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CENTER FOR RESPONSIBLE SCIENCE

CITIZEN PETITION

Asking the U.S. Food and Drug Administration to Increase Protection of Human Subjects in Clinical Drug Trials

May 30, 2014

P.O. Box 443
Pacific Palisades, CA 90272
www.centerforresponsiblescience.org

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May 30, 2014

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane Room 1061
Rockville, MD 20852

The undersigned submit this petition under the relevant statutory sections of the Federal Food, Drug, and Cosmetic Act (FDCA) and/or the Public Health Service Act (PSHA) and/or any other statutory provision for which authority has been delegated to the Commissioner of the U.S. Food and Drug Administration (FDA) under 21 C.F.R. 5.10, to request that the Commissioner amend FDA regulations as described herein.

I. PRELIMINARY STATEMENT

Investigational drugs are tested in clinical trials to determine whether they should be approved for wider use in the general population.[1] Human subjects participating in clinical drug trials rely on FDA regulations to ensure that drug sponsors provide adequate information to enable the subjects to make informed decisions regarding their participation in such research. The FDA disclosure regulations designed to protect the subjects, however, are decades old and need revision.

Over the past 80 years, ethical standards have evolved reflecting the view that increased levels of protection must be afforded to human research subjects[2] and substantial data has been compiled demonstrating that most drugs tested in clinical trials ultimately prove to be either unsafe or ineffective.[3]

Under the current drug development paradigm, animal models are used as the gold standard during preclinical testing. As the

[1] U.S. Food and Drug Admin., *Inside Clinical Trials: Testing Medical Products in People*, http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143531.htm (last visited Dec. 31, 2014). (Exhibit 3)

[2] Todd W. Rice, *The Historical, Ethical, and Legal Background of Human-Subjects Research*, in 53(10) RESPIR CARE 1325 (2008). (EXHIBIT 4)

[3] U.S. Food and Drug Admin., *Innovation or Stagnation; Challenge and Opportunity on the Critical Path to New Medical Products* 8 (2004). (Exhibit 5)

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result of inter-species differences in drug pharmacodynamics and pharmacokinetics,[4] however, it has been well established that data from preclinical animal testing often does not translate to expected results in human clinical trials.[5] Indeed, many drugs that appeared safe in animal studies have resulted in severe adverse reactions and deaths when given to humans.[6] A 2007 comprehensive survey found that eighteen of twenty systematic reviews published in peer-reviewed journals indicate that animal data poorly predict human clinical or toxicological outcomes.[7] Nonetheless, animal models continue to be used in drug testing.

Current FDA regulations governing drug trials require the disclosure of "a description of any reasonably foreseeable risks and discomforts to the subject."[8] Because the regulations do not further specify the content of such disclosure, however, drug sponsors are able to avoid disclosing that preclinical animal testing may not predict the degree of risk to which the trial participants will be subjected.

Studies have shown that many drug trial participants are not only ignorant of the potential risks of participating in a clinical trial, they actually believe they will receive personal benefit from the trial.[9] In fact, for the vast majority of Phase I clinical trials no therapeutic benefit is expected, and in Phase II and III clinical trials such benefits are unlikely. The misconceptions that clinical trials subjects experience reflect a deficiency in the informed consent process.

A study that explored the understanding and expectations of trial participants concerning monitoring and communication of serious adverse events during clinical trials found participants want more information disclosed.[10] If an adverse event has been causally linked to the drug in earlier clinical studies, participants expect this information to be included in the study consent form.[11] Because human clinical trials deal with the unknown, it is important to give participants all information necessary to aid in making the decision whether or not to participate in a study.[12]

At the time that the current FDA informed consent regulations were enacted, there was no reason to suspect that as many as 92% of all drugs that successfully passed preclinical animal testing could fail during human clinical trials. To balance subjects' general belief that clinical drug trials are safe and

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[4] Andrew Knight, THE COSTS AND BENEFITS OF ANIMAL EXPERIMENTS 92 (2011).

[5] *Protecting Participants in First-In-Humans Trials*, in IRB Advisor (May 2011) (Exhibit 6)

[6] Peter J.K. van Meer, *The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events is Limited*, 64 REGULATORY TOXICOLOGY AND PHARMACOLOGY 345, 346 (2012). (Exhibit 7)

[7] *Knight, supra* note 4 at 183.

[8] 21 C.F.R 50.25(a) (West 2013).

[9] Gail E. Henderson & Nancy M. P. King, *Studying Benefit in Gene Transfer Research*, in 23(2) IRB: ETHICS & HUMAN RESEARCH 13 (2001) *available at* http://kie.georgetown.edu/nrcbl/documents/irb/v23/irb23n2p13.pdf. (Exhibit 8)

[10] K.E.Flynn, et al., *Participants' Perspectives on Safety Monitoring in Clinical Trials*, in 10 CLINICAL TRIALS 556. (Exhibit 9)

[11] *Id.* (Exhibit 9)

[12] *Protecting Participants in First-In-Humans Trials, supra*, note 5 (Exhibit 6)

likely to benefit the subjects, the FDA regulations must be amended to require that investigators warn subjects regarding the risks inherent in developing drugs based on animal models. This is a material disclosure without which individuals participating in drug trials are incapable of giving true informed consent.

Clinical trials that test drugs in humans are vital to drug development. Since the current drug development paradigm relies heavily on preclinical animal data, however, human subjects participating in drug trials are subject to unquantifiable risk. Because risk exists that cannot be eliminated, FDA regulations must mandate that prospective clinical trial participants receive adequate disclosure and warnings. With this petition, the undersigned respectfully request that the FDA amend its disclosure regulations to ensure that human subjects entering into clinical drug trials receive sufficient information to enable them to provide true informed consent with regard to their participation in the trials. In light of the convincing evidence that human subjects are currently participating in clinical trials without a full understanding of attendant risks, there is no public policy justification for refusing to act.

II. PETITIONERS

The Center for Responsible Science (CRS) is a non-partisan, public interest watchdog organization founded by scientific, medical, and legal professionals. CRS is dedicated to providing an effective voice for taxpayers and consumers. CRS works to address issues involving the health, public interest, or well-being of Americans. A specific goal is to save lives by improving the drug development process through regulatory and educational changes, and collaboration with stakeholders in academia and industry. CRS has received a determination from the Internal Revenue Service that it is a tax-exempt organization described in Section 501(c)(3) of the Internal Revenue Code.

John Tessmer is a 46-year-old professional actor who lives in San Diego, California. He has been an actor for 25 years. Mr. Tessmer received his B.A. in English from Yale University and his M.F.A. in Theatre/Acting from the University of Wisconsin-Milwaukee. He has taught acting at the University of Colorado-Boulder and the Old Globe Theatre in San Diego, and has been a grant-writer for theatres and social non-profits. Mr. Tessmer has found it to be necessary in the past, and anticipates it will be necessary again in the future, to supplement his income from acting with other jobs and participation in several clinical trials. He began participating in Phase I clinical trials in 2001. He has participated in numerous clinical trials over the past 13 years. (See Declaration of John Tessmer pursuant to 28 U.S.C. § 1746 at Exhibit 1.)

Hal Garcia-Smith is a 49-year-old public health worker. He currently works for the King County Public Health (K.C.P.H.) Sexually Transmitted Disease Clinic at Harborview Medical Center, Seattle, Washington, and has held this position for five years. He has worked in the field of HIV/AIDS since 1985 and has worked as a Disease Intervention Specialist for K.C.P.H. and the University of Washington on and off for the past 15 years. Prior to that, Mr. Garcia-Smith was employed as a Certified Medical Assistant by Marcus A. Conant M.D., in his dermatology and HIV clinics at the University of California, San Francisco, where he helped recruit subjects and assisted in conducting a number of studies in the early years of the HIV/AIDS pandemic.

In 1998 Mr. Garcia-Smith learned of a Phase III AIDSVAX B/B clinical trial to determine the safety and efficacy of AIDSVAX in preventing HIV infection in people at high risk of infection. The trial was sponsored by VaxGen, Inc. and the National Institute of Allergy and Infectious Diseases (NIDA). The VaxGen trial was the first trial testing the efficacy of an HIV vaccine. The purpose of the trial was to determine if people who received the vaccine would have a lower HIV infection rate than those who received a placebo. The 5,000+ volunteer trial participants in North America and Europe were all HIV-negative men who have sex with men (MSM), and HIV-negative women who had HIV-infected sexual partners or were part of a population at high risk for HIV infection. Mr. Garcia-Smith participated in this Phase III clinical trial. (See Declaration of Hal Garcia-Smith pursuant to 28 U.S.C. § 1746 at Exhibit 2.)

III. ACTION REQUESTED

Petitioners request that the FDA amend the regulation that governs informed consent given to clinical trial participants. 21 C.F.R. 50.25, as set forth below. Petitioners acknowledge that pursuant to 21 C.F.R. 50.25 (d), the existing FDA regulations do not "preempt any applicable Federal, State or local laws that require additional information to be disclosed for informed consent to be effective." While this permits other Federal, State and/or local agencies to impose additional disclosure requirements, it does not mandate such disclosure. For the reasons stated in this petition, the action requested is of sufficient importance that the FDA should mandate such disclosure.

Existing Regulation

21 C.F.R. 50.25 Elements of Informed Consent.

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(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 and that notes the possibility that the Food and Drug Administration may inspect the records.

(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.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Requested Amendment

Petitioners request that the FDA add the following new Sections (9) - (11) to 21 C.F.R. §50.25(a), providing a set of standard warnings in the informed consent document for every phase of clinical drug trials:

(9) The drug you will be given has been tested in animals and by other laboratory methods to determine whether it is likely to be safe and effective in humans. The decision to allow testing of this drug on humans relies heavily on the presumption that animal tests predict human response. Due to differences between animals and humans, animal tests may not predict whether a drug is safe and/or effective for use in humans.

(10) Some participants in clinical trials in which other investigative drugs were tested have died or have been seriously injured by the drug that was tested.

(11) The drug you will be given may later prove to be either unsafe for humans or ineffective in treating the condition for which it is being tested. You should not assume the drug will treat a medical condition you may have, because a determination of efficacy in an animal study does not necessarily predict efficacy in humans.

IV. FDA AUTHORITY TO TAKE REQUESTED ACTION

The FDA has authority under the FDCA to issue regulations that govern informed consent in clinical drug trials. [13] Administrative agencies are afforded great deference in their interpretation of the statutes they enforce. If Congress has explicitly left a gap for an agency to fill, the agency is expressly delegated authority to elucidate a specific provision of the statute by regulation. Although legislative regulations and actions are given controlling weight, they will be invalidated where they are arbitrary, capricious, or manifestly contrary to the statute.[14] FDA regulations allow citizens to petition the FDA to amend FDA regulations.[15]

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[13] Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. §§ 355, 371 (West 2013)

[14] Chevron U.S.A. Inc. v. Natural Resources Defense Council, 437 U.S. 837 (1984); Gore, Inc. v. Espy, 87 F.3d 767 (CA 5 Tex. 1996); Roman v. Korson, 918 F. Supp. 1108 (WD Mich. 1995); Doane v. Espy, 26 F.3d 783 (CA 7 Wis. 1994); Apex Oil Co. v. Federal Energy Administration, 443 F. Supp. 647 (D.C. Dist Col. 1977); Louisiana Pub. Serv. Comm'n v. FERC, 337 U.S. App. D.C. 312, 184 F. 3d. 892 (D.C. Cir.1999); Center for Biological Diversity v. National Highway Traffic Safety Administration, 508 F.3d 508 (CA 9 Cal. 2007); El Paseo Electric Co. v. FERC, 201 F.3d 667 (CA 5 2000); Mo. PSC v. FERC, 601 F.3d 581 (App. D.C. 2010); Mo. PSC v. FERC, 358 U.S. App. 24, 337 F.3d 1066 (D.C. Cir. 2003); N. Carolina Utlities Commission v. FERC, 310 U.S. App. 13, 42 F.3d 659 (D.C. Cir.1994); National Fuel Gas Supply Corp. v. FERC, 486 F.3d 831 (App. D.C. 2006).

[15] 21 C.F.R. §10.25 (West 2014).

V. STATEMENT OF GROUNDS

Part One below defines informed consent, describes the development of informed consent requirements for human experimentation, and outlines the current informed consent regulations that govern drug development in the United States. Part Two summarizes the evidence demonstrating that drugs tested in clinical trials often prove to be unsafe or ineffective, and concludes that informed consent regulations are inadequate to protect human subjects, because FDA regulations have not kept pace with changes in ethical standards and the ever-increasing data on deficiencies in the current drug development process. A major cause of such failures is reliance on preclinical animal models, which are poor predictors of human response. Part Three summarizes the data regarding therapeutic misconceptions by clinical trial subjects and the desire of such subjects for more information. It then analyzes the information that should be provided to human subjects prior to their consent to participate in clinical drug trials to enable them to provide true informed consent. Part Four considers analogous standards of disclosure with regard to drugs, as required by other federal regulations and common law principles. Finally, Part Five discusses why the benefits to the public of the proposed regulation amendment outweigh any potential challenges.

A. Part One: Informed Consent

(1) Background

Informed consent in clinical research is a process whereby potential research subjects are provided sufficient information about the study to decide whether they want to participate in the study.[16] Valid informed consent is key to ethical research and is required by federal regulations.[17] As a foundation of ethical medical research,[18] informed consent is intended to protect human research subjects by providing enough information for the person to understand the risks, the potential benefits, and the alternatives to the study.[19] Under recognized ethical principles discussed below, an investigator can obtain true informed consent from a research subject only after meeting adequate disclosure requirements and gaining voluntary consent from the subject to participate in the study.[20]

(2) The Development of Informed Consent Requirements

After World War II, the Nuremberg Trials were conducted in part to prosecute Nazi physicians who performed research on concentration camp prisoners.[21] While no

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[16] *Learn About Clinical Studies*, http://clinicaltrials.gov/ct2/about-studies/learn (last visited Dec. 31, 2013). (Exhibit 10)

[17] James Flory & Ezekiel Emanuel, *Interventions to Improve Research Participants' Understanding in Informed Consent for Research: A Systematic Review*, 292(13) 1593 (2004), *available at* http://jama.jamanetwork.com/article.aspx?articleid=199537. (Exhibit 11)

[18] Zulfiquar A. Bhutta, *Beyond Informed Consent*, in 82(10) Bull World Health Org. 771 (2004), *available at* http://www.scielosp.org/scielo.php?pid=S00429686200400100013&script=sci_arttext. (Exhibit 12)

[19] *Learn About Clinical Studies*, http://clinicaltrials.gov/ct2/about-studies/learn (last visited Dec. 31, 2013). (Exhibit 10)

[20] 21 C.F.R 50.20 (West 2012).

[21] Rice, *supra*, note 2 at 1326. (Exhibit 4)

regulations regarding research on human subjects existed at the time of the trials, or were passed in the years immediately following the trials, the trials laid the foundation for The Nuremberg Code.[22]

The Nuremberg Code is a set of international, ethical principles that investigators are expected to follow when conducting experiments involving human subjects. [23] However, as a set of ethical principles, the Nuremberg Code is not legally binding. [24] Under the Nuremberg Code, informed consent meant the human subject must voluntarily consent to participate in the research after learning the nature, duration, and purpose; the methods to be used in conducting the experiment; the expected inconveniences and hazards associated with the research; and the potential health or personal effects resulting from the research.[25] Despite the United States' integral role in creating the Nuremberg Code, the United States did not regulate research on human subjects until the 1970s, after decades of controversy regarding clinical research on vulnerable humans.[26]

One such controversy was the thalidomide tragedy in the 1950s. Doctors prescribed thalidomide to pregnant women without disclosing that thalidomide was an investigational drug.[27] Ultimately, as a result of using the drug, over 10,000 women from various countries gave birth to babies with deformed or missing limbs.[28] At that time, investigators were not legally required to disclose a drug's approval status and disclosing a drug's status was not standard practice.[29] Soon after, the 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act [30] added a legal requirement that investigators in the United States obtain informed consent from participants before administering an investigational drug.[31]

In 1964, the World Medical Association met in Helsinki, Finland to write and adopt a declaration describing ethical standards to guide biomedical research involving human subjects.[32] Essentially, the Declaration of Helsinki was a medical adaptation of the Nuremberg Code, which eventually became a global guide for research involving human subjects. Recognizing the concern for the individual human research subject over the interests of science and society, the

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[22] *Id.* (Exhibit 4)

[23] Rice, *supra*, note 2 at 1326. (Exhibit 4)

[24] George J. Annas, Michael A. Grodin, The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation 160 (1992).

[25] Nuernberg Military Tribunals, TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS 182 (1949), *available at* http://www.loc.gov/rr/frd/Military_Law/pdf/NT_war-criminals_Vol-II.pdf.

[26] Rice, *supra*, note 2 at 1326. (Exhibit 4)

[27] *Id.* (Exhibit 4)

[28] Rachel Hajar, *Animal Testing and Medicine*, 12 Heart Views 42 (2011). (Exhibit 13)

[29] Rice, *supra*, note 2 at 1326. (Exhibit 4)

[30] Federal Food, Drug, and Cosmetic Act Amendments, Pub. L. No. 87-781, 76 Stat. 1552 (1962).

[31] Joel Sparks, *Timeline of Laws Related to Protection of Human Subjects* (Jun 2002), http://history.nih.gov/about/timelines_laws_human.html.

[32] Rice, *supra*, note 2 at 1326. (Exhibit 4)

Declaration of Helsinki incorporated the principle of informed consent.[33] Under the Declaration of Helsinki, informed consent meant that each human research subject must be adequately informed of the aims of the research; the methods used to conduct the research; the anticipated benefits and potential hazards; the sources of funding and possible conflicts of interest; and the right to withdraw from the study. [34] Like the Nuremberg Code, the Declaration of Helsinki was a set of ethical guidelines that was not legally binding.[35]

Despite the existence of the Nuremberg Code, the Declaration of Helsinki, and the Kefauver-Harris Amendment, deplorable research misrepresentation continued. A striking example was the United States government-funded Tuskegee syphilis study that lasted from 1932 to 1972.[36] The study aimed to determine the natural history of syphilis. [37] Investigators did not inform subjects of the true nature of the study and in fact did not treat the subjects once medication was developed. [38] Once exposed, public outrage ensued which led to congressional hearings regarding research on human subjects.[39]

In 1974, Congress passed the National Research Act (NRA), which established the Office for the Protection of Research Risks under the National Institutes of Health and established the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research (NC).[40] In 1978, the NC issued the Belmont Report, which outlined minimum requirements for ethical human-subjects research. Under the Belmont Report, human research subjects must enter into research voluntarily with adequate information including the purpose of the research; the risks and anticipated benefits; the alternative procedures; and the right to withdraw from the research.[41] The NC also established the Institutional Review Board (IRB) process, which required IRB approval of most research that included human subjects. [42] Ultimately, responsibility for overseeing compliance with human research subjects was placed in the Department of Health and Human Services (DHHS) under the Office for Human Research Protections (OHRP).[43]

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[33] Rice, *supra*, note 2 at 1326. (Exhibit 4)

[34] World Medical Association, *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, http://www.wma.net/en/30publications/10policies/b3/ (last visited Dec. 31, 2013). (Exhibit 14)

[35] Annas, *supra*, note 24

[36] Centers for Disease Control and Prevention, *U.S. Public Health Service Syphilis Study at Tuskegee*, http://www.cdc.gov/tuskegee/timeline.htm (last visited Dec. 31, 2013). (Exhibit 15)

[37] Rice, *supra*, note 2 at 325-1327. (Exhibit 4)

[38] Rice, *supra*, note 2 at 1326. (Exhibit 4)

[39] *Id. at 1328*. (Exhibit 4)

[40] Pub. L. No. 93-348, 1974 HR 7724 (codified as 42 U.S.C. § 289 (2005).

[41] U.S. Dept. of Health and Human Services, *The Belmont Report*, (Apr. 18, 1979), http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html (Exhibit 16)

[42] Rice, *supra*, note 2 at 1329. (Exhibit 4)

[43] *Id.* (Exhibit 4)

Based on the Belmont Report, the OHRP revised the Code of Federal Regulations for the Protection of Human Subjects, which the Secretary of DHHS signed in 1981.[44] The revised code became known as The Common Rule. The Common Rule aimed to eliminate confusion and promote uniformity among the federal departments and agencies that conduct, support, or regulate research involving human subjects.[45] In 1991, multiple federal agencies involved in human subjects research adopted the Common Rule.[46] The FDA did not adopt the policy in its entirety,[47] but adopted certain provisions of the Common Rule into FDA regulations meant to protect human research subjects in clinical trials.[48] Since its inception, the Common Rule has been continually revised in response to scientific advances.[49] The content of the current FDA regulation, 21 C.F.R. 50.25 "Elements of Informed Consent", is detailed in Section III above.

(3) Current Informed Consent Regulations for Drug Development in the United States

DHHS regulates research involving human subjects conducted or supported by DHHS.[50] The FDA regulates research involving human subjects for drug development and medical devices.[51] When research involving human subjects on products regulated by the FDA is funded by the DHHS, informed consent regulation requirements of both organizations must be met.[52]

In addition to federal informed consent requirements, the Institutional Review Board (IRB) that oversees the research may require that additional information be given to subjects if the IRB determines that the information will meaningfully add to the protection of the rights and welfare of subjects.[53] Further, other federal, state, and local regulations can require disclosure of additional information beyond DHHS and FDA requirements.[54]

B. Part Two: Drug Testing in Clinical Trials

(1) Overview of Drug Development and Clinical Trials

The Center for Drug Evaluation and Research (CDER) is the division of the FDA charged with ensuring that drugs are both

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[44] *Id.* (Exhibit 4)

[45] Institutional Review Board Guidebook, http://www.hhs.gov/ohrp/archive/irb/irb_chapter2.htm#d7 (last visited Dec. 31, 2013).

[46] *Id.*

[47] *Id.*

[48] Rice, *supra*, note 2 at 1329. (Exhibit 4)

[49] *Id.*

[50] Institutional Review Board Guidebook, *supra*, note 45.

[51] *Id.*

[52] *Id.* (Because DHHS disclosure regulations are so similar to the FDA regulations, application of the combined regulations does not result in a higher disclosure standard.)

[53] 21 C.F.R. 56.109(b) (West 2013).

[54] 21 C.F.R. 50.25(d) (West 2013).

safe and effective for their intended use.[55] CDER will approve a drug only after a sponsor has demonstrated the drug is safe and effective.[56] In order to meet these criteria and move scientific discoveries into practice,[57] drug sponsors follow a step-by-step testing process, which includes testing the drug in humans[58] to determine if the benefits of the drug outweigh the risks.[59]

Drug development starts with the discovery phase where compounds are designed and synthesized.[60] After a compound is selected during the discovery phase, preclinical testing begins, which includes testing compounds in vitro in cultured cells and in vivo in laboratory animals.[61] If investigators decide the preclinical data indicate the drug is potentially beneficial and safe for use in humans, the drug sponsor submits an investigational new drug application (IND) to the FDA.[62] If the FDA is satisfied that the data submitted in the IND show the drug is reasonably safe for testing in humans and a local IRB approves the clinical trial protocols, investigators can begin human clinical trials.[63]

Investigators conduct three phases of clinical trials.[64] Phase I trials mark the introduction of an investigational new drug into human subjects.[65] Phase I trials generally consist of 20-80 healthy volunteers, and attempt to determine the drug's proper dosing, pharmacokinetics, and side effects.[66] If a drug does not produce unacceptable toxicity

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[55] About the Center for Drug Evaluation and Research, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm (last visited Dec. 31, 2013). (Exhibit 17)

[56] The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm (last visited Dec. 31, 2013). (Exhibit 18)

[57] Barbara A. Koenig, *Fixing Research Subjects Protection in the United States: Moving Beyond Consent*, in 88(5) MAYO CLINIC PROCEEDINGS 428 (2013). (Exhibit 19)

[58] *Id.* (Exhibit 19)

[59] Food and Drug Admin., *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making*, http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm329758.pdf (last visited Dec. 31, 2013). (Exhibit 20)

[60] J. Fred Pritchard, *Making Better Drugs: Decision Gates in Non-Clinical Drug Development*, in 2 NATURE REVIEWS DRUG DISCOVERY 542, 542 (2003). (Exhibit 21)

[61] Michael Dickson, *Key Factors in the Rising Cost of New Discovery and Development*, 3 NATURE REVIEWS DRUG DISCOVERY 417, 418 (2004). (Exhibit 22)

[62] Food and Drug Admin., *Investigational New Drug Application*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm (last visited Dec. 31, 2013). (Exhibit 23)

[63] Food and Drug Admin., *The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm (last visited Dec. 31, 2013). (Exhibit 24)

[64] Food and Drug Admin., *Inside Clinical Trials: Testing Medical Products in People* http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143531.htm (last visited Dec. 31, 2013). (Exhibit 25)

[65] *Guidance for Industry: CGMP for Phase I Investigational Drugs*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070273.pdf (last visited Dec. 31, 2013). (Exhibit 26)

[66] *Inside Clinical Trials*, *supra*, note 64 (Exhibit 25)

in the Phase I trial, Phase II trials follow.[67] During Phase II trials, investigators test a few dozen to 300 patients who have the relevant medical condition to determine whether the drug is effective for the condition it is intended to treat.[68] If Phase II clinical trials show evidence of efficacy at drug doses that do not cause significant toxicity, investigators proceed to Phase III testing. Phase III clinical trials seek to examine safety and efficacy in several hundred to several thousand subjects.[69] Ultimately, the FDA analyzes the human data as part of a New Drug Application and determines whether to approve the drug for use in the general population.[70]

(2) Informed Consent Regulations are Inadequate to Protect Human Subjects Participating in Clinical Trials

The existing informed consent regulations governing drug development are inadequate in light of two significant changes that have occurred since the regulations were enacted: (1) the science of drug development has progressed; and (2) ethical standards have evolved.

a. Preclinical Animal Models Are Generally Poor Predictors of Human Response

Investigators accept animal testing as a precursor to human testing because current regulations require it and investigators are trained to believe that animal testing is the gold standard. Compelling evidence now exists, however, which demonstrates that animal models generally are poor predictors of human response.[71]

(i) Animal Models Have Never Been Validated

To prove that a testing method accurately predicts a specific effect in humans, the method needs to be validated.[72] Animal models are used in preclinical human drug testing despite the fact they have never been scientifically validated for the purpose of testing human drugs.[73] Rather, animal models are accepted on "good-faith that these studies are the best approach for protecting humans"[74] with no proof that any particular animal model actually predicts human response.

One reason animal models have never been validated is that the validation concept did not exist at the time when animal models were developed. Nevertheless, predictive

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[67] *The FDA's Drug Review Process, supra,* note 63 (Exhibit 24)

[68] *Id.* (Exhibit 24)

[69] *Id.* (Exhibit 24)

[70] *Inside Clinical Trials, supra,* note 64. (Exhibit 25)

[71] Pablo Perel, et al, *Comparison of Treatment Effects Between Animal Experiments and Clinical Trials: Systematic Review, in* 334 BMJ 197(2007). (Exhibit 27)

[72] Alison Abbott, *Animal Testing: More than a Cosmetic Change*, 438 NATURE 144, (2005). (Exhibit 28)

[73] Orsolya E. Varga, et al., *Validating Animal Models for Preclinical Research: A Scientific and Ethical Discussion,* in 38(3) ALT. LAB. ANIMAL 245 (2010). (Exhibit 29)

[74] T. Tralau, et al., *Wind of Change Challenges Toxicological Regulators,* in 120(11) ENVTL. HEALTH PERSPECTIVE 1489 (2012). (EXHIBIT 30)

validity is important in drug development because it calculates the reliability and relevance of the testing method.[75] Scientists assess reliability by calculating intra-laboratory repeatability and inter-laboratory reproducibility. [76] Relevance determines whether a model is useful for a particular purpose. [77] Animal models are used even though proof of reproducibility, repeatability, and usefulness has not been shown. Further, "systematic reviews of the human clinical or toxicological utility of animal experiments demonstrate the invalidity of such assumptions, even for animal models in use for long periods."[78]

While animal models are not held to validation standards, emerging human-based testing methods are held to extensive validation requirements. [79] One inherent problem in this system is that validation studies are based on data from the animal testing methods that have never been validated.[80] As a systematic review of animal data demonstrates, "consistent application of formal validation studies to all test models is clearly warranted, regardless of their animal, non-animal, historical, contemporary, or possible future status [...]."[81]

(ii) Data from Animal Models Does Not Extrapolate to Humans

Scientists test their ideas by comparing theoretical predictions to actual events.[82] A method can be considered predictive if it yields the correct answer often enough. By contrast, a method that does not often yield the correct answer cannot be considered predictive.

The purpose of preclinical animal testing is to predict human outcomes. Investigators extrapolate the animal data to predict what is likely to occur when humans receive the drug, and can judge the appropriateness of extrapolation by the models' capacity to explain and predict the observed effects in the target species. [83] Systematic reviews of research data allow scientists to compare animal and human data to confirm or falsify the animal-based hypothesis.[84]

The premise that animal models are generally predictive of human outcomes is the basis for their widespread use in safety and efficacy

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[75] Orsolya, *supra,* note 73. (Exhibit 29)

[76] *Id.* (Exhibit 29)

[77] *Id.* (Exhibit 29)

[78] Andrew Knight, *Systematic Reviews of Animal Experiments Demonstrate Poor Human Utility,* in 14 AATEX 125 (2007) available at http://altweb.jhsph.edu/wc6/paper125.pdf (last visited Jan, 28 2014). (Exhibit 31)

[79] *Id.* (Exhibit 31)

[80] Tralau, *supra,* note 74. (Exhibit 30)

[81] Andrew Knight, *Systematic Reviews of Animal Experiments Demonstrate Poor Human Utility,* in 14 AATEX 125 (2007) available at http://altweb.jhsph.edu/wc6/paper125.pdf (last visited Jan, 28 2014). (Exhibit 31) For clarification purposes, CRS is not requesting validation of all preclinical testing methods as part of this Informed Consent Petition. CRS acknowledges that such a request would exceed the scope of this Informed Consent Petition.

[82] Daniel Sarewitz & Roger Pielke Jr., *Prediction in Science and Policy*, 21 TECHNOLOGY IN SOCIETY 121, 123 (1999). (Exhibit 32)

[83] Jann Hau, et al., *Animal Models*, 2 HANDBOOK OF LABORATORY ANIMAL SCIENCE 6, 8 (2003). (Exhibit 33)

[84] Knight, *supra*, note 4 at 42.

testing before testing in clinical trials.[85] However, data from animal models have been shown to be problematic in screening drugs for humans, because the models often cannot be transposed to human clinical testing.[86] Inter-species differences in drug pharmacodynamics and pharmacokinetics result in extrapolation issues.[87] As a result, data from preclinical animal testing often does not translate to expected results in human clinical trials.[88]

Indeed, the inability to assess and predict drug safety in preclinical studies has led to repeated failures during clinical development,[89] and "[t]he vast majority of drugs that enter into human trials never survive to licensure."[90] As mentioned previously, a 2007 systematic survey found that eighteen of twenty reviews published in peer-reviewed journals indicate animals are insufficiently predictive of human clinical or toxicological outcomes.[91] Likewise, a 2013 study, showed limited concordance between treatment effects in animal experiments and subsequent clinical trials in humans.[92] In studying adverse reactions, another study found that only 46% of visible human adverse reactions occurred in animals, making the predictive likelihood of adverse reactions akin to the results of a coin toss.[93]

To further highlight the extrapolation disparity, the FDA has issued numerous statements acknowledging that reliance on animal models is inadequate and results in high clinical failure rates.[94] For example, a 2006 FDA news release stated: "Currently, nine out of ten experimental drugs fail in clinical studies because we cannot accurately

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[85] Andrew Knight, *Systematic Reviews of Animal Experiments Demonstrate Poor Human Utility*, in 14 AATEX 125 (2007) available at http://altweb.jhsph.edu/wc6/paper125.pdf (last visited Jan, 28 2014). (Exhibit 31)

[86] Michael Spedding, et al., *A Pathophysiological Paradigm for the Therapy of Psychiatric Disease*, 4 NATURE REVIEWS DRUG DISCOVERY 467, 468 (2005). (Exhibit 34)

[87] Knight, *supra*, note 4 at 92.

[88] *Protecting Participants in First-In-Humans Trials*, in IRB Advisor (May 2011) (Exhibit 6)

[89] U.S. Food and Drug Admin., *supra*, note 3 at 17.

[90] *Protecting Participants in First-In-Humans Trials*, in IRB Advisor (May 1, 2011), (Exhibit 6) http://www.highbeam.com/doc/1G1-256460684.html.

[91] Knight, *supra*, note 4 at 183.

[92] Konstantinos K. Tsilidis, et al., *Evaluation of Excess Significance Bias in Animal Studies of Neurological Diseases*, in PLOS BIOLOGY (2013), available at http://www.camarades.info/index_files/journal.pbio.1001609.pdf (last visited Jan. 31, 2014). (Exhibit 35)

[93] J.T. Litchfield, *Evaluation of the Safety of New Drugs by Means of Tests in Animals, in* 3(5) PHARMACOLOGY AND THERAPEUTICS 665 (1962)

[94] "Consider just one stark statistic: Today, nine out of 10 compounds developed in the lab fail in human studies. They fail, in large part because they behave differently in people than they did in animal or laboratory tests." Prepared Statement for FDA Teleconference: Steps to Advance the Earliest Phases of Clinical Research in the Development of Innovative Medical Treatments (January 12, 2006) (on file with FDA); "The main causes of failures before human testing or early in clinical trials dramatically escalates costs. For example, for a pharmaceutical, a 10-percent improvement in predicting failures before clinical trials could save $100 million in development costs per drug." U.S. Food and Drug Admin., *supra*, at 8.

predict how they will behave in people based on laboratory and animal studies."[95]

Current regulations require that drug companies notify the FDA of post-marketing adverse drug reactions.[96] A post-marketing serious adverse reaction encompasses: death; a life-threatening adverse drug experience; an inpatient hospitalization or prolongation of existing hospitalization; a significant disability or incapacity; a congenital anomaly or birth defect; or important medical event that requires medical or surgical intervention to prevent one of the previous listed outcomes.[97] A 2012 study looked at whether post-marketing serious adverse reactions to small molecule drugs could have been detected from animal data.[98] Animal data identified only 19% of human serious adverse reactions, leading the author to conclude that animal data are not relevant to predict serious adverse human reactions to new small molecule drugs.[99]

Many drugs that have been given to humans after the drug appeared safe in animal studies resulted in severe adverse reactions and death in people.[100] Investigators did not learn the drugs were dangerous to humans through animal testing; they learned the drugs were dangerous to humans through epidemiology, clinical observation, and autopsy.[101] Another way to consider this issue is that when the FDA authorizes the sale of drugs to the public it authorizes a human clinical experiment of unlimited size, while none of the people taking the drug even realize they are participating in an experiment.

Extrapolating data from animals to humans can also prevent or delay safe and effective medications from gaining FDA approval.[102] It is difficult to prove that animal models keep good drugs from the market because compounds are generally not developed after faring negatively in animals. However, occasionally drugs are approved for use in other countries that prove safe and effective in humans but were delayed in the United States due to results of animal testing.[103]

(iii) Trial Participants May Receive Unsafe and/or Ineffective Drugs

In 2004, as part of the Critical Path Initiative to drive innovation in drug development, the FDA reported that 92 out of 100 drugs that successfully pass preclinical animal testing subsequently fail during clinical trials when the drug is tested in humans.[104] To determine the likelihood that a human subject participating in a clinical trial will receive an

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[95] News Release, FDA, FDA Issues Advice to Make Earliest Stages of Clinical Drug Development More Efficient (Jan. 12, 2006) (on file with the FDA).

[96] Postmarketing Reporting of Adverse Drug Experiences, 21 C.F.R. §314.80 (2013), available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.80 (last visited Feb. 7, 2014).

[97] Postmarketing Reporting of Adverse Drug Experiences, 21 C.F.R. §314.80(a) (2013), available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.80 (last visited Feb. 7, 2014).

[98] van Meer, *supra*, note 6 (Exhibit 7)

[99] *Id.* (Exhibit 7)

[100] *Id.* at 61-66. (Exhibit 7)

[101] *Id.* at 66. (Exhibit 7)

[102] Christopher Anderegg, et al., A CRITICAL LOOK AT ANIMAL EXPERIMENTATION (2006). (EXHIBIT 36)

[103] van Meer, *supra* note 6 at 71. (Exhibit 7)

[104] *Innovation or Stagnation, supra*, note 3 (Exhibit 5)

unsafe drug, it is necessary to break down the failure rate between safety and efficacy. In a study spanning 1992-2002, 43% of drugs that passed preclinical animal and other testing later failed during Phase I clinical trials for safety reasons, while 36% failed for efficacy.[105] Twenty-five percent of drugs that passed Phase I testing later failed during Phase II clinical trials for safety reasons, while 37% failed for efficacy.[106] Thirty-five percent of drugs that passed Phase II testing later failed during Phase III clinical trials for safety reasons, while 53% failed for efficacy.[107]

While it would be helpful to know how many people die or experience severe adverse reactions as a result of taking drugs administered in clinical trials in the U.S., a published number does not appear to be available. However, many clinical drug trials occur overseas and some data are available from other countries. For example, data from the Drug Controller-General of India reveals that, between 2008 and 2011 alone, more than 2,000 people died in that country as a result of serious adverse events during drug trials.[108]

b. The Law Has Not Kept Pace with Changes in Societal Ethics

While research involving humans is accepted as a vital part of drug development, legal protection of human subjects involved in testing has not kept pace with changes in societal ethics.[109] As a society's ethical standards evolve, the society's laws must undergo a corresponding evolution to reflect the changing views.[110] Essentially, the law reflects a consensus statement about what society believes is ethically appropriate.[111]

For example, our societal views have evolved from accepting women as second-class citizens to accepting women as equal, and from viewing slavery as ethically acceptable to viewing slavery as unacceptable. As a result of the evolution in societal views on slavery and suppression of women, the applicable laws evolved. But the laws only changed when society began questioning the ethics of the prevailing views.

Current FDA regulation requires the disclosure of "a description of any reasonably foreseeable risks and discomforts to the subject."[112] Because the regulation does not further specify the content of such disclosure, however, drug sponsors are able to forego disclosing the fact that preclinical animal

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[105] D. Schuster, et al., *Why Drugs Fail-A Study on Side Effects in New Chemical Entities*, 11 CURRENT PHARM. DESIGN 3545 (2005). (Exhibit 37)

[106] *Id.* (Exhibit 37)

[107] *Id.* (Exhibit 37)

[108] *Shocking Secrets about Clinical Trials: 2,061 Trial Related Deaths. Yet Only 22 Were Compensated,* http://articles.mercola.com/sites/articles/archive/2012/09/03/clinical-trials-related-deaths.aspx (last visited Dec. 31, 2013). (Exhibit 38)

[109] Ethical and Policy Issues in Research Involving Human Participants, *Protecting Research Participants-A Time for Change*, http://bioethics.georgetown.edu/nbac/human/oversumm.html (last visited Dec. 31, 2013). (Exhibit 39)

[110] Charity Scott, *Why Law Pervades Medicine: An Essay on Ethics in Health Care*, in 14(1) Notre Dame Journal of Law, Ethics & Public Policy 245 (2000). (Exhibit 40)

[111] *Id.* (Exhibit 40)

[112] 21 C.F.R 50.25(a) (West 2013).

testing may not predict the degree of risk to which the trial participants will be subjected.

The fact that 92% of compounds that pass preclinical animal studies have historically failed during human clinical trials due to toxicity or lack of efficacy should be disclosed as a "reasonably foreseeable risk." When informed consent regulations were enacted, society did not have the data it now has as the result of numerous compounds having since been tested through the drug development paradigm. What the statistics demonstrate is that the preclinical drug development process does not adequately predict either human safety or efficacy. Ethical consideration of these data requires that the informed consent regulations for drug development be updated to reflect the evolution of scientific knowledge that has occurred since the current regulations were adopted.

C. Part Three: Clinical Trials Participants Do Not Understand the Risks and Want More Information

(1) Therapeutic Misconception

Many drug trial participants not only fail to understand the risks involved in the clinical trial, but actually believe they will receive personal benefit from the research. Therapeutic misconception is a widely recognized problem that occurs when "a research subject fails to appreciate the distinction between the imperatives of clinical research and of ordinary treatment."[113] Many subjects consent to participate in clinical research because they misunderstand the purpose of the research,[114] and inaccurately attribute therapeutic intent to research procedures.[115] Studies show that research subjects frequently have an unrealistic expectation of direct benefit from participating in a clinical trial,[116] and deny "disadvantages to participating in clinical research that stem from the nature of the research process itself."[117]

Appelbaum first described "therapeutic misconception" in a 1982 study that found 40% of subjects believed they would experience therapeutic benefit while participating in a clinical trial despite receiving informed consent and being told about placebo controls.[118] In 2001, the National Bioethics Advisory Commission defined therapeutic misconception as "the belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge."[119]

Despite the fact that the primary goal of clinical trials is to test investigational drugs

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[113] Charles W. Lidz & Paul S. Appelbaum, *The Therapeutic Misconception: Problems and Solutions*, in 40(9) MEDICAL CARE V-55. (Exhibit 41)

[114] *Id.* at V-55-6. (Exhibit 41)

[115] *Id.* at V-57. (Exhibit 41)

[116] Henderson, supra, note 9 (Exhibit 8)

[117] Paul S. Appelbaum, et al. *False Hopes and Best Data: Consent to Research and the Therapeutic Misconception*, 17(2) HASTINGS CENTER REPORT 20 (1987).

[118] P. S. Appelbaum et al., *The Therapeutic Misconception: Informed Consent in Psychiatric Research*, 5 INT'L. J.L. & PSYCHIATRY 319 (1982). (Exhibit 42)

[119] Gail E. Henderson, et al., *Clinical Trials and Medical Care: Defining the Therapeutic Misconception*, in 4(11) PLos Med (2007), *available at* http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.004032. (Exhibit 43)

in human subjects to develop drugs that will be beneficial to patients in the future,[120] studies continue to conclude that subjects believe they will receive therapeutic benefit from the clinical trial.[121] Psychological studies indicate that even subjects who participate in nontherapeutic Phase I trials have high expectations of benefit from their participation.[122] In fact, for the majority of Phase I clinical trials, no therapeutic benefit is possible and in Phase II and III clinical trials such benefits are unlikely.

People sometimes participate in clinical trials because they think they will receive better medical care, not because they want to participate in a study[123], or because they think their particular problem is going to be solved by the study drug.[124] Twenty-nine percent of participants in a recent cancer research study did not understand the treatment was experimental and actually believed the investigational drug was proven to best treat their type of cancer.[125] Overall, participants have very limited understanding about clinical trials and core features of clinical research, including the informed consent process and how risks are managed.[126]

Studies have shown that clinical trial participants take comfort in learning that an external safety board may monitor trials.[127] An analysis of multiple qualitative studies in the United Kingdom found that participant cooperation with medical research is contingent on participants' belief that investigators will not expose them to harm or exploitation; moreover, participants relied on regulation to enforce this.[128]

(2) Clinical Trials Participants Want More Versus Less Information

A study that explored the understanding and expectations of trial participants concerning monitoring and communication of serious adverse events during clinical trials found participants want to have more information disclosed.[129] If an adverse event has been

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[120] Lidz, *supra*, note 113 at V-59. (Exhibit 41)

[121] *See* J. Sugarman, et al., *What Patients Say About Medical Research*, 20 I.R.B. 4 (1998). (Exhibit 44); K. P. Weinfurt, et al. *Patient Expectations of Benefit From Phase I Clinical Trials: Linguistic Considerations in Diagnosing a Therapeutic Misconception*, in THEORETICAL MEDICINE 24, 329 (2003); J.A. Kimmelman, *Theoretical Framework for Early Human Studies: Uncertainty, Intervention Ensembles, and Boundaries*, in 13 TRIALS 173 (2012). (Exhibit 45)

[122] *E.g. Kevin P. Weinfurt*, et al. *Expectations of Benefit in Early-Phase Clinical Trials: Implications for Assessing the Adequacy of Informed Consent*, in 28(4) Med. Decision Making 575 (2008) (Exhibit 46); A.C. Cox, et al., *Communication and Informed Consent in Phase I Trials: A Review of the Literature*, in 14(4) Support Care Cancer 303 (2006). (Exhibit 47)

[123] Susan Brink, *Transform the Informed Consent Process*, in 6(8) Clinical Trials Administrator 91 (2008). (Exhibit 48)

[124] *Id.* (Exhibit 48)

[125] Steven Joffe, et al., *Quality of Informed Consent in Cancer Clinical Trials: A Cross-Sectional Survey*, 358 LANCET 1772, 1775 (2001). (Exhibit 49)

[126] K.E.Flynn, et al., *Participants' Perspectives on Safety Monitoring in Clinical Trials*, in 10 CLINICAL TRIALS 552, 557 (2013). (Exhibit 9)

[127] *Id.* (Exhibit 9)

[128] *Id.* at 553. (Exhibit 9)

[129] *Id.* at 556. (Exhibit 9)

causally linked to the drug, participants expect this information to be included in the study consent form.[130] In fact, many study participants maintained that research subjects should always be told about serious adverse events linked to the drug being tested.[131]

(3) True Informed Consent

Despite scientific data demonstrating that preclinical animal models are poorly predictive of human response, animal models continue to be treated as the gold standard for preclinical testing under the current drug development paradigm. This dichotomy illustrates that the alleged "gold standard" title is meaningless. When the FDA informed consent regulations were enacted, it was not known that 92% of all drugs could fail human clinical testing.

Respect for prospective research subjects requires that they "be given the opportunity to choose what shall or shall not happen to them."[132] Preclinical animal testing does not reliably predict what will happen when an investigational drug is given to a trial subject. Further, solid evidence indicates that much of the preclinical data is not even published.[133] Because human clinical trials deal with the unknown, the importance of giving participants all information necessary to aid in making the decision to participate in a study is essential.[134]

The therapeutic misconception that clinical trial subjects experience reflects an obvious deficiency in the informed consent process. To balance subjects' belief that clinical trials are safe and likely to benefit them, informed consent requires that subjects receive an explicit warning that animal tests may not predict human response to a drug. Disclosure of this information is essential to justify exposing large numbers of human research subjects to unproven compounds.

To meet required ethical standards for disclosure to human subjects participating in clinical trials and offer true informed consent, the FDA regulations that govern information given to clinical trial participants must be updated. History has shown that voluntary guidelines and non-binding principles do not work; rather, a legal mandate is necessary.

So long as clinical trial participants are not provided with warnings regarding the risks inherent in developing human drugs through the use of animal models, they are not able to give true informed consent. The disclosure of this information will also serve as a health risk communication[135] that the clinical trial is an experiment and will force investigators to speak factually with human subjects regarding the potential risks inherent in clinical trials.

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[130] *Id.* (Exhibit 9)

[131] *Id.* (Exhibit 9)

[132] U.S. Dep't of Health and Human Services, *Informed Consent-FAQs*, http://answers.hhs.gov/ohrp/categories/1566 (last visited Dec. 31, 2013). (Exhibit 50)

[133] *Protecting Participants in First-In-Humans Trials, supra,* note 5 (Exhibit 6)

[134] *Id.* (Exhibit 6)

[135] Dana Zikerr, *Reviving Informed Consent Using Risk Perception in Clinical Trials*, in 2 DUKE L. & TECH. REV. 15 (2003). (Exhibit 51)

D. Part Four: FDA Disclosure Standards Should be Analogous to Other Federal Statutory and Common Law Disclosure Standards

The material omissions in disclosure that are status quo in clinical drug trials would likely constitute negligence/malpractice in the context of physician/patient drug prescription disclosure requirements and false advertising and unfair business practice in the context of a drug advertisement under FTC truth in advertising requirements. There is no justification for a more relaxed rule in the context of clinical trials.

(1) Disclosure Standard a Physician is Held to in Prescribing Drugs

While the current informed consent regulation aims to protect human subjects receiving drugs in clinical trials, the information required to be disclosed by investigators under that regulation falls far below the standard of disclosure required by a physician who prescribes a drug to a patient.

Compare, for example, the warnings that a physician would be required to disclose to a patient if the drug given in a clinical trial were actually an FDA approved drug prescribed to a patient. Similar to the FDA informed consent regulation that governs investigators' disclosures to subjects in drug testing, common law requires physicians to obtain informed consent from patients before administering a drug. [136] However, a physician has a common law duty to disclose even small material risks as part of informed consent. [137] In the landmark informed consent case *Canterbury v. Spence*, the Court noted, "[e]very human being of adult years and sound mind has a right to determine what shall be done with [his or her] own body."[138] "True consent to what happens to one's self is the informed exercise of a choice, and that entails an opportunity to evaluate knowledgably the options available and the risks attendant upon each."[139]

Physician informed consent requirements mandate the responsibility of warning the patient of all potential risks associated with a drug.[140] The physician's duty to disclose risk of harm extends to all risks that would potentially affect a reasonable patient's decision,[141] regardless of the probability of risk. [142] A physician's failure to obtain informed consent from a patient is generally treated as negligence, based on the physician's breach of a professional duty "to provide patients with appropriate information before they consent to treatment."[143]

The duty to protect another person typically arises from a special relationship between parties whereby one party is dependent upon

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[136] Roger L. Jansson, Researcher Liability for Negligence in Human Subject Research: Informed Consent and Researcher Malpractice Actions, 78 Wash. L. Rev. 229, 237 (2003). (Exhibit 52)

[137] Canterbury v. Spence, 464 F.2d 772, 778 (1988).

[138] *Canterbury*, 464 F.2d 772 at 780.

[139] *Id.* at 780.

[140] *Id.* at 781.

[141] *Id.*at 787.

[142] *Id* at 788.

[143] Jansson, *supra*, note 136. (Exhibit 52)

the other. [144] Investigator-subject and physician-patient relationships are both considered the type of special relationship from which a duty arises.[145] A physician's duty arises out of the trust patients place in a physician's skill, learning, and experience and includes informing patients of the risks of their treatment.[146] An investigator's duty arises from "the very nature of nontherapeutic scientific research."[147] Like the patient who relies on his or her physician, a subject relies on an investigator's skill, learning, and experience.

Because of the significant similarities that exist between the physician-patient and investigator-subject relationship, the duty of care in disclosure should be comparable. Both patients and human research subjects are dependent upon the physician's or investigator's specialized knowledge. In each case, negligence on the part of the physician or the investigator could cause death or serious injury to the patient or research subject. Both the patient and the research subject rely on the physician's or investigator's communications in order to protect their right of personal autonomy in deciding whether or not to take a drug. Thus the goals of informed consent when a physician prescribes a drug to a patient and when an investigator administers a drug to a human trial subject are analogous.

For these reasons, regulations that govern clinical drug trials should mandate that investigators make disclosures to drug trial participants that are analogous to the disclosures patients would receive from their physician if the drug being tested was being prescribed. Just as the physician's duty extends to all significant risks, regardless of the probability of the risk occurring, the investigator's duty should include disclosure of all significant risks, even small.

There are generally accepted scientific guidelines that apply to all warnings for human subjects participating in research.[148] The guidelines require that the proposed warnings be effective, capture attention, and convey safety information. [149] Because studies suggest that research participants frequently may not understand information disclosed during informed consent, [150] the warnings must adhere strictly to these guidelines. The warnings should provide the information that prospective research subjects need to make judgments regarding the level of risk they are willing to accept in a study.[151]

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[144] Jansson, *supra*, note 136 at 242. (Exhibit 52)

[145] *Grimes v. Kennedy Krieger Institute*, 782 A.2d 807, 858 (2000).

[146] Jansson, *supra*, note 136. (Exhibit 52)

[147] *Grimes*, 782 A.2d 807 at 834.

[148] Kenneth R. Laughery & Michael S. Wogalter, *Designing Effective Warnings*, in Reviews of Human Factors and Ergonomics 259 (2006). (Exhibit 53)

[149] *Id.* at 242-3. (Exhibit 53)

[150] Anvita Pandiya, *Readability and Comprehensibility of Informed Consent Forms for Clinical Trials*, in 1(3) PERSPECTIVES IN CLINICAL RESEARCH 98, (2010), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3146080/. (Exhibit 54)

[151] Laughery, *supra*, note 148 at 244. (Exhibit 53)

Although research suggests that informed consent documents tend to be too long,[152] additional warnings can be drafted to be succinct. The warnings should be brief and "no longer than necessary to communicate the needed information"[153] because too much information would be as problematic as too little. The warnings should be explicit, specific, detailed, clearly stated, and leave nothing implied. Because literacy rates in the United States are low,[154] the warnings should be simple and easy to understand. [155] Ultimately, the warnings should be drafted so the average person can understand and process them in a meaningful way, whether through oral or written communication. The proposed standard warnings described in Section III above, to be added to 21 C.F.R. §50.25(a) as new Sections (9-11), meet these requirements.

(2) Disclosure Standard Under Federal Trade Commission Act

The disclosure requirements applicable to drug trial subjects under the current FDA regulation also fall below the disclosure standards mandated by the Federal Trade Commission Act (FTCA).[156] The Federal Trade Commission (FTC) disclosure standards are of particular interest since FTC is a federal sister agency with unique expertise that focuses on truth in advertising and protection for American consumers.

Under the FTCA, FTC is empowered, among other things, to prevent unfair or deceptive acts or practices in or affecting commerce.[157] Under the FTCA: (1) advertising must be truthful and non-deceptive; (2) advertisers must have evidence to back up their claims; and (3) advertisements cannot be unfair. According to the FTC's Deception Policy Statement,[158] an advertisement is deceptive if it contains a statement - or omits information – that: (1) is likely to mislead consumers acting reasonably under the circumstances; and (2) is "material" – that is, important to a consumer's decision to buy or use the product. According to the FTC and the FTC's Unfairness Policy Statement, [159] an advertisement or business practice is unfair if: (1) it causes or is likely to cause substantial consumer injury which a consumer could not reasonably avoid; and (2) it is not outweighed by the benefit to the consumer.

In determining whether an advertisement or representation is deceptive, a typical FTC inquiry follows these steps:

(1) The FTC looks at the advertisement from the point of view of the "reasonable consumer" – the typical person looking at the advertisement in context to determine what it conveys to consumers.

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[152] Pandiya, *supra*, note 150. (Exhibit 54)

[153] Laughery, *supra*, note 148 at 252. (Exhibit 53)

[154] Brink, *supra*, note 123. (Exhibit 48)

[155] Laughery, *supra*, note 148 at 255. (Exhibit 53)

[156] Federal Trade Commission Act, 15 U.S.C.A §§ 41-58 (West 2013).

[157] 15 U.S.C. §§ 45 (West 2013).

[158] FTC, Policy Statement on Deception (1983) *reprinted in* 4 Trade Reg. Rep. (CCH) 13,205, *appended to* Cliffdale Assocs., 103 F.T.C. 110,174 (1984).

[159] FTC Policy Statement on Unfairness, 17 December 1980.

(2) The FTC looks at both "express" and "implied" claims.

(3) The FTC looks at what the advertisement does not say – that is, if the failure to include information leaves consumers with a misimpression about the product or service.

(4) The FTC looks at whether a claim or omission would be "material" – that is, important to a consumer's decision to buy or use the product or service. Examples of material claims and omissions specifically include representations and omissions regarding a product's safety or effectiveness.

(5) The FTC looks at whether the advertiser has sufficient evidence to support the claims in the advertisement.

Advertising will be deemed deceptive when there is either a representation or an omission in the advertisement that is likely to mislead consumers to their detriment. Because the FTC uses the notion of a reasonable consumer in determining whether advertising is deceptive, an advertisement could be problematic if an average or reasonable consumer would be misled by the representation or omission.[160]

In the context of drug development, the current FDA disclosure requirements fall below the FTC disclosure standards. Under current FDA disclosure requirements, drug sponsors routinely omit information that the average or reasonable consumer would consider material in making an informed decision as to whether to risk his or her health by exposing his or her body to a potentially toxic substance. Specifically, drug trial subjects are misled in clinical trials by the failure of drug sponsors to disclose that animal data is frequently not predictive of human response. Such an omission is likely to mislead a volunteer subject to his or her detriment, as it may result in him or her being unknowingly subjected to physical harm. In an advertisement designed to market a drug to this same individual, an omission of this nature could be construed as false advertising and unfair business practice under FTC rules.

That the disclosure requirement in advertising targeted to a consumer purchasing a drug is subject to a higher standard than the risk disclosure requirement for a drug trial participant under current FDA regulations highlights the deficiency in the regulations.

E. Part Five: The Benefits to the Public of the Proposed Regulation Amendment Far Outweigh Any Potential Challenges

One purpose of a warning is to communicate safety or safety-related information to a target audience.[161] The best method of hazard control is to eliminate the risk.[162] Clinical trials that test drugs in humans are vital to drug development but they present risks that cannot be eliminated since the current drug development paradigm relies on preclinical animal data. Because risk exists that cannot be eliminated under the current drug development paradigm, and simply discontinuing all new drug applications until validated non-animal testing methods are

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[160] Kim Bartel Sheehan, *Controversies in Contemporary Advertising* 51 (2d Ed. 2013).

[161] Michael S. Wogalther, *Factors that Influence the Effectiveness of Warning Signs and Labels*, http://www.safetyhumanfactors.org/wp-content/uploads/2011/12/262-Wogalter2005.pdf (last visited Dec. 31, 2013). (Exhibit 55)

[162] *Id.* (Exhibit 55)

available is not a realistic option, FDA regulations must mandate that prospective clinical trial participants receive adequate warning of the true extent of the risks posed, as part of informed consent.

To obtain true informed consent, the warning information must be given, and it will remain up to the prospective clinical trial participant to determine if he or she will accept the risk posed by the clinical trial. Such warning must be given as a matter of fundamental ethics and regardless of whether doing so may increase the cost of the trial to some degree. Increased cost would result only if more prospective participants can be expected to decline participation when the real risks are understood. The alternative, which is the current status quo, may make it easier for drug sponsors to recruit trial participants by misleading them as to the degree of risk to which they are subjecting themselves, but it is not an approach that should be sanctioned by an ethical society.

While it is arguable that offering true informed consent to potential research subjects could reduce the number of subjects willing to participate in clinical trials or increase the cost, no data exists to support this notion.[163] The point of warnings is to inform prospective subjects, not frighten them. Most trial subjects participate because of the remuneration offered and will likely continue to do so for that reason. However, a drop in number of subjects willing to participate in clinical research, or an increase in the remuneration that must be paid to informed volunteers, may: 1) prompt the FDA to move more quickly to validate and qualify safe and effective human derived drug testing methods, and 2) spur on the scientific community's efforts to develop and use more predictive preclinical models.

VI. CONCLUSION

Informed consent is an ethical and legal doctrine [164] that has evolved to protect persons participating in clinical research trials. In light of the evolving ethical standards and our increased scientific knowledge, the current informed consent regulations are deficient in the context of drug development, as they do not mandate provision of complete information regarding the risks that human subjects accept when participating in a clinical trial.

Trial subjects must receive all information that a reasonable human subject participating in a clinical drug trial would find material.[165] Accordingly, the regulations must be updated to ensure that every prospective trial participant receives the information necessary to evaluate the real risks posed and to provide true informed consent. It is in the best interests of investigators, drug manufacturers, and especially human trial subjects that 21 C.F.R. 50.25 be modified as requested in this petition.

VII. ENVIRONMENTAL IMPACT

A claim for categorical exclusion of the requirements for an environmental assessment is made pursuant to 21 C.F.R. § 25.31.

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[163] Lidz, *supra*, note 113 at V-61. (Exhibit 41)

[164] Jessica Berg, et al., *Informed Consent: Legal Theory and Clinical Practice* (2001), *available at* http://works.bepress.com/charles_lidz/75.

[165] *Protecting Participants in First-In-Humans Trials, supra*. (Exhibit 6)

VIII. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), economic impact information is submitted only when requested by the Commissioner.

IX. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

Jennifer Bergovoy, JD*
Treasurer
Center For Responsible Science
P.O. Box 443
Pacific Palisades, CA 90272
619-660-5067
** Lead Petitioner, Will Accept All Correspondence*

John Tessmer
414 Bonair St.
La Jolla, CA 92307-5912

Hal Garcia-Smith
2122 8th Avenue North #201
Seattle, WA 98109

APPENDIX

Exhibits

1. Declaration of John Tessmer (Pursuant to 28 U.S.C. § 1746)
2. Declaration of Hal Garcia-Smith (28 U.S.C. § 1746)

Attached Literature and other citations

3. U.S. Food and Drug Admin., *Inside Clinical Trials: Testing Medical Products in People,* FDA Website
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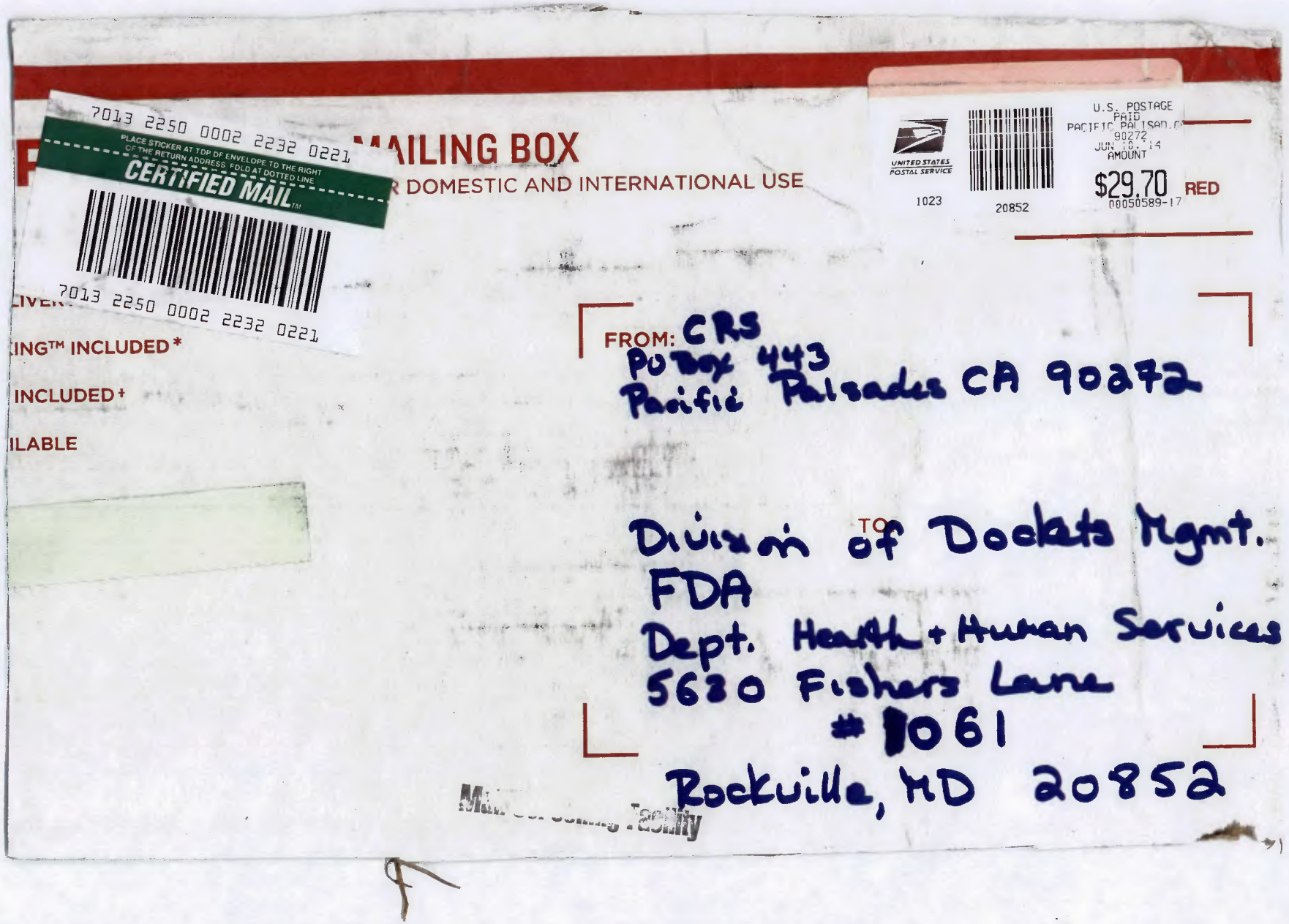
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