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What about the Children?
FDA's Response to Pediatric Drug Testing

Krissy Doerner

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This paper is submitted in satisfaction of the course requirement for Food and Drug law.

ABSTRACT:

The Federal Food and Drug Administration (FDA) has played a critical role in the protection of human subjects in research. Most recently, FDA enacted an interim final rule regarding protection of children in clinical investigations. FDA's interim rule represents its most current policy on human subject protection. Current events illuminate FDA's policies and how FDA has chosen to respond to debates over pediatric drug testing. This paper will provide a brief history of FDA's participation in human subject protection. This paper will then focus on FDA's policies for pediatric research, its interim rule, and how the interim rule relates to current events. Finally, this paper will make a comment about how FDA balances its competing duties of protecting the public but also of promoting research.

I. Introduction

The Federal Food and Drug Administration (FDA) has been a critical player in the protection of human subjects in research. Along with other governmental agencies that oversee human subject protection, FDA has had to address various ethical issues pertaining to clinical investigations. The use of children in clinical trials has been an area of particular sensitivity. Concerns include the inability of children to provide informed consent and the ethical motivation not to expose children to unnecessary levels of risk in the absence of significant benefit.¹ While these ethical issues evoke a need to scrutinize pediatric research, FDA has had a history of encouraging drug testing in children.²

Part of FDA's motivation for encouraging drug testing in children comes from the need to find safe and effective doses of medicine for children, to predict children's adverse reactions to drugs, and to understand diseases and health issues specific to kids.³ In 1963, Dr. Harry Shirkey coined the phrase "therapeutic orphans" to describe children in the drug world.⁴ Few drugs have been studied on children. Pharmaceutical companies have little financial incentive to test drugs in kids.⁵ Additionally, pediatric research can be more complicated than adult research, because tests are often done in children's hospitals, and healthy children are less likely to volunteer.⁶ Most children involved in clinical trials have the disease in question.⁷ The off-label use of medications has been the de facto standard of care in pediatrics.⁸ While doctors may legally use

¹See BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH 48 (Jeffrey P. Kahn, Ph.D., M.P.H. et al. eds., Oxford University Press 1998).

²See, e.g., Paula Botstein, M.D., *Why FDA is Encouraging Drug Testing in Children*, FDA CONSUMER, July-August 1991, available at http://www.mdadvice.com/resources/clinical_trials.children.htm (including questions and answers from an interview pertaining to drugs for children).

³See *id.* (stating why FDA has focused on drugs for children).

⁴See *id.* (using Dr. Shirkey's phrase to explain why little drug testing has been performed on children).

⁵See *id.* (stating that the financial return for testing drugs in children is likely to be small).

⁶*Id.*

⁷*Id.*

⁸BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH 47 (Jeffrey P. Kahn, Ph.D., M.P.H. et al. eds., Oxford University Press 1998); see also Paula Botstein, M.D., *Why FDA is Encouraging Drug Testing in Children*, FDA CONSUMER, July-August 1991, available at http://www.mdadvice.com/resources/clinical_trials.children.htm (stating that physicians prescribe medicine to children based on past experience and accumulated accounts of past experiences with children).

approved drugs for whatever uses they deem appropriate, better information would facilitate more accurate diagnoses for children.

Current events have brought pediatric research into the limelight. The Children's Health Act of 2000⁹ "require[d] that within 6 months of its enactment all research involving children that [was] conducted, supported, or regulated by the Department of Health and Human Services (HHS) be in compliance with HHS regulations providing additional protections for children involved as subjects in research."¹⁰ The Children's Health Act prompted FDA to issue an interim rule containing additional safeguards for children.¹¹ In 2001, the Kennedy Krieger Institute of Johns Hopkins University received national publicity regarding its efforts to understand the success of lead abatement programs in reducing lead exposure to children.¹² Two negligence actions pertaining to the study were brought before the Court of Appeals of Maryland.¹³ The case addresses many of the ethical issues surrounding pediatric research and suggests how other courts will interpret regulations pertaining to protection of children. In 2002, FDA asked for public comment on whether to test smallpox vaccine on children aged two to five.¹⁴ Public and professional debate evaluating the ethical justifications for conducting clinical trials on children emerged over the request for comment on smallpox vaccine.¹⁵ The debate is keenly important due to recent terrorism threats and the implementation of the first stage of the Bush Administration's smallpox vaccination plan.¹⁶ Lastly, on January 21, 2003, HHS

⁹42 U.S.C. § 201 (2003).

¹⁰Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 79,20589 (April 24, 2001) (to be codified at 21 C.F.R. pt. 50, 56). HHS protections for children are codified at 45 C.F.R. pt. 46, subpt. D.

¹¹See Phyllis F. Granade and Mark Lutes, *Recent Developments: FDA to Issue Rule Bolstering Protection of Children in Clinical Trials*, Epstein Becker & Green, P.C. (April 23, 2001), available at http://www.ebglaw.com/article_428.htm (last visited Feb. 23, 2003).

¹²See Lainie Friedman Ross, *In Defense of the Hopkins Lead Abatement Studies*, 30 J.L. MED. & ETHICS 50 (2002).

¹³See *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807 (2001).

¹⁴See Solicitation of Public Review and Comment On Research Protocol: A Multicenter, Randomized Dose Response Study of the Safety, Clinical and Immune Response of Dryvax Administered to Children 2 to 5 Years of Age, 67 Fed. Reg. 211,66403 (Oct. 31, 2002).

¹⁵See VERA SHARAV, ALLIANCE FOR HUMAN RESEARCH PROTECTION, COMMENTS RE: PROPOSED SMALLPOX VACCINE TRIAL TO TEST THE SAFETY OF DRYVAX ADMINISTRATION TO CHILDREN 2 TO 5 YEARS OF AGE, FDA Docket Number 02N-0466, available at <http://www.fda.gov/ohrms/dockets/dailys/02/Dec02/120302/02N-0466-EC-450.htm> (last visited Feb. 22, 2003).

¹⁶AMERICAN ACADEMY OF PEDIATRICS, CHILDREN SHOULD NOT BE GIVEN SMALLPOX VACCINE (Jan. 30, 2003), available at http://www.aap.org/advocacy/washing/smallpox_vaccine.htm (last visited Feb. 22, 2003).

Secretary Tommy G. Thompson, responding to the Best Pharmaceuticals for Children Act,¹⁷ announced that government-supported tests of twelve commonly prescribed drugs on children would begin in fiscal year 2003 and would continue to receive funding in the 2004 budget proposal.¹⁸ These events provide a telling context in which to analyze FDA's policies on protecting children in clinical investigations and illuminate FDA's response to debates over pediatric research.

To set the stage for analysis, this paper will first provide a background of human subject regulation and an overview of the historic efforts of FDA to protect research subjects.

II. History of Human Subject Regulation

A.

Overview of Human Subject Protections

Research regulation began during the Nuremberg War Crime Trials following World War II.¹⁹ The trials produced the Nuremberg Code, which outlines “fundamental ethical principles in human subject research.”²⁰ The code was “the first internationally recognized set of guidelines in human subject research” and is now part of international common law.²¹ The code contains ten basic guidelines that emphasize voluntary consent and avoidance of unnecessary risk.²² Courts in the United States, however, have not used the Nuremberg Code in any criminal case and rarely cite to the code in the civil context.²³ Despite its limited use, the

¹⁷Pub. L. No. 107-109, 115 Stat. 1408 (2002).

¹⁸DEPARTMENT OF HEALTH AND HUMAN SERVICES, HHS IDENTIFIES DRUGS FOR PEDIATRIC TESTING AND ANNOUNCES FY 2003 AND FY 2004 FUNDING (2003), available at <http://www.hhs.gov/news/press/2003pres/20030121.html> (last visited Feb. 22, 2003).

¹⁹See *Module 1: Research Ethics*, available at http://research.bcm.tmc.edu/CR%20Tutorial/1research_ethics.htm (last visited Feb. 22, 2003) (providing a historical perspective on research ethics).

²⁰*Id.*

²¹*Id.*

²²See *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 835 (2001) (listing the complete text of the Nuremberg Code).

²³See *id.*

Nuremberg Code has served as a model for subsequent ethical standards.²⁴

The most influential post-Nuremberg documents have been the Declaration of Helsinki (“The Declaration”), first issued in 1964 and last revised in 1996, and the Belmont Report of 1979.²⁵ The Declaration of Helsinki, adopted by the World Medical Association (WMA) in response to the testing of new polio vaccines on institutionalized mentally retarded children,²⁶ added to the recommendations found in the Nuremberg Code.²⁷ For example, the declaration distinguishes therapeutic from non-therapeutic research,²⁸ suggests that research on humans be justified by prior laboratory and animal experimentation, affirms the need to compare the importance of a study in proportion to its risk, and provides the framework for what has become independent Institutional Review Boards (IRBs).²⁹

In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the *Belmont Report*.³⁰ The Belmont Report contains three basic ethical principles, including respect for persons, beneficence, and justice.³¹ Respect for persons refers to respect for individual autonomy

²⁴See *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission 1979).

²⁵*Module 1: Research Ethics*, available at http://research.bcm.tmc.edu/CR%20Tutorial/1research_ethics.htm (last visited Feb. 22, 2003).

²⁶See *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 836 (2001).

²⁷See *Module 1: Research Ethics*, available at http://research.bcm.tmc.edu/CR%20Tutorial/1research_ethics.htm (last visited Feb. 22, 2003).

²⁸Therapeutic research involves studies designed to help or aid an individual who is suffering from a disease or health condition. Nontherapeutic research involves individuals who are not known to have the health condition addressed by the study or who will not directly benefit from the research; nontherapeutic research is “designed to achieve beneficial results for the public at large (or, under some circumstances, for profit).” *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 812 n.2 (2001).

²⁹See *id.* IRBs evaluate research studies in order to ensure the safety of human subjects. All federally funded research must obtain IRB approval. See 45 C.F.R. § 46.107-115 (2002) (outlining requirements for makeup and operation of IRBs); see also Office of Inspector General, *Institutional Review Boards: A Time for Reform* 3 (Jun. 1998) (including an overview of basic IRB functions).

³⁰See *Module 1: Research Ethics*, available at http://research.bcm.tmc.edu/CR%20Tutorial/1research_ethics.htm (last visited Feb. 22, 2003).

³¹See *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission 1979).

and protection for those with diminished autonomy.³² The principle now appears embodied in requirements of informed consent.³³ Beneficence entails an obligation not to harm and to maximize possible benefits and minimize possible harm.³⁴ Beneficence has become apparent in the risk/benefit calculus.³⁵ Finally, justice includes the idea that people with entitled benefits should receive them and that no one should face undue burdens.³⁶ This concept of justice appears in moral requirements of equitable procedures and outcomes in subject recruitment.³⁷ The recommendations from The Declaration of Helsinki and The Belmont Report have been codified in 45 CFR § 46, which is known as the Common Rule.³⁸ Seventeen government agencies have endorsed the Common Rule.³⁹ The Common Rule serves as the codified federal policy for protection of human subjects.⁴⁰

In 1996, the International Conference on Harmonization (ICH) added to and modified the federal regulations.⁴¹ Collectively, the Common Rule and the recommendations make up what is known as Good Clinical Practice or GCP.⁴² On June 13, 2000, HHS created the Office of Human Research Protections (“OHRP”).⁴³ OHRP has responsibility for developing, monitoring and exercising compliance oversight for regulations and

³²See *id.*

³³See *Module 1: Research Ethics*, available at http://research.bcm.tmc.edu/CR%20Tutorial/1research_ethics.htm (last visited Feb. 22, 2003).

³⁴See *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission 1979).

³⁵See *Module 1: Research Ethics*, available at http://research.bcm.tmc.edu/CR%20Tutorial/1research_ethics.htm (last visited Feb. 22, 2003).

³⁶See *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission 1979).

³⁷See *Module 1: Research Ethics*, available at http://research.bcm.tmc.edu/CR%20Tutorial/1research_ethics.htm (last visited Feb. 22, 2003).

³⁸See *id.*

³⁹The agencies endorsing the Common Rule include the Department of Agriculture, Department of Energy, National Aeronautic and Space Administration, Department of Commerce, Consumer Product Safety Commission, Agency for International Development, Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veteran Affairs, Environmental Protection Agency, Department of Health & Human Services, National Science Foundation, Department of Energy, Central Intelligence Agency, and the Social Security Administration. See *Terms of the Federalwide Insurance*, available at <http://ohrp.osophs.dhhs.gov/humansubjects/assurance/filasurt.htm> (last visited Feb. 18, 2003).

⁴⁰See 45 C.F.R. § 46 (2002). The Common Rule requires written assurances of a commitment to human subject protection from institutions engaged in research and existence of an IRB and compliance with IRB requirements. See *id.*

⁴¹See *Module 1: Research Ethics*, available at http://research.bcm.tmc.edu/CR%20Tutorial/1research_ethics.htm (last visited Feb. 22, 2003).

⁴²See *id.*

⁴³65 Fed. Reg. 114,37136 (June 13, 2000).

for research conducted by all HHS component agencies.⁴⁴ While FDA, as part of HHS, attempts to remain consistent with the Common Rule, its regulatory structure is unique.

B.

Overview of FDA Regulations

FDA's regulatory structure is distinctive, because in addition to attempting to remain consistent with the Common Rule, FDA must also consider the requirements of the Federal Food, Drug, and Cosmetic Act.⁴⁵ Moreover, the fact that FDA seldom supports or conducts research of its own also contributes to its unique framework.⁴⁶ FDA regulations apply to IRBs that review clinical investigations regulated by FDA and that support applications for research or marketing permits for products regulated by FDA.⁴⁷ Included in this category are experiments that must meet the requirements for prior submission to FDA and experiments intended for later submission to or inspection by FDA as part of an application for a research or a marketing permit.⁴⁸ All individuals, including healthy patients, who participate in research as recipients of a test article or as controls, receive FDA's protections.⁴⁹

Various sets of FDA regulations apply to clinical practice and clinical trials. Among the regulations are standards for investigational new drug applications,⁵⁰ standards for applications for FDA approval to market

⁴⁴*See id.*

⁴⁵56 Fed. Reg. 280003 (Jun. 18, 1991). The Federal, Food, Drug, and Cosmetic Act of 1938, revised by the FDA Modernization Act of 1997, establishes the basic legal framework controlling the activities of producers of food, drugs, cosmetics, and medical devices. Key components of the act include definitions and regulations pertaining to adulteration and misbranding. An example of how the FDCA may affect human subject protection appears in Section 528, which includes special instructions for investigations of drugs for rare diseases and conditions.

⁴⁶Instead of conducting or supporting research of its own, "FDA regulates research conducted by outside sponsors and investigators, where the research is subject to IRB review and approval." Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 79,20591 (April 24, 2001) (to be codified at 21 C.F.R. pt. 50, 56).

⁴⁷*See* 21 C.F.R. § 56.101 (2002).

⁴⁸*See* 21 C.F.R. § 56.102 (2002).

⁴⁹*See id.*

⁵⁰*See* 21 C.F.R. pt. 312 (2002).

new drugs and approval for biologic licenses,⁵¹ standards pertaining to investigational device exemptions,⁵² and standards regarding premarket approval of medical devices.⁵³ Similar to other departments, FDA requires that researchers conform to GCP standards.⁵⁴ To ensure compliance, FDA “inspects and audits the conduct and reporting of clinical trials.”⁵⁵ Inspections are in addition to internal review of new product applications and cover all involved parties, including clinical investigators, IRBs, sponsors, monitors, and contract research organizations.”⁵⁶

Certain sets of FDA regulations refer specifically to human subject protection, including rules regarding electronic signatures,⁵⁷ informed consent,⁵⁸ financial disclosure by clinical investigators,⁵⁹ and IRB requirements.⁶⁰ While these regulations have been harmonized with the Common Rule,⁶¹ differences still exist.⁶² Unlike the Common Rule, FDA regulations do not require assurances.⁶³ In their place, FDA utilizes its Biosearch Monitoring program and educational efforts to assure compliance with FDA regulations.⁶⁴ Similar to the Common Rule, FDA requires continuing review by IRBs but exempts certain investigations, such as trials commencing prior to July 7, 1981 and emergency uses of test articles.⁶⁵ Other disparities from the Common Rule pertain to how FDA may respond to noncompliance situations and the requirements for informed consent.⁶⁶

⁵¹ See 21 C.F.R. pt. 314, 601 (2002).

⁵² See 21 C.F.R. pt. 812 (2002).

⁵³ See 21 C.F.R. pt. 814 (2002).

⁵⁴ See U.S. Food and Drug Administration, *Good Clinical Practice in FDA-Regulated Clinical Trials*, available at <http://www.fda.gov/oc/gcp/default.htm> (last visited Feb. 23, 2003).

⁵⁵ *Id.* The program is known as the Biosearch Monitoring (BIMO) program. *Id.*

⁵⁶ *Id.*

⁵⁷ See 21 C.F.R. pt. 11 (2002).

⁵⁸ See 21 C.F.R. pt. 50 (2002).

⁵⁹ See 21 C.F.R. pt. 54 (2002).

⁶⁰ See 21 C.F.R. pt. 56 (2002).

⁶¹ The regulations were harmonized in 1991. See *Comparison of DA and HHS Human Subject Protection*, available at <http://www.fda.gov/oc/gcp/comparison.html> (last visited Feb. 28, 2003).

⁶² See *id.* (stating that differences in the rules are due to differences in the statutory scope or requirements).

⁶³ See *id.* FDA believes that adopting the assurance mechanism would create too large of an administrative burden to justify the benefits that would come from assurance of IRBs that are subject to FDA jurisdiction but not otherwise subject to HHS jurisdiction. See *id.*

⁶⁴ See *id.*

⁶⁵ See *id.*; see also 21 C.F.R. § 56.104 (2002).

⁶⁶ See *id.* For example, FDA regulations exempt certain life threatening and emergency situations from informed consent.

III. FDA Regulations Pertaining Specifically to Children in Clinical Trials

FDA's issuance of its interim final rule, Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products,⁶⁷ adopted in response to the Children's Health Act, represents its most successful effort at codifying regulations pertaining specifically to children in clinical investigations. Prior to the Children's Health Act, if an FDA-regulated clinical investigation was not conducted or supported by HHS, HHS regulations on protection of children did not impose requirements on the investigation.⁶⁸ Historically, however, FDA turned to HHS regulations for guidance on pediatric studies.⁶⁹ Much of the interim rule is based on the HHS regulations, "with only those changes necessary due to differences between FDA's and HHS's regulatory authority."⁷⁰ Research involving FDA-regulated products that is also conducted or supported by HHS must satisfy both sets of regulations.⁷¹

Prior to the interim rule, in addition to relying upon guidance from HHS regulations, FDA had some safeguards in place for pediatric research.⁷² 21 C.F.R. § 56, which pertains to governance of IRBs, identifies children as a class of vulnerable subjects, and portions of § 56 address pediatric issues.⁷³ For example, Section 56.111(a)(3) requires that selection of research subjects be "cognizant of the special problems of research involving vulnerable populations, such as children."⁷⁴ Section 56.111(b) requires special attention to the rights and welfare of children, because they are vulnerable to coercion or undue influence.⁷⁵ Section 56.107(a) provides for consideration of including one or more individuals who are knowledgeable about and

See 21 C.F.R. § 50.23(a)-(c) (2002). FDA regulations also contain a waiver of informed consent for military personnel, which has no comparable provision in the Common Rule. *See* 21 C.F.R. § 50.23(d) (2002).

⁶⁷21 CFR pt. 50, subpt. D (2002).

⁶⁸Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 79,20590 (April 24, 2001) (to be codified at 21 C.F.R. pt. 50, 56). HHS regulations are codified at 45 C.F.R. part 46, subpart d.

⁶⁹*See id.*

⁷⁰*Id.*

⁷¹*See id.*

⁷²Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 79,20590 (April 24, 2001) (to be codified at 21 C.F.R. pt. 50, 56).

⁷³*Id.*

⁷⁴*Id.* (citing 21 C.F.R. § 56.111(a)(3)).

⁷⁵*Id.*

experienced in working with children to sit on an IRB that regularly reviews research that involves children.⁷⁶ Other safeguards were FDA publications regarding informed consent and the assent of children.⁷⁷ Lastly, FDA published guidance entitled E11 Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11), which addressed issues in pediatric drug development including ethical considerations in pediatric studies.⁷⁸

FDA designed the interim rule with hopes of helping researchers address ethical issues that were to accompany an expected increase in the enrollment of children in clinical trials.⁷⁹ FDA expected increases in the number of children participating in clinical investigations due to, then recent, pediatric initiatives, including FDA's 1998 pediatric rule and the pediatric provisions of the Food and Drug Administration Modernization Act of 1997.⁸⁰ The interim rule became effective on April 30, 2001.

The interim rule is divided into seven parts, all codified at 21 C.F.R. Part 50, subpart D. Much of the rule focuses on duties of IRBs. Part 50.50 requires IRBs to review clinical investigations involving children as subjects and to approve only those investigations that satisfy the criteria described in Section 50.51, Section 50.52, or Section 50.53 and the conditions of all other applicable sections of" subpart D.⁸¹

⁷⁶*Id.*

⁷⁷*See id.* (referring to the information sheets, which state that HHS regulations may be used as guidance for all pediatric studies).

⁷⁸*Id.* at 20590-91.

⁷⁹Phyllis F. Granade and Mark Lutes, *Recent Developments: FDA to Issue Rule Bolstering Protection of Children in Clinical Trials*, Epstein Becker & Green, P.C. (April 23, 2001), available at <http://www.ebglaw.com/article.428.htm> (last visited Feb. 23, 2003).

⁸⁰*See* Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 79 20589 (April 24, 2001) (to be codified at 21 C.F.R. pt. 50, 56).

The 1998 pediatric rule (63 Fed. Reg. 231,66632 (Dec. 2, 1998)) requires manufacturers to "assess the safety and effectiveness of certain drug and biological products in pediatric patients" and authorizes FDA to require pediatric studies of marketed drug and biological products that: "(1) Are used in a substantial number of pediatric patients for the labeled indications, and where the absence of adequate labeling could pose significant risks to pediatric patients; or (2) would provide a meaningful therapeutic benefit over existing treatments for pediatric patients for one or more of the claimed indications, and the absence of adequate labeling could pose significant risks to pediatric patients." *Id.*

The Modernization Act (Public Law 105-115) "establishe[s] economic incentives for manufactures to conduct pediatric studies on drugs for which exclusivity or patent protection is available under the Drug Price Competition and Patent Restoration Act (Public Law 98-417) or the Orphan Drug Act (Public Law 97-414)." *Id.* FDA has also published several pediatric guidance documents, which also could have contributed to increased numbers of pediatric studies for FDA-regulated products. *Id.* at 20590.

⁸¹21 C.F.R. § 50.50 (2002) (IRB duties).

Section 50.51 requires that in clinical trials in which no greater than minimal risk to children is present, the IRB must find and document adequate provisions “soliciting the assent of the children and the permission of their parents or guardians as set forth in Sec. 50.55.”⁸² Thus, so long as there is only minimal risk, and so long as proper consent is obtained, FDA permits the use of children as research subjects.

In its notice to the public announcing its intent to establish an interim rule, FDA recognized that the level of risk in a study might change during the course of a clinical investigation.⁸³ FDA, however, noted that measures, such as “exit strategies in the case of adverse events or a lack of efficacy,” or establishment of a data monitoring committee (DMC) to review ongoing data collection might help mitigate unexpected risk.⁸⁴ Section 50.52 allows clinical investigations with more than minimal risk to children to take place if the risk is “presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject’s well-being.”⁸⁵ Thus, research for therapeutic benefit may take place even with enhanced risk. For the investigation to be allowed, however, the IRB must find and document that:

(a)

The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in Sec. 50.55.⁸⁶

⁸²21 C.F.R. § 50.51 (2002) (Clinical investigations not involving greater than minimal risk).

⁸³See Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 79,20593 (April 24, 2001) (to be codified at 21 C.F.R. pt. 50, 56).

⁸⁴*Id.*

⁸⁵21 C.F.R. § 50.52 (2002) (Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects).

⁸⁶*Id.*

If an intervention or procedure poses more than minimal risk to children in a clinical investigation and the risk “does not hold out the prospect of direct benefit for the individual subject,” or if a monitoring procedure “is not likely to contribute to the well-being of the subject,” then Section 50.53 applies.⁸⁷ Section 50.53 allows trials of this nature to take place, provided that the IRB finds and documents that:

(a)

The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition that is of vital importance for the understanding or amelioration of the subjects’ disorder or condition; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in Sec. 50.55.⁸⁸

Thus, even in cases lacking direct benefit to the subjects, minor increases in risk that replicate normal amounts of risk in a child’s everyday life, may be justified by benefits of generalizable knowledge. The knowledge gained, however, must contribute to bettering or understanding the specific subject’s condition; therefore, whether nontherapeutic research is permissible under Section 50.53 remains open to interpretation.

Remaining consistent with its desire to encourage drug testing in children, FDA allows even questionable trials that do not meet the requirements of Section 50.51, Section 50.52, or Section 50.53 to take place if the

⁸⁷21 C.F.R. § 50.53 (2002) (Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects’ disorder or condition).

⁸⁸*Id.*

requirements of Section 50.54 are met. Section 50.54 allows investigations to proceed provided that:

(a)

The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

(1)

That the clinical investigation in fact satisfies the conditions of Sec. 50.51, Sec. 50.52, or Sec. 50.53, as applicable, or

(2) That the following conditions are met:

(i)

The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Sec. 50.55.⁸⁹

Section 50.54 clearly leaves room open to allow for nontherapeutic studies. To alleviate ethical concerns, FDA makes the approval process burdensome and calls for consultation with experts and public comment

⁸⁹21 C.F.R. § 50.54 (2002) (Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children).

to hold FDA accountable.

In any clinical investigation, no matter how much risk is present, FDA has required that proper procedures be followed to obtain adequate consent. Section 50.55 outlines the requirements for soliciting the assent of children and the permission of their parents or guardians.⁹⁰ The requirements are in addition to the “determinations required under other applicable sections of [] subpart D.”⁹¹

Section 50.55 requires the IRB to “determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.”⁹² Thus, FDA places importance in obtaining the actual child’s consent where feasible. To determine whether a child is capable of providing assent, the IRB must take into account the age, maturity, and psychological state of the child.⁹³ The IRB may make this judgment “for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.”⁹⁴ The assent of children in an investigation is not a necessary condition for proceeding with the investigation if the IRB finds:

(1)

That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or

(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.⁹⁵

⁹⁰ See 21 C.F.R. § 50.55 (2002) (Requirements for permission by parents or guardians and for assent by children).

⁹¹ 21 C.F.R. § 50.55(a) (2002).

⁹² *Id.*

⁹³ 21 C.F.R. § 50.55(b) (2002).

⁹⁴ *Id.*

⁹⁵ 21 C.F.R. § 50.55(c) (2002).

Section 50.55 further provides that even where the IRB determines that the children are capable of assenting, the IRB may waive the assent requirement if it finds and documents that:

- (1)
The clinical investigation involves no more than minimal risk to the subjects;
- (2) The waiver will not adversely affect the rights and welfare of the subjects;
- (3) The clinical investigation could not practicably be carried out without the waiver; and
- (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.⁹⁶

In addition to all other requirements under applicable sections of subpart D, “the IRB must determine that the permission of each child’s parent or guardian is granted.”⁹⁷ Where clinical investigations are covered by Section 50.51 or Section 50.52, “the IRB may find that the permission of one parent is sufficient, if consistent with State law.”⁹⁸ For trials covered by Section 50.53 or Section 50.54, “both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with State law.”⁹⁹ Thus, nontherapeutic research, if allowed, may only take place where both parents consent to the investigation.

In all situations requiring parental consent, “permission by parents or guardians must be documented in

⁹⁶21 C.F.R. § 50.55(d) (2002).

⁹⁷21 C.F.R. § 50.55(e) (2002).

⁹⁸*Id.*

⁹⁹*Id.*

accordance with and to the extent required by Sec. 50.27.”¹⁰⁰ Moreover, the IRB “must also determine whether and how much assent must be documented.”¹⁰¹

The final additional safeguard found in the interim rule pertains to children who are wards of the State or wards of any other agency, institution, or entity.¹⁰² Section 50.56 allows these children to be included in clinical investigations only if such investigations are:

(1)

Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.¹⁰³

¹⁰⁰21 C.F.R. § 50.55(f) (2002).

¹⁰¹21 C.F.R. § 50.55(g) (2002).

¹⁰²*See* 21 C.F.R. § 50.56 (2002) (Wards). These requirements prohibit investigators from using children who are wards merely because of convenience. *See* Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 79,20595 (April 24, 2001) (to be codified at 21 C.F.R. pt. 50, 56).

¹⁰³21 C.F.R. § 50.56(a) (2002).

Investigations meeting these requirements must mandate appointment of an advocate for each child who is a ward.”¹⁰⁴ The advocate “will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.”¹⁰⁵ An advocate may represent more than one child.¹⁰⁶ To qualify, the advocate must have “the background and experience to act in, and agree to act in, the best interest of the child for the duration of the child’s participation in the clinical investigation.”¹⁰⁷ Finally, “[t]he advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.”¹⁰⁸ This safeguard resembles protections pertaining to financial disclosure and efforts to avoid conflicts of interest.

In summary, the interim rule seems consistent with FDA’s policy of encouraging drug testing in children. At the same time, the rule seems to represent good faith efforts to recognize ethical dilemmas and to provide adequate safeguards for children. Looking at how provisions of the rule relate to issues raised in current events may illuminate FDA’s response to pediatric research.

IV. Application of Interim Rule to Recent Events

A.

John Hopkins Lead Abatement

Study

Although not directly related to FDA, the Maryland court case addressing the Kennedy Krieger Institute’s

(KKI) lead abatement study raises many of the issues inherent in debates about pediatric research.¹⁰⁹ The purpose of KKI's study was to determine how effective varying degrees of lead paint abatement procedures were in reducing levels of lead in housing.¹¹⁰ After arranging for various degrees of lead abatement modification to be performed in certain homes, KKI encouraged landlords to rent the homes to families with young children.¹¹¹ The researchers anticipated that children living in the homes "would, or at least might, accumulate lead in their blood from the dust," thus enabling them to measure the success of various abatement procedures.¹¹² Although nontherapeutic in nature,¹¹³ arguably, the research protocol was justified by anticipated future benefits that would result from knowing which abatement procedures were effective. This knowledge would help children at large, especially due to the fact that deteriorating lead paint in older housing is the number one source of lead exposure in children in the United States.¹¹⁴

The Court of Appeals for Maryland found the nontherapeutic nature of the program to be problematic.¹¹⁵ The court stated, "In our view, otherwise healthy children should not be the subject of nontherapeutic experimentation or research that has the potential to be harmful to the child."¹¹⁶ Later in the opinion, the court held that "in Maryland a parent, appropriate relative, or other applicable surrogate, cannot consent to the participation of a child... in nontherapeutic research or studies in which there is any risk of injury or

¹⁰⁹While the case does not specifically concern FDA regulations, it does address HHS regulations and portions of the Common Rule. See *Grimes v. Kennedy Krieger, Inst., Inc.*, 782 A.2d 807, 846-49 (2001).

¹¹⁰See *id.* at 812.

¹¹¹See *id.* at 811-12. In one of the cases at bar, the Institute arranged for the landlord to receive public funding to aid in the modifications. See *id.*

¹¹²*Id.* at 813.

¹¹³But see *id.* at 817 (explaining that the IRB reviewing the study encouraged the researchers to misrepresent the purpose of the study in order to bring it under the label of "therapeutic").

¹¹⁴See DIXIE FARLEY, U.S. FOOD AND DRUG ADMINISTRATION, *Dangers of Lead Still Linger*, FDA CONSUMER (Jan.-Feb. 1998), available at <http://www.cfsan.fda.gov/~dms/fdalead.html> (last visited Feb. 22, 2003) (discussing dangers of lead paint).

¹¹⁵See *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 814-15 (2001) (declaring that otherwise healthy children should not be enticed into a situation in which they accumulate lead in their blood; also finding that the study should not have been presented in the nontherapeutic context in the first place).

¹¹⁶*Id.* at 850.

damage to the health of the subject.”¹¹⁷

In addition to the nontherapeutic nature of the study, other issues rendered the research problematic. Most of the families involved in the study were of lower economic status.¹¹⁸ Arguably, KKI influenced these families to participate by promising, in the consent form, to pay them periodic sums and by providing ongoing incentives, such as coupons for food and gifts for the children.¹¹⁹ Subject recruitment has been an evolving concern in human subject protection.

Much of the case focused on whether the researchers owed a duty of care to the parents and their children. Assuming there was a duty, plaintiffs argued that KKI was negligent in failing to completely and accurately inform the parents of the risk involved in the study and in failing to provide proper information about test results during the study. The consent agreements did not fully explain the design of the study.¹²⁰ Parents did not completely understand that their children “might, and perhaps were anticipated to, accumulate some level of lead contaminations in their blood, and that the lead content of the children’s blood would be one of the methods” by which KKI would measure the success of the abatement programs.¹²¹ Moreover, in one of the cases before the court, KKI neglected to timely inform a child’s mother that dust testing in her home revealed higher levels of lead than what might be found in a completed abated house.¹²² KKI disclosed the information nine months later, after the child’s blood was found to contain elevated levels of blood.¹²³ Failing to disclose this information could have resulted in adverse health consequences. By the time symptoms of lead poisoning appear in children, damage is often irreversible.¹²⁴ Moreover, symptoms

¹¹⁷ *Id.* at 858.

¹¹⁸ *See id.* at 813.

¹¹⁹ *See id.* at 843 n.4.

¹²⁰ *See id.* at 813.

¹²¹ *Id.* at 828. *But see* Lainie Friedman Ross, *In Defense of the Hopkins Lead Abatement Studies*, 30 J.L. MED. & ETHICS 50 (2002) (arguing that “the consent forms clearly explained that living in housing that had undergone renovation for lead abatement may not fully protect one’s child from lead exposure.”).

¹²² *See Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 825 (2001).

¹²³ *Id.*

¹²⁴ *See* DIXIE FARLEY, U.S. FOOD AND DRUG ADMINISTRATION, *Dangers of Lead Still Linger*, FDA CONSUMER (Jan.-Feb. 1998), available at <http://www.cfsan.fda.gov/~dms/fdalead.html> (last visited Feb. 22, 2003) (discussing dangers of lead poisoning).

of lead poisoning “can be highly variable depending, in part, on the age of the child, the amount of lead to which the child is exposed, and how long the exposure goes on.”¹²⁵ Without disclosure by KKI, the mother would have been unable to take preventive measures to help her child. The court overruled the lower court’s summary judgment ruling on the negligence issues and found that a special relationship could exist between a researcher and its research subjects.

Whether the findings in this case will affect FDA is unclear. Amici to the case pointed out that some of the court’s rulings are inconsistent with the federal regulations pertaining to participation of children in research.¹²⁶ For example, similar to the provisions in FDA’s interim rule, the federal regulations permit children to participate in nontherapeutic research posing only minimal risk or posing more than minimal risk if certain conditions are present.¹²⁷ The Maryland court’s holding seems to suggest that studies with any risk are not appropriate if nontherapeutic in nature. Later, however, the court, denying the motion for reconsideration, clarified its decision.¹²⁸ The court stated that whether nontherapeutic research is lawful depends upon the amount of risk inherent in a study and its expected benefit.¹²⁹ The court clarified that these issues were left open for further factual development on remand.¹³⁰ Thus, the case can be reconciled with the federal regulations and any challenges based upon the court’s holdings probably would not affect FDA’s regulations on their face. Room for argument, however, exists over whether it is ethical to expose healthy children to nontherapeutic research; these issues may be important if a future case occurred. While

¹²⁵*Id.* (quoting pediatrician Randolph Wykoff, M.D., FDA associate commissioner for operations) (internal quotations omitted).

¹²⁶*See* Lainie Friedman Ross, *In Defense of the Hopkins Lead Abatement Studies*, 30 J.L. MED. & ETHICS 50 (2002).

¹²⁷*See id.* (citing 45 C.F.R. §§ 46.404, 46.406, 46.407, 45.408 (1991)). For example, 45 C.F.R. § 46.404 allows nontherapeutic research that poses more than minimal risk to take place if the research has potential to offer generalizable knowledge of vital importance about the subjects’ disorder or condition. *See id.* (citing 45 C.F.R. § 46.404). Additionally, 45 C.F.R. § 46.407 allows nontherapeutic research posing more than a minor increase over minimal risk to take place if the research will help alleviate serious health problems and a national panel of experts approves the research. *See id.* (citing 45 C.F.R. § 46.407).

¹²⁸*See id.* (citing *Grimes v. Kennedy Krieger, Inst., Inc.*, No. 128 (Md. Oct. 11, 2001) (order denying motion for reconsideration) at 1, available at <http://www.hopkinsmedicine.org/press/2001/October/CourtofAppeals.pdf>).

¹²⁹*See id.* (citing *Grimes v. Kennedy Krieger, Inst., Inc.*, No. 128 (Md. Oct. 11, 2001) (order denying motion for reconsideration) at 2, available at <http://www.hopkinsmedicine.org/press/2001/October/CourtofAppeals.pdf>).

¹³⁰*See id.* (citing *Grimes v. Kennedy Krieger, Inst., Inc.*, No. 128 (Md. Oct. 11, 2001) (order denying motion for reconsideration) at 2, available at <http://www.hopkinsmedicine.org/press/2001/October/CourtofAppeals.pdf>).

the value of the court's holdings as precedent is unclear, the case does affirm a right of human subjects to go to court to seek redress for any wrongs committed in a research study.¹³¹ If future litigation becomes prevalent, FDA's regulations could be challenged.

B. Children's Smallpox Vaccine Trial

Another current event that relates to FDA's policies for protection of children involves the smallpox vaccine. The vaccine has brought FDA's policies under public scrutiny. On October 31, 2002, FDA placed a notice in the *Federal Register* to seek public opinion on whether FDA should proceed with a trial to vaccinate young children with smallpox vaccine.¹³² While it is highly unusual for FDA to seek public opinion on research,¹³³ 21 C.F.R. § 50.54 requires that public comment be sought where it is unclear whether the proposed research meets the requirements of Section 50.1, Section 50.2, or Section 50.3. In this case, the IRB "was unable to assess the prospect of direct benefit" to the children "but found that the research presented a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of the children."¹³⁴ These facts made Section 50.54 relevant. Additionally, the climate of the country and the fact that "[s]mallpox vaccine is the most highly reactive vaccine that has ever been routinely used in humans" probably motivated the FDA to go public.¹³⁵ Hundreds of people voiced opinions in response to the notice.¹³⁶

¹³¹ See *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 851 (2001) (stating that the rights of human subjects "are afforded the protection of the courts when such subjects seek redress for any wrongs committed").

¹³² See Susan J. Landers, *Prudent to Test Smallpox Vaccine in Kids?*, American Medical News (Dec. 2, 2002), available at <http://www.ama-assn.org/sci-pubs/amnews/pick.02/hlsc1202.htm> (last visited Feb. 28, 2002).

¹³³ See FoxNews.com, *FDA Mulls When Smallpox Vaccine Study Should Begin for Children* (Nov. 1, 2002), at <http://www.foxnews.com/story/0,2933,68722,00.html>.

¹³⁴ Solicitation of Public Review and Comment On Research Protocol: A Multicenter, Randomized Dose Response Study of the Safety, Clinical and Immune Response of Dryvax Administered to Children 2 to 5 Years of Age, 67 Fed. Reg. 66404 (Oct. 31, 2002).

¹³⁵ See VERA SHARAV, ALLIANCE FOR HUMAN RESEARCH PROTECTION, COMMENTS RE: PROPOSED SMALLPOX VACCINE TRIAL TO TEST THE SAFETY OF DRYVAX ADMINISTRATION TO CHILDREN 2 TO 5 YEARS OF AGE, FDA Docket Number 02N-0466, at 1, available at <http://www.fda.gov/ohrms/dockets/dailys/02/Dec02/120302/02N-0466-EC-450.htm> (last visited Feb. 22, 2003).

¹³⁶ See Susan J. Landers, American Medical News, *Prudent to Test Smallpox Vaccine in Kids?* (Dec. 2, 2002), available at <http://www.ama-assn.org/sci-pubs/amnews/pick.02/hlsc1202.htm> (last visited Feb. 28, 2002).

The proposed trial would involve inoculating forty children, aged two to five, with the vaccine, called Dryvax.¹³⁷ Dryvax was pulled out of storage after being frozen for approximately thirty years.¹³⁸ The government terminated routine vaccination against smallpox in 1971, partly because of the severe side effects of the disease and partly because of the low risk of exposure to smallpox.¹³⁹ In 2001, the Center for Disease and Control (CDC) began inoculating members of its staff with Dryvax to prepare for a possible outbreak of smallpox due to terrorist threats.¹⁴⁰ CDC, however, allegedly stopped vaccinating, because the adverse reactions were greater than anticipated.¹⁴¹ Currently, as prompted by the Bush Administration, smallpox vaccines are being administered to public health officials to prepare for a possible biological attack.¹⁴²

Much of the criticism of the smallpox trial has focused on the risk/benefit calculus. Based on data from the 1960s, “CDC estimates that for every 1 million people vaccinated for the first time about 1,000” will experience serious reactions.¹⁴³ In 14 to 52 of those cases, the effects may be life threatening.¹⁴⁴ Moreover, children less than five years of age are at greater risk of developing adverse side effects than other age groups.¹⁴⁵ Also involved in the risk factor is the possibility of exposure to third parties. In the past, fatalities occurred in close household contacts of recently vaccinated family members.¹⁴⁶ To minimize third party exposure, researchers plan to take vaccinated children out of day care and school.¹⁴⁷ Researchers have

¹³⁷See FoxNews.com, *FDA Mulls When Smallpox Vaccine Study Should Begin for Children* (Nov. 1, 2002), at <http://www.foxnews.com/story/0,2933,68722,00.html>.

¹³⁸See VERA SHARAV, ALLIANCE FOR HUMAN RESEARCH PROTECTION, COMMENTS RE: PROPOSED SMALLPOX VACCINE TRIAL TO TEST THE SAFETY OF DRYVAX ADMINISTRATION TO CHILDREN 2 TO 5 YEARS OF AGE, FDA Docket Number 02N-0466, at 3, available at <http://www.fda.gov/ohrms/dockets/dailys/02/Dec02/120302/02N-0466-EC-450.htm> (last visited Feb. 22, 2003).

¹³⁹See *id.* at 1.

¹⁴⁰See *id.* at 3.

¹⁴¹See *id.*

¹⁴²See FoxNews.com, *FDA Mulls When Smallpox Vaccine Study Should Begin for Children* (Nov. 1, 2002), at <http://www.foxnews.com/story/0,2933,68722,00.html>; see also Declaration Regarding Administration of Smallpox Countermeasures, 68 Fed. Reg. 18,4212 (Jan. 28, 2003).

¹⁴³VERA SHARAV, ALLIANCE FOR HUMAN RESEARCH PROTECTION, COMMENTS RE: PROPOSED SMALLPOX VACCINE TRIAL TO TEST THE SAFETY OF DRYVAX ADMINISTRATION TO CHILDREN 2 TO 5 YEARS OF AGE, FDA Docket Number 02N-0466, at 1, available at <http://www.fda.gov/ohrms/dockets/dailys/02/Dec02/120302/02N-0466-EC-450.htm> (last visited Feb. 22, 2003).

¹⁴⁴See *id.*

¹⁴⁵See *id.*

¹⁴⁶See *id.* at 2.

¹⁴⁷See FoxNews.com, *FDA Mulls When Smallpox Vaccine Study Should Begin for Children* (Nov. 1, 2002), at <http://www.foxnews.com/story/0,2933,68722,00.html>.

also implemented a response plan that will treat possible severe reactions with vaccinia immune globulin and cidofovir.¹⁴⁸ Cidofovir has FDA approval “but not to combat adverse smallpox vaccine events.”¹⁴⁹ Even if some of the risk can be contained, there is an ethical question of whether there is enough benefit involved in the trial to justify exposing healthy children to the risk. Vaccinated children will only benefit in the event of a bioterrorist attack.¹⁵⁰ There are no current cases of smallpox. Many critics, such as the American Academy of Pediatrics, believe that children should not receive the vaccine prior to an outbreak of smallpox.¹⁵¹ If an outbreak does occur, experts say the vaccine can be administered three to four days after exposure to the virus and still be effective.¹⁵² On the other hand, those in favor of the trial believe that not testing the vaccine on children is unethical. If an outbreak occurred without prior testing, they argue, the government would be letting “millions of children be part of an emergency experiment.”¹⁵³ Arguably, this would be worse than testing a selected number of children now.

Another criticism focuses on the vulnerability of children and the possibility of misinformed parents. The Alliance for Human Protection has criticized the CDC’s consent form.¹⁵⁴ The organization argued that the form misrepresents the fact that children are not currently at any particular risk of smallpox.¹⁵⁵ Additionally, critics argue that parents may be improperly influenced. The form talks about a \$120 reimbursement and a \$40 gift certificate for children before the form mentions risks.¹⁵⁶ Many commentators agree that

¹⁴⁸See Susan J. Landers, American Medical News, *Prudent to Test Smallpox Vaccine in Kids?* (Dec. 2, 2002), available at <http://www.ama-assn.org/sci-pubs/amnews/pick.02/hlsc1202.htm> (last visited Feb. 28, 2002).

¹⁴⁹*Id.*

¹⁵⁰See FoxNews.com, *FDA Mulls When Smallpox Vaccine Study Should Begin for Children* (Nov. 1, 2002), at <http://www.foxnews.com/story/0,2933,68722,00.html>.

¹⁵¹See AMERICAN ACADEMY OF PEDIATRICS, *CHILDREN SHOULD NOT BE GIVEN SMALLPOX VACCINE* (Jan. 30, 2003), available at http://www.aap.org/advocacy/washing/smallpox_vaccine.htm (last visited Feb. 22, 2003).

¹⁵²See VERA SHARAV, ALLIANCE FOR HUMAN RESEARCH PROTECTION, COMMENTS RE: PROPOSED SMALLPOX VACCINE TRIAL TO TEST THE SAFETY OF DRYVAX ADMINISTRATION TO CHILDREN 2 TO 5 YEARS OF AGE, FDA Docket Number 02N-0466, at 2, available at <http://www.fda.gov/ohrms/dockets/dailys/02/Dec02/120302/02N-0466-EC-450.htm> (last visited Feb. 22, 2003).

¹⁵³See AMERICAN ACADEMY OF PEDIATRICS, *CHILDREN SHOULD NOT BE GIVEN SMALLPOX VACCINE* (Jan. 30, 2003), available at http://www.aap.org/advocacy/washing/smallpox_vaccine.htm (last visited Feb. 22, 2003).

¹⁵⁴See VERA SHARAV, ALLIANCE FOR HUMAN RESEARCH PROTECTION, COMMENTS RE: PROPOSED SMALLPOX VACCINE TRIAL TO TEST THE SAFETY OF DRYVAX ADMINISTRATION TO CHILDREN 2 TO 5 YEARS OF AGE, FDA Docket Number 02N-0466, at 6, available at <http://www.fda.gov/ohrms/dockets/dailys/02/Dec02/120302/02N-0466-EC-450.htm> (last visited Feb. 22, 2003).

¹⁵⁵*See id.*

¹⁵⁶*See id.*

fully explaining risks to parents is crucial.¹⁵⁷ Some experts have suggested that FDA limit inoculations to children of adults enrolled in vaccine studies, “because those parents may better understand the risks.”¹⁵⁸ Better informed parents, however, does not seem to justify exposing helpless children to a potentially life threatening disease.

FDA accepted comments regarding the trial until Dec. 2, 2002.¹⁵⁹ Final determination on whether to proceed with the trial was left with Secretary of the Department of Health and Human Services Tommy Thompson and FDA Commissioner Mark McClellan, MD, PhD.¹⁶⁰ On January 28, 2003, HHS placed a declaration of smallpox countermeasures in the *Federal Register*.¹⁶¹ The declaration approves the use of Dryvax as a countermeasure but limits its administration to certain health care workers, members of smallpox response teams, public safety personnel, and personnel associated with certain U.S. Government facilities abroad.¹⁶² The declaration makes no mention of children or the proposed trial. It is likely that HHS and FDA have decided to halt the trial.

The smallpox situation is particularly telling, because it tests the FDA’s regulations at its fringes. Section 50.54 only applies to the most questionable trials. Even then, the regulations state that the IRB must find and document that the investigation will help further understand, prevent, or alleviate a serious problem affecting the health or welfare of children.¹⁶³ Because the threat of an outbreak of smallpox is speculative, it does not seem to qualify as a “serious health problem affecting the health or welfare of children.”¹⁶⁴

Additionally, Section 50.54 requires the involvement of various experts and the involvement of the public.

¹⁵⁷See FoxNews.com, *FDA Mulls When Smallpox Vaccine Study Should Begin for Children* (Nov. 1, 2002), at <http://www.foxnews.com/story/0,2933,68722,00.html>.

¹⁵⁸*Id.*

¹⁵⁹Solicitation of Public Review and Comment On Research Protocol: A Multicenter, Randomized Dose Response Study of the Safety, Clinical and Immune Response of Dryvax Administered to Children 2 to 5 Years of Age, 67 Fed. Reg. 211,66403 (Oct. 31, 2002).

¹⁶⁰See Susan J. Landers, American Medical News, *Prudent to Test Smallpox Vaccine in Kids?* (Dec. 2, 2002), available at <http://www.ama-assn.org/sci-pubs/amnews/pick.02/hlsc1202.htm> (last visited Feb. 28, 2002).

¹⁶¹Declaration Regarding Administration of Smallpox Countermeasures, 68 Fed. Reg. 18,4212 (Jan. 28, 2003).

¹⁶²See *id.* at 4212-13.

¹⁶³See 21 C.F.R. § 50.54 (2002).

¹⁶⁴*Id.*

Because FDA has not issued any formal ruling on whether the trial will proceed, it seems as if, in this case, public comment and expert opinion were persuasive. Thus, one could conclude that FDA's regulations do work and do provide proper mechanisms for ensuring ethical standards and judgments. On the other hand, if FDA does decide to proceed with the trial, the ethical impact of the regulations may be suspect.

Finally, for research not at the fringes, HHS's announcement of its intent to fund testing of twelve commonly prescribed drugs in children during fiscal year 2003 and 2004 reinforces FDA's policy of encouraging pediatric drug testing.¹⁶⁵ For now, it seems as if FDA's policies will stand.

V. Conclusion

FDA's response to debates over pediatric drug testing reveals the competing duties of FDA to protect the public but also to promote research. How risk adverse FDA will be in a given situation will depend upon its analysis of the risk/benefit calculus. FDA's interim rule seems to provide a workable framework for assessing different ratios of risk and benefit and seems to provide adequate opportunity for outside validation in the most controversial situations. Although it has enormous power, FDA does remain accountable to the public and to HHS, and its response to pediatric drug testing is an illustrative example of how FDA balances its competing roles.

¹⁶⁵See DEPARTMENT OF HEALTH AND HUMAN SERVICES, HHS IDENTIFIES DRUGS FOR PEDIATRIC TESTING AND ANNOUNCES FY 2003 AND FY 2004 FUNDING (2003), *available at* <http://www.hhs.gov/news/press/2003pres/20030121.html> (last visited Feb. 22, 2003).