exclusively on the review of consent forms.[148] Yet, the forms do not always adequately ensure the function – informed consent. Research suggests that they have become too long, too technical, too formal, and too similar to a boilerplate contract to facilitate meaningful informed consent.[149]

There are other impediments to truly informed consent. Clinical trials tend to be long and easily confused with ordinary treatment.[150] Many participants expressed uncertainty whether or not they were participating in a study.[151] This confusion is heightened when a participant is recruited to a study by her own physician. These participants may be exposed to "unrealistic expectations" regarding the study protocol and access to new treatment thereafter.[152] Patients generally trust their physicians, their hospitals, and the research process[153] and assume that if their doctor recommends participation or even just presents the study as an option, then participation must be in their best interest.

Payment of participants also complicates the informed consent process. Money can cloud participants' ability to make an informed decision on the study's risks and benefits.[154] Yet it would be unrealistic to insist that non-therapeutic subjects participate without compensation. Better guidance and safeguards are needed here.

*b) Caught in the Gaps: Research Subjects at Risk*

Inadequate consent processes hinder a participant's right to autonomy and make a mockery of an informed decision to participate in a clinical trial. The poor, immigrants, and those without health care have been particularly exploited by gaps in the informed consent processes.[155] So too have other vulnerable populations, including: children[156], second-hand subjects (e.g. individuals affected by the research who are not directly participants themselves), HIV-positive people in Africa[157], individuals subjected to emergency research or disaster response research[158], individuals with limited mental capacity[159], international subjects[160], patients/participants in practice-based private physician offices or public clinics[161], and prisoner research[162].

*c) Legal Gaps*

The informed consent process is one of the most regulated as well as most criticized IRB features.[163] 46 C.F.R. § 46.116 specifies the general requirements for informed consent (*See* Appendix 10). Although the law as written contains many of the elements required for effective informed consent, its application allows for troubling gaps in human research protections.

The law does not require IRBs to regularly observe consent interviews or the conduct of the study protocol[164]; this function may be delegated to a third party. In practice, this critical process is left to self-regulation by the investigators themselves, who have an inherent bias to recruit and retain subjects. In effect, few IRBs truly examine the informed consent *process*; they only review the consent forms. This is problematic because most participants decide to participate before even receiving the informed consent form.[165] Their signature is more of an afterthought in the consent process. A legally sufficient form should not overshadow an unethical consent process. More attention must be afforded the role of oral communications leading up to the signing of the informed consent form.

Compensation for research participation is an institutional decision, not an FDA directive. An institution also generally determines if and when a research participant is eligible for medical treatment(s) for conditions being studied.[166]

*d) GAP Suggested Reform*

The informed consent process is grounded in the principle of participant autonomy and the right to know. Too often it is reduced to a liability shield to protect investigators and institutions rather than a tool to protect participants in the research process. Truly informed consent means that the subject is fully aware of the distinction between research and treatment. Participation should include the right to meaningfully decline to engage in risks that do not outweigh the benefits. The only material endpoint must be full confidence that the patient's consent is truly informed and voluntary.

GAP proposes that pilot projects be funded to elicit processes by which truly informed consent can be obtained. Special attention should be given to sample diverse populations, particularly ensuring adequate representation from ethnic minority backgrounds and lower socio-economic populations. Likewise, studies should over-sample vulnerable populations, such as the mentally ill, children, and those with limited access to health care.

Further research is also needed to effectively screen subjects who participate in more than one trial, which results in combining multiple drug interactions and that may confound study results. Participants in multiple studies – concurrently or sequentially – may be concealing side effects out of fear they might be dropped from the study or barred from enrolling in others. Even participants in only one study may be self-prescribing reductions or increases in drug dosages.[167]

While a study participant's time and risk deserve compensation, money should not create an undue inducement.[168] The amount of payment should be reasonable and needs to account for the circumstances of the predominant subject population. Compensation should be fair but not an inducement. Payment systems also need to ensure that participants do not hide side effects in order to receive full reimbursement. The right to withdraw without penalty needs to be examined.

**6) Comparative and Non-Inferiority Trials**

*a) Unaddressed Gap*

The standard means of testing the efficacy of a new, investigational drug is to compare it to a placebo. But proof that a new drug is more effective than a sugar pill fails to answer the question whether it is an improvement over other drugs that treat the same indication. If other, already available drugs are more effective and have a comparable or better safety profile, why should the investigational

drug be approved? Or, if it is approved, why doesn't the FDA provide practitioners and the public comparative effectiveness and safety data?

Comparative trials are the only ethical option in testing for serious and life-threatening conditions where it would be unconscionable to give a trial subject a placebo. But in trials for relatively minor or self-resolving conditions, comparative testing in the form of so-called "non-inferiority trials" has been abused by industry and the FDA has largely turned a blind eye.

In a "non-inferiority trial", a drug may be approved even if it is demonstrably less effective than the comparator drug. Indeed, the new drug might even be less effective than a placebo yet may be approved by the FDA as within an acceptable margin of inferiority.

*b) Caught in the Gaps: Patients at Risk*

Because all drugs run some safety risks, approving a drug whose actual efficacy is in doubt is itself unconscionable. As former FDA antimicrobial specialist Dr. John Powers testified before Congress in 2007:

> "Over the last twenty five years, FDA approved approximately 68 new drugs applications for ear, sinus, and bronchial infections. All of these drugs were approved based on so-called 'non-inferiority' trials. While the word 'non-inferior' means 'not worse', the purpose of these trials is to rule out an amount by which the new drug's effectiveness may be *worse* compared to an old drug. Showing a new drug is potentially worse than an old drug whose effectiveness itself is unclear is like the Billy Preston song, 'nothing from nothing leaves nothing'. Previous placebo controlled trials show twelve of seventeen studies in sinusitis and nine of fourteen studies in bronchial infections lack evidence of a benefit for antibiotics and the situation is similar for ear infections. Therefore, showing that Ketek may be less effective than older drugs is not evidence that Ketek is effective at all in sinus and bronchial infections, and this was clear at the time the drug was approved in 2004."[169]

*c) Legal Gaps*

Non-inferiority trials comparing a new drug to a comparator are currently permitted to study even drugs for less serious and self-resolving conditions, including ear infections. The FDA has been reluctant to jettison inappropriate non-inferiority trials, with their low bar to approval, even though they are typically for "me-too" drugs to treat a common ailment. Industry threatens that it will not invest in developing less profitable drugs unless these more lucrative "me-too" drugs are approved. The record demonstrates, however, that the approval of dozens of profitable drugs via non-inferiority trials has not produced the promised pipeline of needed but less remunerative drugs.

*d) GAP Suggested Reform*

Trials comparing an investigational drug to both a placebo and an existing drug of known effectiveness are the preferred methodology for conducting drug trials (except for life-threatening ailments). The FDA should revisit its permissive approach allowing drug-makers to use non-inferiority trials to test drugs for less serious ailments. At a minimum, non-inferiority trials should be limited to testing subpopulations that do not respond, or experience adverse reactions, to existing drugs.

**7) Federal Funding & Resulting Conflicts of Interest Issues**

*a) Unaddressed Gap*

Despite the American leadership in publicly funding clinical research, NIH clinical research budgets since 2003 have stagnated and not kept pace with inflation, or have even slightly decreased.[170]

*b) Caught in the Gaps: The "Lost Generation of Scientists"*

Reduced federal funds means clinical trials are eliminated, terminated, limited, or delayed. The climate of funding uncertainty has forced researchers to do more with less, or more with industry support or do nothing at all. This environment undermines the capacity of clinical centers to make discoveries of new treatments and drugs. Patients simply do not receive access to clinical trials and the potential treatments these cancelled trials may have generated. Tight financial times also foster factors that may increase the likelihood of unsafe and unethical trials:

- Overworked investigators may overlook important risks emerging in a trial;
- Research staff are less likely to blow the whistle on an unethical trial for fear that they will risk future lab funding and their livelihood;
- Fewer personnel review the ethics of trials; and
- Fewer clinical researchers replicate basic and applied components of ongoing clinical trial work.

Tragically, the funding horizon has pushed young investigators to leave the field and discouraged students from even entering the field, creating a "lost generation of scientists" at a time when the population is aging and the burden of chronic diseases intensifies.[171]

*c) Legal Gaps*

**Conflicted Connections among Industry, the Academy, and the Government**

The instability of federal clinical research funding policies and appropriations has made industry support indispensable to university research.[172] This reliance on nongovernmental funding sources is in stark contrast to what had been a tradition of limited academic-industry partnerships. Inadequate federal funding is not the only reason for this change. Rather, a key catalyst to industry-academic interactions was the government's enactment of the laws listed in Table 3.

**Table 3: Laws that Encourage Academic-Industry-Government Partnerships**

| |
|---|
| ***Bayh-Dole Patent and Trademark Laws Amendment Act of 1980*** *(P.L. 96-517)*<br>Assigned intellectual property rights to the institutions carrying out the government-funded research. Grantee institutions could thereby patent and license their developments as well as collect and retain royalties. |
| ***Steveson-Wydler Act of 1980*** *(P.L. 96-480)*<br>Enabled technology transfer within the federal government by requiring that federal agencies allocate 0.5 percent of its research and development budgets for technology transfer activities, thereby facilitating the flow of information from the federal government to industry. Federal government laboratories were also required to take more proactive efforts to cooperate with potential users of federally-developed technology. |
| ***Small Business Patent Procedures Act of 1980*** *(P.L 96-517)*<br>Reversed the Federal policy of nonexclusive licensing by assigning patent rights to small businesses, universities, and some nonprofit organizations that were involved with government contracts. |
| ***National Cooperative Research Act of 1984*** *(P.L. 98-462)*<br>Enabled joint research ventures to avoid the risk of antitrust litigation. |
| ***Federal Technology Transfer Act of 1986*** *(P.L. 99-502)*<br>Authorized government operated laboratories to establish Cooperative Research Development Agreements (CRADAs) with other federal agencies, state, or local governments, and industrial and non-for-profit organizations for the licensing of government-owned inventions. Inventors and their laboratories kept part of the royalties received from these licenses. |

The rationale for encouraging industry-academic-government connections was to benefit society by facilitating the more effective development of new medical treatments, diagnostic tools, and other practical ramifications of the research.[173] The ability to transfer knowledge and materials among academia, government, and industry was thought to increase productivity. Evidence suggests that post-Bayh-Dole collaborations have resulted in more products in development, more products on the market, and more employees.[174]

Another factor in increasing industry support of clinical research is its complexity and cost.[175] Government, through the NIH, and universities conduct the majority of the basic research needed to understand and manufacture a drug. Industry has increasingly done less and less of basic research. Yet the current multifaceted dimensions of clinical investigations exceed the financial means of academic and medical not-for-profit organizations.[176] Trials demand time, money, resources, infrastructure, and expertise at the scientific, logistical, bureaucratic, regulatory, and legal levels. Government funding has not adjusted to meet the financial realities of today's trials. As a result, pharmaceutical companies have jumped into the void. In exchange, academic centers offer medical and scientific expertise, along with access to patients.

Despite the benefits of industry-academic endeavors, the relationship is often referred to as an "uneasy alliance."[177] The licensing agreements enabled by Bayh-Dole facilitated the commercialization of university research, which led to tremendous growth in biotechnology and pharmaceutical companies[178] and a dramatic increase in university patenting.[179] While patents generate much needed revenue for universities, the assertion of intellectual property rights often disserves science and transparency.

Academic research was historically viewed as common property that was openly shared among competing scientists.[180] The race to the patent office has created a more secretive culture in university labs and subverted the discovery focus of academic centers to economic endpoints. The income universities generate from royalties and fees has surpassed $350 million.[181] Not surprisingly, a drastic rise in intellectual property disputes has erupted since the passage of Bayh-Dole among industry, scientists, and institutions.[182]

Federal regulations have helped re-open science by requiring data sharing.[183] A need, however, remains for NIH and the scientific community to have easier access to products developed with federal funds.

Competitive grants offered by industry to academia may unduly direct investigators towards more industry-patentable and profitable drugs rather than the less traveled disease pathways that merit research but lack blockbuster potential.[184] Research indicates that faculty members who have relationships with industries are more likely to consciously direct their efforts in a commercial direction.[185] Corporate sponsorship of laboratories also increasingly blurs the lines between business research and academic research. Academic centers historically served as venues that generated research that benefited the public, not satellite operations of for-profit pharmaceutical manufacturers.[186]

Likewise, industry influence on university scientists compromises the credibility of their expert opinion offered to the public. Tenured-faculty, historically, have been valued as free and independent scholars. Who can the public rely on for an expert, unbiased opinion if the views of tenured-faculty are clouded by their source of financial support?

Equally troubling, industry has used its relationship with academic centers to hinder the dissemination of unfavorable results.[187] This comes overtly in formal corporate contractual constraints as evidenced by the recent revelation of possible censorship underlying the sponsorship deal between Phillip Morris USA, a tobacco company, and the Virginia Commonwealth University.[188] This is no small matter – approximately one-quarter of faculty members receive industry sponsorship.[189] An estimated 50 percent have served as consultants to industry.[190] But the pressures to conceal are sometimes more subtle than a restrictive contract – investigators are often reluctant to publish news that the industry may not like.

Not only are the study results from self-serving industry sponsored research suspect, serious ethical and safety repercussions emerge for study participants, scientists, and science. Can the managers of a study that is executed to favor the drug sponsor be relied upon to inform study participants of potential dangers or accurately monitor actual adverse events? Should not industry sponsorship of clinical research be disclosed to a research participant?

Ultimately, an agreement to conceal results, whether overt or subtle, is antithetical to science. Scientific advancement is built upon the exchange of accurate and complete data, and analysis from one scientist to another and to the public.[191] Restricting open communication and the replicative process are anathema to the very essence of the scientific methods.[192]

*d) GAP Suggested Reform*

**i. Federal Funding & Policies**

Providing academic centers more federal funding to conduct clinical research may help reform the clinical trial system, but money alone will likely not improve the conduct of clinical trials. Further research should examine the impact that intensified funding competition, increased research costs, and the realignment of federal funding priorities has had on the recruitment and retention of clinical researchers. This work should also consider the impact the increased commercialization of public health research has on the public health.

The industry-academy-government interactions are essential and can be beneficial. The reliance on for-profit entities or non-governmental support, nonetheless, raises vital concerns regarding the reliability of the process, as well as academic integrity and the autonomy of science.[193] Preserving the integrity of clinical research and protecting research participants and patients at academic centers, hospitals, and clinics are paramount.

**ii. Conflict of Interest Disclosures**

***Investigator Reform***

As with federal conflicts of interest policies, institutional conflicts policies are vague, weakly enforced, and address predominantly investigator conflicts, not institutional or CRO conflicts. It is not at all clear whether conflicts disclosures influence the choices of potential research participants.[194] Absent proof that they do, institutions should cease operating under the assumption that the disclosures of conflicts alone discharges their duty to protect research participants. The only consistent consensus on conflicts is that there is a lack of clarity regarding the goals of disclosure at the federal and institutional level.[195]

Attention should be given to whether or to what extent federal guidelines should allow for continued variation among local grantee institutions. While “one size fits all” may not apply, certain standards seem uniformly applicable.[196] Why, for example, should there be any variation in determining whether an English-language disclosure at an eighth-grade reading level is adequate to protect at-risk populations and immigrants who are increasingly the subjects of clinical trials? [197]

There should also be uniformity as to what must be disclosed. A reasonable requirement could include: information about the nature of the financial relationship; the oversight systems in place to keep conflicts in check; and information sources for potential participants to learn about conflicts of interest and how they may affect their participation in a clinical trial. It also makes sense to require disclosure of how funds are allocated. Further research should examine which forms of disclosure work best to ensure an informed and empowered decision making process.

Well-defined and meaningful conflicts of interest policies and processes can empower potential research participants to make an informed decision. It may also limit an investigator's and institution's risks of legal liability.[198] Policies should be written in a manner that fosters clarity, consistency, and fairness in enforcement.[199] Progress at the institutional level has been made, but conflicts policies still lack the specificity necessary to effectively guide reviewers on how to evaluate conflicts, enforce the policy, and assess penalties.[200]

Overly lenient conflicts policies and inadequate enforcement are commonplace. While institutions have created independent reviewer committees to monitor conflicted investigators[201], there is considerable variance in the make up of these committees and their authority.[202] Viewed in their best light, the committees aim not to impede research, but rather to work with the investigators to ensure the ethical design, implementation, data analysis, interpretation of results, and publication of findings.[203] Some committees have the authority to: suggest appropriate management of the conflicts; modify the research protocol; disqualify conflicted investigators from participating in the study; and require that conflicted investigators sever certain conflicts before embarking on the study.[204] However, committee members are, themselves, not always free of conflicts.[205]

### *Institutional Reform*

Conflicts policies tend to address individual investigators: Few policies at the federal or institutional level address conflicts at the institutional level.[206] Such polices are sorely needed given the pervasiveness of industry-sponsored research. Indeed, institutional conflicts of interest are more distorting than individual conflicts; yet, institutional conflicts are largely unregulated[207], under-investigated[208], and largely consigned to self-policing.[209] Unmonitored, institutions may (and do) stack their conflicts review committees with favorable reviewers, or simply override their decisions.[210] Public representation is minimal. To create an effective culture of ethics at grantee institutions nationwide, federal guidance is needed to develop more effective, consistent, and transparent institutional-level conflicts policies.[211]

### *FDA Reform*

In approving or denying approval of new drugs and devices, the FDA relies on the recommendations of advisory committees. But these too have been often mired in financial conflicts.[212] Although each committee member must complete an FDA conflict of interest form and report conflicts that may be related to the committee topic[213], the FDA issues waivers where a committee member's conflicts are deemed minimal or their expertise is deemed critical to the committee's deliberations.[214] The majority of FDA advisory committees include scientists that received such waivers.[215] Conflicts allegations were made regarding committee recommendations for: silicone breast implants[216], labeling of high-blood pressure drugs[217], and Tysabri, a multiple sclerosis drug.[218] A study found that at least one advisory committee member had a financial link to the drug's maker or a competitor in 73 percent of FDA advisory committee meetings.[219] In a number of drug and device approvals, the votes of conflicted advisory committee members have been determinative.

Early in 2005, the FDA convened an advisory committee meeting to discuss the toxicity of the COX-2 inhibitors Vioxx, Celebrex, and Bextra.[220] Had the committee members with industry ties been precluded from voting, this committee would have voted against continued marketing for Vioxx and Bextra; instead, all three drugs received favorable votes.[221] At least as to Vioxx, that tainted recommendation proved fatal.

In October 2005, Congress passed an amendment to the FDA appropriations bill that required the agency to post copies of all waivers on the FDA's website at least 15 days before the meeting date.[222] Waivers provide information on the nature of a member's conflicts of interest.

On August 4, 2008, the FDA announced improved policies for advisory committees[223], including: stricter limits on financial conflicts of interest, improved voting procedures, and improved processes for disclosing information pertaining both to advisory committee members and to specific matters considered at advisory committee meetings.

Consumer advocates, among others, call for stricter prohibitions on members with financial conflicts of interest, observing that the FDA can find qualified, conflict-free scientists if it tries.[224] Another useful reform would be to lessen the influence exercised by the FDA's Office of New Drugs. The OND works closely with drug manufacturers, shepherding new drug applications through the approval process. The FDA's Dr. David Graham and others have criticized the power OND exercises over advisory committee panel appointments, the assignment of drugs to specific committees, and what information is presented to panelists.

The existence of conflicts, of course, does not prove a drug or device is bad. But the existence of conflicts inevitably taints the integrity of the process and the reputation of even genuinely innovative, effective, and safe products, and thereby undermines public confidence in medicine. Although conflicted experts may be able to provide valuable insights to an advisory committee, they should never be voting members.

***Communication Outlet Reform***

Journal publication guidelines may also help raise the ethical standards by which an investigator designs and conducts a study. But journals themselves have increasingly become commercialized[225] and their record in detecting unethical research practices is not reassuring.[226] This affects not only scholarly journals but the daily press, which rarely mentions conflicts when reporting scientific findings.[227] Clinical research journals should include conflicts of interest information in their press releases used to promote study publications.

Full disclosure in scholarly and media outlets should help build public trust in clinical research. Consistent disclosure in all forms of research communications, including the press, should facilitate a more accurate evaluation of clinical research by both journalists and the public. Conflicted scientists should be required to reveal to the publisher their potentially compromising interests. Journalists should scrutinize whether a scientist's conflicts may have affected a study's findings.

**Summary**

Conflicts of interest challenge the credibility of the clinical research system. Government and institutional policies must help clarify how investigators, research partners and participants, and oversight reviewers may avoid, disclose, recognize, manage, acknowledge and accept, and eliminate conflicts of interest. To protect human research participants and the integrity of the data being collected, conflicts should be eliminated. In those extraordinary circumstances where they cannot be wholly eliminated, they must be fully disclosed.

# CONCLUSION

We started this White Paper with a description of what we referred to as the "perfect storm" – the murky approval of Ketek in which all institutional actors critical to protecting clinical trial participants and the public came up short. We followed that with numerous other examples of similar failures in the drug and medical device approval and monitoring process. We saw that the clinical trial reforms have been reactive, cosmetic, and piece-meal, leaving gaps in the oversight system that are conflict ridden, damage the public health, and tarnish the integrity of the drug approval process.[228] We also saw that rather than serving as a watchdog guarding public health and safety, the FDA is itself a deeply conflicted institution, caught in the financial headlock of a drug company user fee system and inadequate public funding. As a result, the FDA has come to view the drug companies with which it regularly engages and negotiates as its primary clients.

Throughout, we have drawn attention to courageous, public-spirited officials and corporate employees who spoke out for drug safety and accountability. Invariably, they collided with their employer's bureaucratic or financial prerogatives and interests, and suffered threats and retaliation in response. These whistleblowers need and deserve effective legal protection. As we have seen, however, too often the laws that Congress intended to protect employees of conscious have been traps for the unwary, leaving whistleblowers vulnerable to losing their job, reputation, livelihood, and family. Congress needs to clarify, strengthen, and extend these whistleblower protections.

Congress must also ensure that patients injured by faulty medical devices and drugs are not barred by corrupt or imprudent approval decisions by the FDA – and by the US Supreme Court – from bringing manufacturers to justice. As Dr. David Ross testified to Congress, the FDA is in the throes of a "culture of approval." Tragically, approval by the FDA is no assurance at all that a drug or device is reliably safe.

Conflicts of interest afflicting the integrity of the clinical research and drug approvals need to be removed or more effectively minimized and disclosed. Incentives for government-academic-industry collaboration must be weighted and reexamined in light of the often pernicious, corrupting influence of commercialization.

Companies that submit false or deceptively incomplete new drug applications must know they will face enforcement and meaningful penalties. The FDA needs to put a firm end to permitting the use of scientifically dubious short-cuts to approvals, like non-inferiority trials.

Serious, inherent financial conflicts in the conduct and oversight of IRBs were manifest in the six-year denial by Copernicus that it had been alerted to unethical practices in Ketek Study 3014 but remained silent. In general, IRBs literally tend to elevate form over substance in complying with informed consent requirements. In too many instances, a participant's signature on an informed consent form has failed to ensure that she was adequately informed about the study's true risks and benefits. Moreover, once an informed consent form is signed and on file, IRBs have failed to consistently monitor the participant's safety.

The purpose of this White Paper was to identify flaws in clinical trials and the drug approval process and propose effective reforms. Throughout we have emphasized the systemic failures and the fatal impact caused by gaps in the system. We have done so to make the stakes crystal clear: Getting clinical trials and drug safety right is literally a life and death matter.

We can do a lot better, starting with effective whistleblower protections for employees, effective legal recourse for trial participants whose consent is less than truly voluntary, and by instituting mechanisms to remove or effectively diminish the corrupting influences of financially conflicted relationships.

Just like learning to speak a new language, we believe reformers will be successful at addressing gaps in drug safety and the clinical trial process if they simply start with developing legislation, initiatives, and an overall attitude that emphasizes the ABCs: Accountability, Balance, and Citizen Empowerment.

# APPENDICES

## Appendix 1: Example Research-Related Cases by Cause of Action[1]

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| | | **General Health Law: Standard of Care** | |
| *Hall v. Hilbun*, 466 So.2d 856 (Mississippi Supreme Court 1985) | Malpractice | The plaintiff's wife died following an exploratory laporatomy. The plaintiff's expert witnesses were not allowed to testify because they were from another state; at the time, the standard of care was determined locally. Without local expert testimony, the court directed a verdict for the defense. (Note: Unrelated issues from this case were overturned by statute.) | Standard of care is now nationally based: Doctors are required to perform with same level of competence as minimally competent doctors throughout the US. |
| *Helling v. Carey*, 519 P.2d 981 (Washington Supreme Court 1974) | Malpractice (Negligence) | A doctor failed to diagnose a patient's glaucoma because he did not perform an inexpensive "puff test". The failure delayed the diagnosis and caused permanent visual impairment. The universal practice was not to test patients who are under 40 for glaucoma because the likelihood of occurrence is so small for those patients. | The doctor was negligent, as a matter of law. Reasonable care is not necessarily just limited to following universal industry customs. Customs can be negligent. |
| *Cobbs v. Grant*, 502 P.2d 1 (California Supreme Court 1972) | Negligence: Lack of Informed Consent | The plaintiff suffered several complications, including an injured spleen, following surgery. The plaintiff claimed, among other things, that he was not adequately informed of risks prior to trial. (Note: For unrelated reasons, the court vacated the jury's verdict for the plaintiff and remanded the case for retrial on the issue of consent alone.) | Adopted the majority rule: Failure to obtain informed consent is a negligence tort (rather than a technical battery). Standard is whether the patient was informed about everything material to her decision. |
| | | **General Health Law: Institutional Liability** | |
| *Petrovich v. Share Health Plan of Illinois, Inc.*, 719 N.E.2d 756 (Illinois Supreme Court 1999) | Malpractice (Negligence) Against a Health Maintenance Organization ("HMO") | A patient's cancer went undiagnosed for some time because her doctors initially refused to authorize an MRI and then later performed the MRI incorrectly. The patient sued the HMO alleging vicarious liability for the actions of the doctors, who were independent-contractors. | An HMO may be held vicariously liable for the negligence of its independent-contractor physicians under the doctrines of apparent authority or implied authority. |

[1] The case citations follow bluebook format with the exception of using bluebook abbreviations for the deciding court. That is, to assist the lay reader, we fully write out the deciding court. For example, the blue book citation for *Hall v. Hilbun* is 466 So.2d 856 (Miss. 1985) and we instead reference the case as the following: *Hall v. Hilbun*, 466 So.2d 856 (Mississippi Supreme Court 1985).

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| *Baptist Memorial Hospital v. Sampson,* 969 S.W.2d 945 (Texas Supreme Court 1998) | Malpractice (Negligence) Against Hospital | A patient brought medical malpractice action against hospital for negligence of emergency room physicians for failing to diagnose and treat poisonous spider bite. | The hospital is not vicariously liable for negligence of its emergency room contract physicians |
| *Mejia v. Community Hospital of San Bernardino,* 122 Cal. Rptr. 2d 233 (California Court of Appeal, Fourth District, Division 2 2002) | Malpractice (Negligence) Against Hospital | A patient brought medical malpractice action against hospital for negligence of emergency room physicians for failure to diagnose her broken neck. | The hospital can be held liable as, an ostensible agency, for the negligence of its emergency room contract physicians |
| | | **General Health Law: Institutional Records** | |
| *HCA Health Services of Virginia, Inc. v. Levin*, 530 S.E.2d 417 (Virginia Supreme Court 2000) | Subpoena for Doctor's Peer Review Records | A doctor sued a television station for defamation. The station responded by subpoenaing peer review records. The doctor objected that those records were privileged | Peer review records are privileged; privilege applies to any litigation, not just medical malpractice actions. |
| *State ex rel Cincinnati Enquirer v. Daniels*, 844 N.E.2d 1181 (Ohio Supreme Court 2006) | Mandamus Action | The plaintiff asked the court to order the Health Commissioner to release records of lead citations issued. The Commissioner objected, claiming the release would violate HIPAA; the citations included health information (identities of children who tested positive for lead). | The reports requested do not contain "protected health information" as the term was used in HIPAA. |
| *Head v. Colloton,* 331 N.W.2d 870 (Iowa Supreme Court 1983) | Injunction Suit | A leukemia patient sought hospital records revealing the identity of a possible bone marrow donor under public records statute. | Potential marrow donors are considered patients; typing records are confidential. |
| | | **General Health Law: Consent** | |
| *Natanson v. Kline,* 350 P.2d 1093 (Kansas Supreme Court 1960) | Negligence: Lack of Informed Consent | A patient sued her doctor and hospital after being badly burned by radiation therapy. She claimed that the doctors were negligent, in part, because they did not inform her of burn risks. | A physician has a duty to inform the patients of known hazards of proposed treatments. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| *Miller v. HCA, Inc.*, 118 S.W.3d 759 (Texas Supreme Court 2003) | Negligence: Failure to Obtain Consent | Parents sued a hospital for allowing a doctor to provide emergency medical care to an infant without their consent. The infant was born extremely premature and in distress. The neonatologist provided life-saving medical care without first obtaining parental consent. | The hospital can provide emergency care without parental consent when there is no time to obtain a court order. |
| *Ferguson v. City of Charleston*, 532 U.S. 67 (U.S. Supreme Court 2001) | Violation of Fourth Amendment: Testing Without Consent | A state hospital was testing certain pregnant patients for cocaine use without the patients' consent. The testing program was designed to get pregnant cocaine users into drug treatment and a central part of the program involved the threat of prosecution. | Drug testing without consent violates the Fourth Amendment, partly because of the threat of prosecution. |
| *Veronia School District. 47J v. Acton*, 515 U.S. 646 (U.S. Supreme Court 1995) | Violation of Fourth Amendment | The School District implemented a policy requiring students to consent to drug tests in order to participate in competitive sports. | The policy does not violate the Fourth Amendment (special needs exception). |
| *Bd. Of Ed. Of Ind. School Dist. 92 v Earls*, 536 U.S. 822 (U.S. Supreme Court 2002) | Violation of Fourth Amendment: Testing Without Consent | The School District implemented a policy requiring students to consent to drug tests in order to participate in any competitive extracurricular activities including, but not limited to, athletics. | The policy does not violate the Fourth Amendment (special needs exception). |
| *Arato v. Avedon*, 858 P.2d 598 (California Supreme Court 1993) | Negligence: Lack of Informed Consent | The widow and children of a patient who died of pancreatic cancer brought action against treating physicians, claiming that the physicians failed to obtain patient's informed consent for the particular course of treatment by failing to disclose information regarding the life expectancy of pancreatic cancer patients. | Doctors have no duty to disclose statistical life expectancy data, nor do they have duty to disclose information relating to a patient's non-medical interests. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| *Johnson By Adler v. Kokemoor*, 545 N.W.2d 495 (Wisconsin Supreme Court 1996) | Negligence: Lack of Informed Consent | A patient alleged failure to obtain her informed consent to surgery. Jury found that surgeon failed to adequately inform patient regarding risks associated with surgery and that a reasonable person in patient's position would have refused to consent to the surgery if she had been fully informed. The Court of Appeals, 525 N.W. 2d 71, reversed on basis that admission of evidence of the surgeon's failure to refer the patient to more experienced physicians constituted prejudicial error. The patient appealed. | Statistical life expectancy data is relevant to consent as it relates to the experience levels of the doctor(s) performing a given operation. Also, whether a more experienced doctor was available for a given procedure is relevant. |
| *Neade v. Portes*, 739 N.E.2d 496 (Illinois Supreme Court 2000) | Negligence (Lack of Informed Consent) and Breach of Fiduciary Duty | A patient came to his doctor (at an HMO) several times complaining of chest pain. During the first visit, the doctor ordered a thallium stress test that did not reveal any cardiac problems. During subsequent visits, the doctor refused to perform other tests recommended by two other doctors. The tests would have been paid for by a "medical incentive fund" which would otherwise be dispersed partly to the doctor. The doctor did not disclose his financial interest. The patient died shortly after from a massive heart attack. | Breach of fiduciary duty, based on physician's failure to disclose alleged financial interest in medical incentive fund, was duplicative of medical negligence claim. |
| *Moore v. Regents Uni. Cali.*, 51 Cal. 3d 120 (California Supreme Court 1990); *Cert. Denied*, 499 U.S. 936 (U.S. Supreme Court 1991) | Negligence (Lack of Informed Consent) and Breach of Fiduciary Duty | A patient brought action against physician, university researcher, university regents, and licensees of rights to patented cell lines and its products, alleging breach of physician's disclosure obligations. | Physicians must disclose personal interests unrelated to patient's health, whether research or economic, in obtaining patient's consent to medical treatment. Failure to disclose such information may give rise to a cause of action for performing medical procedure without informed consent or breach of fiduciary duty. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| *Canterbury v. Spence*, 464 F.2d 772 (U.S. Court of Appeals, District of Columbia Circuit 1972) | Negligence: Lack of Informed Consent | Plaintiff suffered partial paralysis and other ailments following a spinal surgery. He was not informed that the surgery carried a greater than 1 percent chance of paralysis. At trial, the judge directed a verdict for the defense. | Remanded for retrial: Failure to inform of a 1 percent chance of paralysis presented a question for the jury about whether consent was informed. |
| *Grimes v. Kennedy Krieger Institute*, 782 A.2d 807 (Maryland Supreme Court 2001) | Negligence | Minors who participated in a non-therapeutic research program sued the research institute claiming that their blood levels of lead increased during the experiment. | Parents cannot give informed consent for minors to participate in non-therapeutic research trial if there is any risk of harm. |
| | | **General Health Law: Conversion** | |
| *Moore v. Regents Uni. Cali.*, 51 Cal. 3d 120 (California Supreme Court 1990); *Cert. Denied, 499* U.S. 936 (U.S. Supreme Court 1991) | Conversion | A patient brought suit against physician, university researcher, university regents, and licensees of rights to patented cell line and its products, alleging conversion of his excised cells to produce patented cell line. | Theory of conversion could not be extended; extension of conversion law would hinder research by restricting access to necessary raw materials. Patient's rights, the court held, were protected through informed consent. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| | | **General Health Law: Substantive Due Process** | |
| *Abigail Alliance for Better Access to Development Drugs v. von Eschenbach*, 495 F. 3d 695 (U.S. Court of Appeals for the District of Columbia Circuit 2007); *Cert. Denied*, 128 S.Ct. 1069 (U.S. Supreme Court 2008) | Violation of Fifth Amendment Substantive Due Process | Abigail, after whom the Alliance is named after, died awaiting the opportunity to take an experimental drug and Alliance, in conjunction with Washington Legal Foundation sued the FDA in 2003 in order to make experimental drugs that have not been approved by the FDA more accessible to patients, who generally do not qualify for clinical trials. | Terminally ill patients have no fundamental right protected by Due Process Clause to have access to investigational drugs. The common law doctrine of necessity did not weigh in favor of recognizing a fundamental right of access. The FDA policy did not amount to a tort of intentionally preventing person from giving necessary aid to another. The common law doctrine of self-defense did not weigh in favor of recognizing a fundamental right of access. The FDA policy bore a rational relationship to a legitimate state interest. |
| | | **Medical Trials: Negligence, Generally** | |
| *Grimes v. Kennedy Krieger Inst.*, 782 A.2d 807 (Maryland Supreme Court 2001) | Negligence | Parents sued after their children were exposed to lead through a procedure that they were told would remove lead from their homes. The Institutional Review Board ("IRB") approved the protocol, despite the dangers to the children. | Remanded for trial. |
| *Baker v. Univ. of Vt*, 2005 WL 5895214 (Superior Court of Vermont 2005) | Negligence | The subject of a heroin withdrawal study killed the plaintiff in a car accident after a session. The family of the deceased brought suit against university and IRB. | Dismissed—Defendant does not owe a duty. |
| *Gelsinger v. Trustees of Univ. of Pa*, No. 000901885 (Pennsylvania District Court filed Sept. 18, 2000) | Negligence: Wrongful Death Complaint | Gelsinger died while participating in gene transfer experiment. The suit named the individual IRB. | Case settled. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| *Hamlet v. Fradin*, 03 CVS 1161 (North Carolina Superior Court Division filed July, 2003) | Negligence Complaint | Hamlet sued his doctor, the trial sponsor, and the IRB for violating duty to protect patients. The plaintiff alleged in the complaint that the study was unethical, because the sponsor and the overseeing IRB allowed the plaintiff who was suffering from a treatable condition to be randomized into the placebo arm, receiving no treatment, despite the fact that an existing therapy was available. Therefore, the plaintiff alleged he was unethically subjected to the risk of suffering significant harm. | Case settled. |
| | | **Medical Trials: Negligence, Consent** | |
| *Whitlock v. Duke Univ.*, 637 F.Supp. 1463 (U.S. District Court, M.D. North Carolina 1986) | Negligence: Lack of Informed Consent | Whitlock suffered brain damage after an experimental simulated deep dive. | Dismissed on summary judgment motion, since the risk could not be reasonably expected. |
| *Kus v. Sherman Hosp.*, 644 N.E.2d 1214 (Appellate Court of Illinois, Second District 1995) | Negligence: Lack of Informed Consent | The doctor implanted an intraocular lens in Kus, without informing him that the lens was still under the U.S. Food and Drug Administration ("FDA") investigation. The doctor changed the consent form that was approved by the IRB. | Directed verdict on negligence affirmed. |
| *Scheer v. Burke*, No. 000375 (Pennsylvania District Court filed July 10, 2003) | Negligence: Wrongful Death/Lack of Informed Consent | Plaintiff, the wife of a deceased patient alleges negligence by the doctors and investigators, and specifically by the IRB in approving the study and the informed consent documents. The plaintiff alleges the informed consent form failed to note, amongst other material risks: that the study drug was not used for normal male hypertension, which the plaintiff had; the possible adverse reactions to the study drug, including renal failure and death; and that the study participants would not be receiving the usual sequence of care in common practice for hypertension management. | Complaint is pending. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| | | **Medical Trials: Federal Common Rule** | |
| *Robertson v. McGee*, 2002 WL 535045 (U.S. District Court, N.D. Oklahoma 2002) | Violation of Common Rule (45 CFR Part 46) and a Violation of Nuremberg Code (§1983) | 18 plaintiffs sued the IRB and others after participants in clinical trial for melanoma cancer died. | Dismissed for lack of subject matter jurisdiction, because there is no private right of action under the common rule. |
| *Wright v. Hutchinson Center*, 269 F. Supp.2d. 1286 (U.S. District Court, W.D. Washington 2002) | Violation of Common Rule | Deceased had participated in a trial to test the effectiveness of depleting T cells in donor marrow in order to reduce disease following a transplant. | The court dismissed the suit on the pleadings since there is no private right of action under the common rule. |
| *Berman v. Hutchinson Center*, C01-5217-RSL (U.S. District Court, W.D. Washington Filed March 26, 2001) | Violation of Common Rule | The plaintiff's wife died while participating in a breast cancer study called protocol 681. Whistleblower complained to HHS about study risks. | Case settled. |
| *Whitlock v. Duke Univ*., 637 F.Supp. 1463 (U.S. District Court, M.D. North Carolina 1986) | Violation of Common Rule | Whitlock suffered brain damage after an experimental simulated deep dive. | The court granted defendant's motion for summary judgment, because the risk could not be reasonably expected. |
| *Cordy & Wade v. Oregon Health & Sci. Univ.*, No. 02-CV-877KI (U.S. District Court, Oregon filed July, 2002) | Violation of Common Rule | Class action suit against university, school officials, and IRB for drug testing student athletes. | Case settled. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| | | **Medical Trials: False Claims Act ("FCA")** | |
| *U.S. ex rel. Gross v. AIDS Research Alliance*, No. 04-2566 (U.S. Court of Appeals, Seventh Circuit 2005) | FCA | Gross sued the IRB and others for defrauding the government by giving false information about its clinical trial. | Affirmed district court decision to dismiss for failure to plead with particularity. |
| *U.S. ex rel. Zissler v. University of MN*, 154 F.3d 870 (U. S. Court of Appeals, Eighth Circuit 1998) | FCA | An employee brought qui tam action under FCA against state university for alleged false and misleading statements in administering federal research grant. U.S. intervened. District Court dismissed action, but appeal was taken. | Dismissal reversed; The FCA applies to states. |
| *U.S. ex rel. Chandler v. Cook County, Ill.*, 277 F.3d 969 (U.S. Court of Appeals, Seventh Circuit 2002), *Cert. Aff'd*, 536 U.S. 956 U.S. 956 (U.S. Supreme Court 2002) | FCA | Dr. Janet Chandler brought this qui tam action as a relator on behalf of the U.S. to recover funds allegedly fraudulently obtained by Hektoen Institute for Medical Research and Cook County, Illinois, in administration of a drug treatment program. The district court dismissed the claim against Cook County for failure to state a claim since Cook County, as a municipality, was immune from damages liability under the FCA. | The U.S. Court of Appeals for the Seventh Circuit reversed the lower court's decision, finding that Cook County is a person within the meaning of the FCA and does not enjoy immunity from the FCA's damages scheme. The U.S. Supreme Court unanimously affirmed. |
| *U.S. ex rel. Sarafoglou v. Weill Medical College of Cornell*, 451 F.Supp.2d 613 (U.S. District Court, S.D. New York 2006) | FCA | Defendant retaliated against doctor after the doctor complained that the defendant defrauded the government. The U.S. intervened and settled. | Retaliation claim may go to trial, all others are barred. |
| | | **Medical Trials: Nuremberg Code/Belmont** | |
| *Robertson v. McGee*, 2002 WL 535045 (U. S. District Court, N.D. Oklahoma 2002) | Violation of Federal Common Rule (45 CFR Part 46)/ Nuremberg Code (§1983) | 18 plaintiffs sued the IRB and others after participants in clinical trial for melanoma cancer died. Court dismissed because there is no private right of action under the Common Rule. | Dismissed for lack of subject matter jurisdiction. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| *Berman v. Hutchinson Center*, C01-5217-RSL (U.S. District Court, W.D. Washington Filed 2001-03-26) | Violation of Federal Common Rule (45 CFR Part 46)/ Nuremberg Code (§1983) | The plaintiff's wife died while participating in a breast cancer study called protocol 681. A whistleblower complained to HHS about the study's risk. | Case settled. |
| *Steubing v. Kornak & Holland*, Case No. 03CV0332 (U.S. District Court for the N.D. New York Filed 2003-03-18) | Violation of Nuremberg Code and Rights under the Fifth Amendment | Class action was brought on behalf of all persons who participated in a human research experiment by Defendants—oncologist Dr. James Holland and his research assistant, Paul Kornak—between 1999 and 2003 at the Stratton Veterans Affairs Medical Center in Albany, N.Y. Federal authorities were warned by staff members seven years prior that veterans were at risk of dying from drugs given to them in violation of medical protocols. | Case settled. Kornak pled guilty to criminal charges. Dr. Holland was subjected to FDA disqualification proceedings. Federal Tort Claims were considered. |
| | | **Medical Trials: Contract Claims** | |
| *Abney v. Amgen, Inc.*, 443 F.3d 540 (U.S. Court of Appeals, Sixth Circuit 2006); *Suthers v. Amgen Inc.*, 441 F.Supp.2d 478 (U.S. District Court, S.D. New York 2006) | Breach of Contract/ Promissory Estoppel | Plaintiffs participated in a clinical drug trial and sued to continue to receive the drug after the trial had ended. Defendants claim that they terminated the use of the drug for safety concerns, but plaintiffs allege that it had become too expensive for the defendants to continue treatment. | The protocol did not give rise to an enforceable contract or promise to provide treatment after the study concluded. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| | | **Medical Trials: Alien Tort Act ("ATA")** | |
| *Abdullahi v Pfizer, Inc.*, 2005 WL 1870811 (U.S. District Court S.D. New York 2005) | Alien Tort Act – Violation of Nuremburg/Helsinki: Lack of Informed Consent | Pfizer tested a new antibiotic in Nigeria, to accelerate the drug's approval process, during an outbreak of measles, meningitis, and cholera. However, to enhance the contrast between control and experimental groups, the control group received only a 1/3 dose of an alternative treatment. No informed consent was obtained. The case was brought under the Alien Tort Claims Act for violating Nuremburg/Helsinki. | Dismissed on forum non-conviens grounds. However, the court also stated, in the *dicta*, the ATA gave no cause of action for failure to obtain consent. |
| | | **Medical Trials: Violation of Civil Rights** | |
| *Wright v. Hutchinson Center*, 269 F. Supp.2d. 1286 (U.S. District Court, W.D. Washington 2002) | Violation of Civil Rights | Deceased had participated in a trial to test the effectiveness of depleting T cells in donor marrow in order to reduce disease following a transplant. The court dismissed the suit because there is no private right of action under the 42 U.S.C. § 1983. | Motion for judgment on the pleadings granted. |
| *Berman v. Hutchinson Center*, C01-5217-RSL (U.S. District Court, W.D. Washington Filed March 26, 2001) | Violation of Civil Rights | The plaintiff's wife died while participating in a breast cancer study called protocol 681. | Case settled. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| | | **Medical Trials: Wrongful Discharge** | |
| *Chelly v. Knoll Pharmaceuticals*, 685 A.2d 498 (Superior Court of New Jersey, Appellate Division 1996) | Wrongful Discharge | Chelly, Knoll's Director of Research, complained that his employer failed to report to the FDA elevated liver enzyme readings of patients participating in a new drug study, and in retaliation Knoll fired Chelly. | Judgment for the defendant affirmed. The court found that there was merely a difference of opinion between Chelly and the company, and the company had no duty to report the concerns to the FDA. Hence, Chelly's discharge was not in violation of a "clear mandate of public policy." |
| *Cheatham v. Mannkind*, 2006 WL 3804495 (California Court of Appeal, Second District, Division 1 2006) | Wrongful Discharge | Doctor was fired in retaliation for blowing the whistle on insulin study. The Doctor appealed from an order denying his special motion to strike the cross-complaint of defendant Mannkind Corporation. | The Court of Appeals affirmed the lower court's denial of three of Doctor's cause of actions and reversed and remanded the denial of two causes of actions: libel per se and trade libel. |
| | | **Medical Trials: Procedural** | |
| *Guckin v. Nagle*, 259 F.Supp.2d 406 (United States District Court, E.D.Pennsylvania 2003) | Motion to Remand (To State Court) | Plaintiff brought personal injury suit against surgeon, hospital, and manufacturer after she was injured during a clinical trial of a medical device. | The investigatory device exception in the Food, Drug, and Cosmetics Act does not completely preempt state claims. Remanded to state court. |
| *Riegel v. Medtronic, Inc.*, 128 S.Ct. 999 (U.S. Supreme Court 2008) | Products (Strict) Liability for Defective Catheter. | Plaintiff's husband died from a balloon catheter used in an angioplasty surgery. The FDA had approved the catheter as a class-III medical device. | FDA pre-market approval process established federal requirements for class III medical devices, so patient's state common-law claims were preempted. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| *Wyeth v. Levine*, No. 06-1249 (U.S. Supreme Court) | Products Liability | Vermont musician Levine lost her hand and forearm due to complications from an off-label "IV push" of a popular anti-nausea drug known as Phenergan. | The Supreme Court decided in early 2009 that federal law does not preempt state tort claims imposing liability based on drug labeling that the FDA had previously approved. |
| | | **Medical Trials: Social Science** | |
| *164 Mulberry Street Corp. v. Columbia Univ.*, 4 A.D.3d 49 (Supreme Court, Appellate Division, First Department, New York 2004) | Libel, Libel Per Se, Intentional Infliction of Emotional Distress | Defendants conducted social science research studying responses to complaints regarding food poisoning. During the research, defendants allegedly published false information about plaintiffs' restaurants' hygienic safety. | Case settled. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| | | **Medical Trials & Post-Market: Products Liability Act** | |
| *Sinclair v. Merck & Co., Inc.*, 948 A.2d 587 (New Jersey Supreme Court 2008); Other similar class action and individual cases were filed regarding Vioxx in other state courts. For plaintiffs that died while taking Vioxx, wrongful death causes of actions were brought. Courts tended to reduce monetary verdict awards. Merck reached settlement in certain cases and established a settlement program for 49,960 eligible claimants. Some courts ruled that federal law preempted certain state products liability provisions. | Negligence, Violation of Products Liability Act and Consumer Fraud Act, Breach of Express and Implied Warranties, and Unjust Enrichment | Users of prescription drug Vioxx who sought to recover the cost of medical monitoring, after drug was voluntarily withdrawn from the market due to an increased risk of serious cardiovascular events brought class action against drug manufacturer. | Court determined that:<br>1) Action was encompassed by the Products Liability Act;<br>2) The Products Liability Act requires physical injury;<br>3) Drug users who did not allege a personal or physical injury could not satisfy the definition of harm to state a product liability claim under Products Liability Act; and<br>4) Drug users could not avoid the requirements of the Act by asserting their claims as Consumer Fraud Act claims. |

| Case | Cause of Action | Summary | Holding |
|---|---|---|---|
| *Gregg & Gregg v. Sanofi-Aventis*, No. L-1982-07 (New Jersey Superior Court Middlesex County filed February 9, 2007); Other similar cases regarding Ketek filed in other state courts. | Negligence, Products Liability Act, Defective Design, Failure to Warn, Consumer Fraud Act, Breach of Express Warranty, Breach of Implied Warranties, Common Law Fraud, Negligent Misrepresentation, Punitive Damages, Unjust Enrichment, and Loss of Consortium | Mr. Gregg was prescribed Ketek and suffered adverse side effects. | At this writing, the case is in discovery. |

## Appendix 2: A Comparison of Some Clinical Trial Participation Benefits & Risks

| BENEFITS | RISKS |
|---|---|
| Playing an active role in one's own health. | Suffering possible life-threatening side effects as the first humans to test a treatment. |
| Gaining access to new research treatments before they are widely available. | Receiving ineffective or inferior treatment. |
| Obtaining expert medical care at leading health care facilities during the trial. | Enduring more extensive and intensive treatment regimens for poorer outcomes. |
| Helping others by contributing to medical research. | Taking a placebo—an inactive pill, liquid, or powder with no treatment value. |

## Appendix 3: Clinical Trial Phases

| PHASE | DEFINITION |
|---|---|
| I | Researchers test an experimental drug or treatment in a small group of people (n=20-80) for the first time to: (1) evaluate its safety; (2) determine a safe dosage range; and (3) identify side effects. |
| II | Researchers test the experimental drug with a larger number of participants (n=100-300) to learn more about its safety and effectiveness by examining: (1) the drug's side effects; (2) how the body uses the drug; and (3) how the drug helps the condition. |
| III | Researchers test the experimental drug in a yet larger number of participants (n=1,000-3,000) to: (1) confirm its effectiveness; (2) monitor side effects; (3) compare it to commonly used treatments; and (4) collect information that will allow the experimental drug or treatment to be used safely. |
| IV | Researchers monitor the approved FDA drug in post-market studies to further analyze the drug's risks, benefits, and optimal use. |

## Appendix 4: Historical Progression of Clinical Trials & Ethical Codes[2]

| DATE | EVENT |
|---|---|
| 500 B.C. | Hippocrates of Cos II, the "father of medicine", developed a systematic approach to clinical medicine and an Oath of Medical Ethics for physicians to follow. |
| 130-210 A.D. | Galen introduced the notion of experimentation to medicine. |
| 1631-1691 | Richard Lower experimented with blood transfusions. |
| 1632-1704 | John Locke, a medical doctor known more for his philosophical ideology than his medical knowledge, practiced medicine utilizing revolutionary "clinical" methods on humans. |
| 1751 | Researchers observed the effects of the vitrum antimonii ceratum—glass of antimony or the vitrified oxide of antimony with wax. |
| 1751 | Dr. Branchini conducted experiments comparing the substance of interest to a placebo—a substance or procedure with no therapeutic effect. |
| 1753 | Dr. James Lind conducted what is often considered the first research trial—an evaluation of six different inventions on 12 sailors for the treatment of scurvy, a deficiency disease resulting from intake of vitamin C. |
| 1767 | The first recorded mention of consent occurs in a British law suit *Slater v. Baker & Stapleton* in which two physicians were held liable for re-breaking a bone because the Court determined that the surgeons should not have broken the bones without the patient's consent. |
| 1770 | Dr. John Gregory published the first definition of medical ethics in English. |
| 1775 | Dr. William Withering illustrated the importance of medicinal plants by publishing one of the initial studies using clinical trials on a traditional herbal remedy for cardiovascular conditions. |
| 1776 | Robert Robertson worked with the British Navy to observe the comparative efficacy of bark on the treatment of "continuous fever". |
| 1798 | Dr. Edwards Jenner experimented with cowpox in the development of a vaccine for smallpox. |
| 1803 | Dr. Thomas Percival published a code of medical ethics, which the American Medical Association adopted at its first meeting in 1847. |
| 1822 | Dr. William Beaumont experimented with a patient to observe the digestive processes. |
| 1867 | Dr. Joseph Lister invented the anti-sepsis. |
| 1879 | Dr. Armauer Hansen experimented without consent on his patients with leprosy. |
| 1860 | Louis Pasteur developed and conducted experiments that confirmed the germ theory of disease. |
| 1898 | Dr. Albert Ludwig Sigesmund Neisser conducted clinical trials without consent in patients with syphilis. |
| 1892 | Dr. William Coley injected patients with cancer to induce artificial erysipelas. He describes how he began treatment with a patient who had a sarcoma and only "after some deliberation he consented" and injections began. |
| 1897 | Guiseppe Sanarelli announced he discovered the bacillus of yellow fever and produced yellow fever in five patients. |
| 1898 | Dr. William Osler condemned Sanarelli: "To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal." |
| 1898 | Dr. Johannes Fibieger in Denmark treated every other patient with anti-diphtheria serum to establish suitable controls. |
| 1900 | Yellow Fever Board is established in the U.S. |

[2] National Research Ethics Service. Research Ethics Timeline. London: National Patient Safety Agency; 2008. Available at: www.nres.npsa.nhs.uk. Accessed on: August 3, 2008; The U.S. National Institute of Health. What Makes Research Ethical? Bethesda, Maryland: The U.S. Department of Health and Human Services; 2003. Available at: www.bioethics.nih.gov/slides/10-29-03-Emmanual.pdf. Accessed on: August 3, 2008.

**Appendix 4, Continued: Historical Progression of Clinical Trials & Ethical Codes**

| DATE | EVENT |
|---|---|
| 1900 | The Berlin Code set forth that an experiment should not be conducted: if a subject is not competent to consent; does not have the capacity to understand the information; or fails to provide unambiguous consent. |
| 1901 | After the death of Dr. Jesse Lazear, a member of the U.S. Army Yellow Fever Commission, due to self-experimentation with Yellow Fever, Dr. Walter Reed put forth research ethics addressing the following: (1) self-experimentation, (2) written agreements with other subjects, (3) payment in gold, (4) restrictions to adult subjects, and (5) using the phrase "with his full consent" in all journal articles. |
| 1902 | Dr. Albert Moll wrote a code of medical ethics. |
| 1917 | Dr. Joseph Golderberger conducted a comparative study of diet in two orphanages for treatment of pellagra. |
| 1930 | Nazi doctors performed medical experiments on concentration camp prisoners during World War II. |
| 1931 | First randomization and patient blinding in a tuberculosis trial. |
| 1932 | The U.S. Public Health Service ("PHS") conducted the Tuskegee Syphilis Study—a government study that obtained no informed consent and steered men with syphilis away from treatment even after the discovery in the 1940s that penicillin could effectively treat the disease. |
| 1934 | First multi-center trial in Britain evaluated serum treatment of pneumonia in London, Edinburgh, and Aberdeen. |
| 1937 | Sir Austin Bradford Hill, a leader in medical statistics, pioneered the use of randomized clinical trials and was the first to demonstrate a strong connection between cigarette smoking and lung cancer. |
| 1938 | First placebo control in a trial of cold vaccines. |
| 1948 | First modern randomized placebo controlled trial of Streptomycin for tuberculosis. |
| 1946-1949 (Post-war) | Doctors' Trial revealed the medical abuses taking place under the Nazi regime, which led to the formulation of the Nuremberg Code of Medical Ethics. |
| 1953 | The National Institute of Health ("NIH") established guidelines for intramural research conducted at its clinical center. |
| 1955 | In response to the early 1950s Wichita Jury Study in which University of Chicago social scientists deceived jurors in criminal trials by not informing them that they were part of a research study examining a juror's decision making process, Congress passed a law that prohibited the recording of jury deliberations in any setting. This law was the first time that federal guidelines were enacted to protect the public from exploitation of well-meaning researchers. |
| 1962 | Kefauver Amendments directed FDA to require pharmaceutical manufacturers to report adverse events to the Food and Drug Administration ("FDA"). |
| 1964 | The World Medical Association adopted the Declaration of Helsinki, which established ethical principles for physicians and other participants in medical research involving human subjects. |
| 1966 | Dr. Henry Beecher published a study in the *New England Journal of Medicine* delineating 22 studies that used vulnerable, disadvantaged, and unaware human subjects. |
| 1966 | Dr. William Stewart, the United States Surgeon General issued a policy statement: "To receive funding, individuals or institutions had to provide the PHS with an assurance of compliance with its human research regulations, which required that research be reviewed by a committee of associates." |
| 1966 | The United Kingdom assembled its first Research Ethics Committee ("REC"). |
| 1967 | Dr. Maurice Pappworth published the *Human Guinea Pigs*, a book harshly criticizing the clinical experimentation that took place in the United States and the United Kingdom. |

**Appendix 4, Continued: Historical Progression of Clinical Trials & Ethical Codes**

| DATE | EVENT |
|---|---|
| 1970s | Several consumer groups petition the Joint Commission on the Accreditation of Hospitals ("JCAH") to redraft its standards to address patients' concerns. |
| 1973 | The American Medical Association published a patient bill of rights—the first explicit statement of the rights of patients and the responsibilities of physicians and medical institutions. |
| 1974 | The National Research Act (Pub. L. 93-348) was signed into law after a series of Congressional hearings into the Tuskegee study. Congressional hearings also discussed issues such as research on human fetuses (in reaction to a study in Finland with perfused heads of aborted fetuses), sterilization of the mentally handicapped, and use of prisoners. The National Research Act called for the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This Commission was to establish ethical principles that should guide the conduct of biomedical and behavioral research involving human subjects, with special attention to vulnerable populations. The Act mandated the establishment of the Institutional Review Board ("IRB") in all research organizations receiving federal funds to support research using human subjects. |
| 1979 | Based on the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research reports, the United States Department of Health, Education, and Welfare published a report entitled: "Ethical principles and guidelines for the protection of human subjects of research," which is more commonly referred to as the Belmont Report. |
| 1981 | The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, established by P.L. 95-622, sponsored a Workshop on Whistleblowing in Biomedical Research and reported formal recommendations from this Workshop to the President, Congress, and pertinent federal agencies. |
| 1982 | Council for International Organization for Medical Science/World Health Organization ("CIOMS/WHO") set forth International Ethical Guidelines for Biomedical Research Involving Human Subjects. |
| 1988 | Representative John Dingell (D-MI) and other Congressional members responded to rising scientific fraud with the establishment of the Office of Scientific Integrity ("OSI"), charged with investigating alleged scientific wrongdoing. The creation of this agency demonstrated Congressional support for protecting whistleblowers regarding bad research and lack of academic or government oversight, who were often junior faculty, and Congressional reluctance against allowing scientists to continue to self-regulate. NIH officials, however, moved quickly to preempt Congress and their "science police" legislative endeavors. |
| 1989 | NIH published a notice in the Federal Register announcing the creation of OSI. This new office would investigate research misconduct reported by grantee institutions and also have the authority to conduct its own investigations when necessary. OSI merged in 1992 with the Office of Scientific Integrity Review into the Office of Research Integrity ("ORI"). An agency of the Office of the Public Health and Science, ORI: (1) creates policies and regulations to prevent and detect scientific misconduct; (2) investigates allegations of scientific misconduct in biomedical and behavioral research supported by the PHS; and (3) provides education and training resources to promote research integrity. |
| 1990 | The Joint Commission on Accreditation of the Health Care Organization ("JCAHO") proposed new accreditation standards on patients' rights that included a requirement for "mechanism(s) for consideration of ethical issues in the care of patients and to provide education to caregivers and patients on ethical issues in health care." |
| 1991 | Common Rule established that 17 federal government agencies would use a common federal policy for the protection of human research subjects. |

**Appendix 4, Continued: Historical Progression of Clinical Trials & Ethical Codes**

| DATE | EVENT |
|---|---|
| 1992 | NIH required all grantees of National Research Service Act Institutional Research Training Grants (T32 and T34) to instruct pre-doctoral and postdoctoral NRSA trainees in the responsible conduct of research. |
| 1995 | President Bill Clinton issued an Executive Order creating the National Bioethics Advisory Commission to provide advice on bioethical issues arising from research on human biology and behavior and the applications, including the clinical application of that research. |
| 1996 | International Conference on Harmonisation ("ICH") Harmonized Tripartite Guidelines-Good Clinical Practice ("GCP"). |
| 1998 | Office of Inspector General ("OIG") of the Department of Health and Human Services issued its systematic, one-year study: *Institutional Review Boards: A Time for Reform.* |
| 2001 | European Directive issued requiring all clinical trials in 25 nations of the European Union thereafter to conform to the Directive in line with U.S. law. |
| 2002 | Maryland, the state in which the NIH is located, enacted a law to protect human subjects in all research, regardless of funding source. |
| 2004 | The United Kingdom set forth clinical trial regulations and within three years established a National Research Ethics Service. |

## Appendix 5: Ethical & Legal Codes

**Nuremberg Code**

- In response to experiments conducted on prisoners in Nazi concentration camps, American authors in 1947 set forth 10 principles, including:

    1) The voluntary consent of the human subject is absolutely essential.
    2) The experiment should be structured to yield fruitful results for the good of society that cannot be achieved by other means; it must not be random and unnecessary in nature.

- A gap identified in the Nuremburg Code is that a participant's informed consent would not have made the Nazi experiments ethical. That is, the Code inadequately addresses coerced subjects and unfavorable risk-to-benefit ratios.

**Declaration of Helsinki**

- 1964 World Medical Assembly issued the Declaration of Helsinki with 22 recommendations "as a guide to every physician in biomedical research involving human subjects."
- Revised five times since 1964—most recently in 2000.
- Distinguished therapeutic versus non-therapeutic research and required independent review of the design.
- Explicitly allowed informed consent from a legal guardian.
- Research not in accordance with Helsinki principles should not be accepted for publication.
- The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, and therapeutic method exists.
- Trial is justified only if there is a reasonable likelihood that the populations in which research are carried out stand to benefit from the research.
- Every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified at the conclusion of the study.

**Belmont Report**

- Formally titled, the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research of 1979".
- Established boundaries between research and practice.
- Set forth ethical principles underlying the conduct of research:

*Respect for persons*: Individuals should be treated as autonomous agents (capable of self-determination); persons with diminished autonomy deserve protection

Application: Informed Consent

*Beneficence*: Application of the "do no harm" principle, which maximizes possible benefits and minimizes possible harms

Application: Risk/Benefit Assessment

*Justice*: Fairness in the distribution of the benefits and burdens of research (distributive justice)

Application: Fair procedures and outcomes in the selection of subjects, along with special safeguards for vulnerable subjects.

**Council for International Organization for Medical Science/World Health Organization ("CIOMS/WHO") International Ethical Guidelines for Biomedical Research Involving Human Subjects**

- Proposed 21 guidelines with extensive commentary (1982), addressing topics such as the conduct of studies in third world countries.
- Required all study protocol's to have an ethical justification and scientific validity, along with an evaluation of benefits and risks.
- Set limitations on risk for those who cannot consent and addressed topics such as choice of controls (i.e., to whom it would be ethical to give a placebo).
- Provided guidelines for the study sponsor to: respond to the health needs and priorities of the community; provide reasonable availability to the treatment after the study is complete; and compensate the participant for research injury.

**International Conference on Harmonisation ("ICH") Harmonized Tripartite Guidelines-Good Clinical Practice ("GCP") 1996**[3]

- To provide a unified standard for the European Union, Japan, and the United States for mutual acceptance of clinical data by regulatory authorities in those jurisdictions.
- GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.
- Compliance with this standard provides public assurance that the rights, safety, and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki and that the clinical data are credible.

**45 CRF 46 Protections of Human Subjects—the 1991 Common Rule**

- Composition and function of a local Institutional Review Board ("IRB").
- IRB to assure that risks are minimized, research risks are reasonable in relation to expected benefits, subject selection is equitable, and informed consent will be obtained from each subject.
- 45 CFR 46.111 (2): "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."
- Specifically addressed: Fetuses, pregnant women, human *in vitro* fertilizations, prisoners as subjects, and children.

[3] Adopted by the U.S. FDA and Good Clinical Practice: Consolidated Guidelines in 1997. 45 CFR 46 Protection of Human Subjects. PHS policy 1966, National Research Act 1974, DHEW regulations 1981, Common Rule-17 federal agencies, including HHS.

## Appendix 5, Continued: Ethical & Legal Codes

**The National Institute for Health ("NIH") Guidelines on the Inclusion of Women & Minorities**

- NIH Reauthorization Act 1993
- Women and members of ethnic minority groups are to be included (some exceptions), outreach programs for recruitment, sufficient to provide for a valid analysis of differences between groups.

**The National Institute for Health ("NIH") Policy and Guidelines on the Inclusion of Children as Participants in Research**

- Effective October 1, 1998, children must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

## Appendix 6: Federal Research Regulations

*The Department of Health & Human Services Regulations*

- Title 45 Part 46 Protection of Human Subjects
- Title 45 Parts 160 & 164 Standards for Privacy & Individually Identifiable Health Information
- Title 45 Parts 160, 162, & 164 Health Insurance Reform: Security Standards

*The Department of Health & Human Services Food & Drug Administration Regulations*

- Title 21 Part 50 Protection of Human Subjects
- Title 21 Part 56 Institutional Review Board
- Title 21 Part 312 Investigational New Drug Application
- Title 21 Part 812 Investigational Device Exemption

**Appendix 7: A Comparison of Human Subject Protection Regulations at the U.S. Food and Drug Administration ("FDA") and the U.S. Department of Health and Human Services ("HHS")[4]**

| FDA | HHS |
|---|---|
| *56.101 Scope*<br><br>IRBs that review clinical investigations regulated by the FDA under sections 505(i), 507(d), and 520(g) of the Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products | *46.101 Scope*<br><br>All research involving human subjects conducted or supported by HHS or conducted in an institution that agrees to assume responsibility for the research in accordance with 45 CFR 46 regardless of the source of funding. |
| *56.102 & 50.3 Definitions*<br><br>Definitions for "Act"; "Application for research or marketing permit"; "Emergency use"; "Sponsor"; "Sponsor-Investigator"; "Test Article" do not have comparable terms defined in 45 CFR 46.<br><br>FDA has defined "clinical investigation" to be synonymous with "research." "Clinical investigation" means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA...or the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.<br><br>"Human subject" means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. | *46.102 Definitions*<br><br>Definitions for "Department or agency head"; "Certification" do not have comparable terms defined in 21 CFR 50 or 56.<br><br>HHS has defined "research" as a systematic investigation, including research development, testing and evaluation, designed to develop and contribute to general knowledge.<br><br>HHS has defined "Research subject to regulation" and similar terms as intending to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the FDA).<br><br>"Human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains: 1) data through intervention or interaction with the individual, or 2) identifiable private information. |

[4] Appendix 7 is for the most part reproducing a U.S. Department of Health and Human Services, Food and Drug Administration Good Clinical Practice Program resource entitled: Comparison of FDA and HHS Human Subject Protection Regulations. Rockville, Maryland: U.S. Department of Health and Human Services; 2000. Available at: http://www.fda.gov/oc/gcP/comParison.html. Accessed on: August 3, 2008.

**Appendix 7, Continued: A Comparison of Human Subject Protection Regulations at the U.S. Food and Drug Administration ("FDA") and the U.S. Department of Health and Human Services ("HHS")**

| FDA | HHS |
|---|---|
| *56.102 & 50.3 Definitions, Continued*<br><br>"Institutional Review Board" means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of rights and welfare of the human subjects. The term has the same meaning as the phrase "institutional review committee" as used in section 520(g) of the Act. | *46.102 Definitions, Continued*<br><br>"IRB" means an institutional review board established in accordance with and for the purposes expressed in this policy. |
| *Definitions for "IRB approval"; "Minimal Risk"; "Institution"; "Legally authorized representative" are identical.* | |
| *56.103 Circumstances in which IRB review is required.*<br><br>Except as provided in 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission to the FDA or is considered in support of an application for a research or marketing permit must have been reviewed and approved by, and remain subject to continuing review by, an IRB meeting the requirements of this part. [In diverging from the assurance requirement, the FDA stated its belief that it is inappropriate for it to adopt the assurance mechanism. The benefits of assurance from IRBs that are subject to FDA jurisdiction, but not otherwise to HHS jurisdiction, do not justify the increased administrative burdens that would result from an assurance system. FDA relies on its Bioresearch Monitoring Program, along with its educational efforts, to assure compliance with these regulations.] | *46.103 Assuring compliance with this policy—research conducted or supported by any federal Department or Agency*<br><br>Sections dealing with assurances and certifications (a), (b)(1)-(3), (c)-(f) are unique to the Common Rule and the HHS regulations. |

**Appendix 7, Continued: A Comparison of Human Subject Protection Regulations at the U.S. Food and Drug Administration ("FDA") and the U.S. Department of Health and Human Services ("HHS")**

<table>
<tr><th>FDA</th><th>HHS</th></tr>
<tr><td>56.104 Exemptions from IRB Requirements<br><br>a) Any investigation which commenced before 7/27/81, and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigations remains subject to review for an IRB which meets the FDA requirements in effect before 7/27/81.<br><br>b) Any investigation that commenced before 7/27/81 and was not otherwise subject to requirements for IRB review under FDA regulations before that data.<br><br>c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.</td><td>46.101(b) Exemptions from this Policy<br><br>a) Research conducted in established or commonly accepted educational settings…<br><br>b) Research involving the use of educational tests…, survey procedures, interview procedures or observation of public behavior..<br><br>c) Research involving the use of educational tests (cognitive, diagnostic, aptitude achievement), survey procedures, interview procedures, …that is not exempt if the human subjects are elected or appointed…or if these sources are publicly available…<br><br>d) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study…public benefit or service programs…</td></tr>
<tr><td colspan="2">Identical Exemption: Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe…</td></tr>
<tr><td>56.105 Waiver of IRB Requirement<br><br>On the application of a sponsor or sponsor-investigator, the FDA may waive any of the requirements contained in these regulations, including the requirement for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.</td><td>No comparable provision.</td></tr>
<tr><td colspan="2">56.107 and 46.107 IRB Membership requirements are identical.</td></tr>
<tr><td colspan="2">56.108 and 46.108 "IRB functions and operations" are closely aligned except that 56.108 requires reporting to the FDA; 46.108 requires reporting to the department or agency head.</td></tr>
<tr><td colspan="2">56.109 and 46.109 "IRB review of research" are virtually identical with the following exceptions:<br><br>▪ 46.109 (c) refers to the criteria in .117 for waiving the requirement for a signed consent form—.117 (c)(1) is not included in FDA's regulations because FDA does not regulate research in which "the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality."<br>▪ 56.109 (c) and (e) contain additional language related to FDA's emergency research rule; HHS published identical criteria for emergency research in a Secretarial announcement of waiver of the applicability of 45 CFR 46, 10/2/96.</td></tr>
</table>

**Appendix 7, Continued: A Comparison of Human Subject Protection Regulations at the U.S. Food and Drug Administration ("FDA") and the U.S. Department of Health and Human Services ("HHS")**

<table>
<tr><th>FDA</th><th>HHS</th></tr>
<tr><td colspan="2">56.110 and 46.110 "Expedited Review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research" are virtually identical, except:<br><br>▪ 56.110 refers to the FDA and 46.100 refers to the Secretary, HHS, or the department or agency head<br>▪ 56.100 (d) states "The FDA may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedures when necessary to protect the rights or welfare of subjects." 46.100 (d) states that "The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedures."</td></tr>
<tr><td colspan="2">56.111 and 46.111 "Criteria for IRB approval of research" are virtually identical except 56.111 contains references to sections in part 50 and 46.111 contains references to sections in part 46.</td></tr>
<tr><td colspan="2">56.112 and 46.112 "Review by institution" are identical.</td></tr>
<tr><td colspan="2">56.113 and 46.113 "Suspension or termination of IRB approval of research" are virtually identical except 56.113 refers to FDA and 46.113 refers to the department or agency head.</td></tr>
<tr><td>56.114 Cooperative research<br><br>In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.</td><td>46.114 Cooperative Research<br><br>Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.</td></tr>
<tr><td colspan="2">56.115 and 46.115 "IRB Records" are virtually identical except<br><br>▪ The list of IRB members by 56.115(a)(5) is cross-referenced in 46.115(a)(5) to 46.103(b)(3)<br>▪ 56.115(b) refers to FDA rather than the department or agency<br>▪ 56.115(c) states that "The FDA may refuse to consider a clinical investigation…if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section." Part 46 does not contain a comparable requirement.</td></tr>
</table>

**Appendix 7, Continued: A Comparison of Human Subject Protection Regulations at the U.S. Food and Drug Administration ("FDA") and the U.S. Department of Health and Human Services ("HHS")**

| FDA | HHS |
|---|---|
| *56.120 Lesser administrative actions*<br><br>The agency may:<br>1) Withhold approval of new studies; 2) Direct that no new subjects be added to ongoing studies;<br>3) Terminate ongoing studies when doing so would not endanger the subjects; or 4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.<br><br>The parent institution is presumed to be responsible for the operation of an IRB, and the FDA will ordinarily direct any administrative action against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, FDA may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB. | *46.123 Early termination of research support; Evaluation of applications and proposals*<br><br>1) The department or agency head may require that…support for any project be terminated or suspended…when the department or agency head finds an institution has materially failed to comply with the terms of this policy.<br><br>2) In making decisions about supporting or approving applications or proposals…the department or agency head may take into account…factors such as whether the applicant has been subject to a termination or suspension under…this section and whether the applicant or the person or persons who would direct or has directed the scientific and technical aspects of an activity has, in the judgment of the department…materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation). |
| *56.121 Disqualification of an IRB or an institution*<br><br>…The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:<br><br>1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part; and<br><br>2) The noncompliance adversely affects the rights and welfare of the human subjects in a clinical investigation… | *46.120 Evaluation and disposition of application and proposals for research to be conducted or supported by a federal Department or Agency*<br><br>The department or agency head will evaluate all applications and proposals involving human subjects… This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.<br><br>*46.122 Use of Federal funds*<br><br>Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied. |

**Appendix 7, Continued: A Comparison of Human Subject Protection Regulations at the U.S. Food and Drug Administration ("FDA") and the U.S. Department of Health and Human Services ("HHS")**

| FDA | HHS |
|---|---|
| *56.122 Public disclosure of information regarding revocation*<br><br>A determination that the FDA has disqualified an institution and the administrative record regarding that determination can be disclosed to the public under part 20.<br><br>*56.123 Reinstatement of an IRB or an institution*<br><br>An IRB or an institution may be reinstated if the Commissioner determines…that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part… | *No comparable provisions.* |
| *56.124 Actions alternative or additional to disqualification*<br><br>Disqualification of an IRB…is independent of…other proceedings or action authorized by the Act. The FDA may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of or after disqualification. The agency may also refer pertinent matters to another federal, State, or local government agency for any action that the agency determines to be appropriate. | *46.124 Conditions*<br><br>With respect to any research project…the department…head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects. |
| *50.20 and 46.116 General requirements for informed consent are virtually identical.* | |
| *50.25 and 46.116(a) Elements of informed consent are virtually identical except:*<br><br>▪ 50.25(a)(5) requires the confidentiality statement to note "the possibility that the FDA may inspect the records."<br>▪ 46.116(c) and (d) state the conditions under which the IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent [the conditions could not apply in FDA regulated research]. | |
| *50.27 and 46.117 Documentation of informed consent are virtually identical except:*<br><br>▪ 46.117(c)(1) is not included in FDA's comparative section contained in 56.109(c). 46.117(c)(1) allows the IRB to waive the requirement for the investigator to obtain a signed consent form if it finds that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. | |

**Appendix 7, Continued: A Comparison of Human Subject Protection Regulations at the U.S. Food and Drug Administration ("FDA") and the U.S. Department of Health and Human Services ("HHS")**

| FDA | HHS |
|---|---|
| *50.23(a)-(c) Exception from general requirements*<br><br>Describes an exception from the general requirements for obtaining informed consent in circumstances that are life-threatening; informed consent cannot be obtained from the subject; time is not sufficient to obtain consent from the subject's legal representative; and there is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject. | *No comparable provisions.* |
| *50.23(d) Waiver of informed consent for military personnel*<br><br>Describes the criteria and standards that the President is to apply in making a determination that informed consent is not feasible or is contrary to the best interests of the individual in military exigencies in accordance with the Strom Thurmond Defense Authorization Act for FY 1999. | *No comparable provision.* |

## Appendix 8: Basic Ethical Requirements

1) *Collaborative Partnership*

Must involve the community in which it occurs. This requires: community participation in planning, conducting and overseeing research, and integrating research results into the health system. An ethical study should avoid supplanting existing health care services and aim to share its research findings with the community. Mechanisms to achieve collaborative partnership can be achieved by: community advisory boards, patient advocates on scientific advisory boards, and advocates for funding of research.

2) *Social Value*

Must lead to improvements in health or advancement in generalizable knowledge. Must consider how the research will improve the health of: participants in the research, community in which research is conducted, and larger global society. Valueless research includes non-generalizable studies, "me too" studies, and non-disseminated research.

3) *Scientific Validity*

Must be conducted in a methodologically rigorous manner that is practically feasible. To be ethical research must produce reliable and valid data that can be interpreted. Invalid research includes underpowered studies, studies with biased endpoints, instruments, or statistical tests, and studies that cannot enroll sufficient subjects.

4) *Fair Subject Selection*

Must not select study population from only rich, politically powerful, or otherwise well-connected people for "promising research" studies. The scientific objectives of the study—not vulnerability or privilege—should guide inclusion criteria and targeted populations. Lowering risk and enhancing generalizability can then be considered. Fair subject selection-convenient groups should not be selected. Groups cannot be excluded without scientific reasons. Higher risk is a reason to exclude certain groups.

5) *Favorable Risk-Benefit Ratio*

Must be conducted in a manner consistent with the standards of clinical practice. Four step evaluation:
(1) Risks identified, assessed, and minimized. Risks must include: physical (death, disability, infection), psychological (depression and anxiety), social (discrimination), and economic (job loss). Evaluate the likelihood of harm and magnitude of harm. Identify mechanisms to minimize risks: additional diagnostic tests and hospitalization. (2) Potential benefits to individual participants enhanced. Consider physical, psychological, social, and economic benefits from added health services or payment that are not necessary to the research goals. (3) If potential benefits to the individual outweigh risks to the individual, then proceed.
(4) If risks outweigh benefits to the individual, then evaluate risks against social benefit of knowledge gained.

6) *Independent review*

Must have independent review, because investigators have multiple legitimate interests and could thereby have potential conflicts of interest. Independent review of the research minimizes these conflicts. Independent review also helps assure society it will not benefit from abuse of subjects.

## Appendix 8, Continued: Basic Ethical Requirements

*7) Informed Consent*

Must include informed consent, which should be a continuing process that empowers the participant to understand the benefits and risks of the clinical trials. Informed consent ensures individuals decide whether they enroll in research and whether research fits with their own values, interests, and goals. For those who cannot consent—such as children and mentally impaired—there must be special procedures to ensure research fits with their interests. The four elements of informed consent are: (1) Competence of the participant; (2) Disclosure of information to the participant; (3) Ability of the participant to understand or comprehend the informed consent disclosures; and (4) Voluntariness of the participant's decision. The federal regulations require eight elements in each informed consent form: (1) Purpose and duration of participation; (2) Risks; (3) Alternatives; (4) Benefits; (5) Confidentiality; (6) Compensation for injuries; (7) Person to contact for answers to questions; and (8) Voluntariness and right to withdraw. Even if a participant provides informed consent, she can terminate her participation in the trial at any time.

*8) Respect for human subjects*

Must: (1) Protect confidentiality; (2) Permit withdrawal; (3) Provide new information; (4) Monitor welfare; and (5) Inform them of what was learned from the research.

**Appendix 9**: **Whistleblower Protections for Drug Industry Related Employees**

(a) IN GENERAL. – Any person or party subject to the provisions of this Act, or any manufacturer, supplier, distributor, retailer or wholesaler of food, drugs, or devices, as those terms are defined in section 321 of title 21, a group purchasing organization ("GPO"), a contract research organization ("CRO"), an Institutional Review Board ("IRB") or any contractor or subcontractor thereof, a State or local government agency, a contractor or subcontractor of the Food and Drug Administration ("FDA"), or an officer or employee of any such entity, may not discharge, demote, suspend, reprimand, threaten, or in any other way discriminate against an employee if such discrimination is due, in whole or in part, to the employee's lawful, good faith act done, or perceived by the employer to have been done or about to be done, including within the ordinary course of the employee's job duties -

(1) to provide information, directly cause information to be provided, or otherwise directly assist in any investigation regarding any conduct which the employee reasonably believes constitutes a violation of any federal law, rule, or regulation relating to this Act, or gross fraud, waste, or abuse of federal grants or other public funds intended to be used for food, device or drug research, approval or safety, including information concerning any effort to compromise the validity or accuracy of federally-funded research or analysis related to food, device or drug research, approval or safety or any attempt to censor, distort or suppress any scientific an/or technical research, analysis, opinion or recommendation related to food, device or drug research, approval or safety, if the information or assistance is provided to or an investigation stemming from the provided information is conducted by -

(A) a federal, State, or local regulatory or law enforcement agency (including an office of the Inspector General under the Inspector General Act of 1978 (5 U.S.C. App.; Public Law 95–452);

(B) any Member of Congress, any committee of Congress, or the Government Accountability Office; or

(C) a person with supervisory authority over the employee or such other person who has the authority to investigate, discover, or terminate the misconduct;

(2) to refuse to violate or assist in the violation of any federal law, rule, or regulation relating to this Act or to food, device or drug research, approval or safety;

(3) to file a complaint, or directly cause to be brought a proceeding related to the enforcement of this Act, or to testify in such a proceeding;

(4) to furnish information to or to cooperate with an investigation by the Food and Drug Administration, the Secretary of Health and Human Services, the Secretary of Agriculture, or any federal, State, or local regulatory or law enforcement agency as to the facts relating to any federal law, rule, or regulation relating to food or drug research, approval, safety or security.

(b) ENFORCEMENT ACTION. -

(1) IN GENERAL. - An employee who alleges discharge, discipline, or other discrimination in violation of subsection (a) of this section, may seek relief in accordance with the provisions of this section, with any petition or other request for relief under this section to be initiated by filing a complaint with the Secretary of Labor.

(2) PROCEDURE. -

(A) IN GENERAL. - Any action under paragraph (1) shall be governed under the rules and procedures set forth in section 42121(b) of title 49, United States Code, including:

(i) BURDENS OF PROOF. - Any action brought under this subsection shall be governed by the legal burdens of proof set forth in section 42121(b) of title 49.

(ii) STATUTE OF LIMITATIONS.—An action under paragraph (1) shall be commenced not later than 1 year after the date on which the alleged violation of subsection (a) of this section occurs.

(iii) CIVIL ACTIONS TO ENFORCE.—If a person fails to comply with an order issued by the Secretary of Labor pursuant to the procedures in section 42121(b) of title 49, the Secretary of Labor may bring a civil action to enforce the order in the district court of the United States for the judicial district in which the violation occurred, as set forth in 42121.

(B) EXCEPTION. - Notification made under section 42121(b)(1) of title 49 shall be made to the person named in the complaint and the person's employer.

(3) DE NOVO REVIEW. - With respect to a complaint under paragraph (1), if the Secretary of Labor issues a decision denying relief in whole or in part, or has not issued a final decision within 210 days after the filing of the complaint, and if the delay is not due to the bad faith of the employee, the employee may bring an original action at law or equity for de novo review in the appropriate district court of the United States, which shall have jurisdiction over such an action without regard to the amount in controversy, and which action shall, at the request of either party to such action, be tried by the court with a jury.

(4) APPEALS. - Any person adversely affected or aggrieved by an order issued pursuant to the procedures in section 42121(b) of Title 49, may obtain review of the order in the United States court of appeals for the circuit in which the violation, with respect to which the order was issued, allegedly occurred or the circuit in which the complainant resided on the date of such violation. The petition for review must be filed not later than 60 days after the date of the issuance of the final order of the Secretary of Labor. The review shall conform to chapter 7 of title 5. The commencement of proceedings under this paragraph shall not, unless ordered by the court, operate as a stay of the order.

(c) REMEDIES. -

(1) IN GENERAL. - An employee prevailing in any action under subsection (b) shall be entitled to all relief necessary to make the employee whole.

(2) DAMAGES. - Relief in an action under subsection (b) (including an action described in subsection (b)(3)) shall include -

(A) reinstatement with the same seniority status that the employee would have had, but for the discrimination;

(B) any back pay, with interest; and

(C) compensatory damages, including compensation for any special damages sustained as a result of the discrimination, including litigation costs, expert witness fees, and reasonable attorney fees.

(3) POSSIBLE RELIEF. - Relief in any action under subsection (b) may include punitive damages in an amount not to exceed $250,000.

(e) NO PREEMPTION. - Nothing in this section preempts or diminishes any other safeguards against discrimination, demotion, discharge, suspension, threats, harassment, reprimand, retaliation, or any other manner of discrimination provided by federal or State law.

(f) RIGHTS RETAINED BY EMPLOYEE. - Nothing in this section shall be deemed to diminish the rights, privileges, or remedies of any employee under any federal or State law or under any collective bargaining agreement. The rights and remedies in this section may not be waived by any agreement, policy, form, or condition of employment.

## Appendix 10: Regulatory Requirements for Informed Consent

**46 C.F.R. § 46.116 General Requirements for Informed Consent**

…no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

a) Basic elements of informed consent

1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2) A description of any reasonably foreseeable risks or discomforts to the subject;
3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained;
7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
   A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

# ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome
ATA: Alien Tort Act
CFR: Code of Federal Register
CIOMS: The Council of International Organization of Medical Science
CIRB: Central Institutional Review Board
COX-2: A drug that targets specific enzymes (COX-2s) that produce pain
CPA: Cooperative Project Assurance
CRO: Contract Research Organization
D: Democrat
FCA: False Claims Act
FDA: The United States Department of Health and Human Services Food and Drug Administration
FDCA: Federal Food, Drug, and Cosmetic Act
FWA: Federalwide Assurance
GAP: The Government Accountability Project
GCP: Good Clinical Practices
HHS: The United States Department of Health and Human Services
HIPAA: The Health Insurance Portability and Accountability Act
HIV: Human Immunodeficiency Virus
HMO: Health Maintenance Organization
ICH: International Conference on Harmonisation
ICMJE: International Committee of Medical Journal Editors
IRB: Institutional Review Board
ISRCTN: International Standard Randomized Controlled Trial Number
JCAH: Joint Commission on the Accreditation of Hospitals
JCAHO: Joint Commission of the Accreditation of the Health Care Organization
MPA: Multiple Project Assurance
MSPB: Merit Systems Protection Board
NIH: The United States Department of Health and Human Services National Institute of Health
OHRP: The United States Department of Health and Human Services Office of Human Research Protections
OIG: The United States Department of Health and Human Services Office of Inspector General
ORI: The United States Department of Health and Human Services Office of Research Integrity
OSI: The United States Department of Health and Human Services Office of Scientific Integrity
PPD: Pharmaceutical Product Development, Incorporated
PhRMA: The Pharmaceutical Research and Manufacturers of America
PHS: The United States Department of Health and Human Services Public Health Service
P.L.: Public Law (United States)
P&G: Proctor & Gamble
R: Republican
REB: Regional Ethics Boards
REC: The United Kingdom Research Ethics Committee
SPA: Singe Project Assurance
SOX: Sarbanes-Oxley Act
U.S.: United States of America
WHO: The World Health Organization
WPA: Whistleblower Protection Act

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Under the three-part test used by the Fourth, Fifth, Sixth, Seventh, and Ninth Circuits, the plaintiff must prove that: (1) the employee was engaged in conduct protected under the FCA; (2) the employer knew that the employee was engaging in such conduct; and (3) the employer discriminated against the employee because of the protected conduct. *Brandon v. Anesthesia & Pain Management Associates, Ltd.*, 277 F.3d 936, 944 (7th Cir. 2002); *Eberhardt v. Integrated Design & Const., Inc.*, 167 F.3d 861, 866, 42 Fed. R. Serv. 3d 1311 (4th Cir. 1999); *U.S. ex rel. Hopper v. Anton*, 91 F.3d 1261, 1269, 111 Ed. Law Rep. 676 (9th Cir. 1996); *Kaminski v. Teledyne Industries, Inc.*, 121 F.3d 708 (6th Cir. 1997); *Robertson v. Bell Helicopter Textron, Inc.*, 32 F.3d 948, 951 (5th Cir. 1994); *Gublo v. NovaCare, Inc.*, 62 F. Supp. 2d 347, 356 (D. Mass. 1999); *Mikes v. Strauss*, 889 F. Supp. 746, 752 (S.D. N.Y. 1995).

A four-part test used by the Eighth Circuit requires a showing that: (1) the plaintiff was engaged in conduct protected by the FCA; (2) the plaintiff's employer knew that the plaintiff engaged in the protected activity; (3) the employer retaliated against the plaintiff; and (4) the retaliation was motivated solely by the plaintiff's protected activity. *Wilkins v. St. Louis Housing Authority*, 314 F.3d 927, 932-3 (8th Cir. 2002); *see also Mann v. Olsten Certified Healthcare Corp.*, 49 F. Supp. 2d 1307, 1317 (M.D. Ala. 1999).
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