

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Parts 50, 56, 312, 314, 601, 812, and 814**

[Docket No. 95N-0158]

RIN 0910-AA60

Protection of Human Subjects; Informed Consent**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Proposed rule; opportunity for public comment.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its current informed consent regulations to permit harmonization of Federal policies on emergency research, and to reduce confusion as to when such research can proceed without obtaining informed consent. The regulation provides a narrow exception to the requirement for obtaining and documenting informed consent from each human subject prior to initiation of an experimental treatment. The exception would apply to a limited class of research activities involving human subjects who, because of their life-threatening medical condition and the unavailability of legally authorized persons to represent them, are in need of emergency medical intervention and cannot provide legally effective informed consent. FDA is proposing this action in response to growing concerns that current rules are making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized.

DATES: Written comments by November 6, 1995.**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.**FOR FURTHER INFORMATION CONTACT:** Glen D. Drew, Office of Health Affairs (HFY-20), Food and Drug Administration, Rockville, MD 20852, 301-443-1382.**SUPPLEMENTARY INFORMATION:****I. Harmonization**

Recently, the Department of Health and Human Services (HHS) authorized Institutional Review Boards (IRB's) to waive informed consent requirements for one specific National Institutes of Health-funded project under strictly defined circumstances similar to those authorized by these FDA proposed

rules. (See HHS Notice of Action Related to Emergency Research Activity at 60 FR 38353 through 38354, July 26, 1995.) HHS is considering a general IRB authorization to waive informed consent requirements under the same strictly defined circumstances as those identified in the specific project waiver authorization and in the FDA proposed rule. Any HHS decision to grant a general informed consent waiver authority to IRB's for emergency research activities will be made with attention to harmonization with action on these FDA proposed rules and will be published in the Federal Register. It is the intent of HHS to bring the HHS (45 CFR part 46) and FDA (21 CFR part 50) regulations into harmony on this matter at the time this rule is made final.

II. Informed Consent Regulations

Much of what has become standard, accepted, medical therapies for use in acute or resuscitation clinical care has not been evaluated by adequate trials that demonstrate either safety or effectiveness. Controlled clinical trials have demonstrated that some therapies that have become standard medical practice are ineffective or even harmful. Other standard therapies, although shown to be effective in clinical trials, have significant limitations, in that, for example, they only work in a small percentage of those individuals who receive the therapies, so that testing of improved or additional therapies remains critically important. By permitting certain adequate and well-controlled clinical trials to occur that involve human subjects who are confronted by a life-threatening condition and who also are unable to give informed consent because of that condition, the agency expects the clinical trials to allow individuals in these situations access to potentially life-saving therapies and to result in advancement in knowledge and improvement of therapies used in emergency medical situations that currently have poor clinical outcome.

Sections 505(i), 507(d), and 520(g) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i), 357(d), and 360j(g)) require FDA to publish regulations governing the use in humans of drugs, including certain biologics and antibiotics, and devices in clinical investigations (hereafter "investigational drugs" and "investigational devices," respectively).

In 1962, amendments to the act (Section 505(d)) provided that drugs could be approved for marketing only if they were found, on the basis of adequate and well-controlled clinical

investigations, to be effective as well as safe for their intended use. Section 505(i) of the act also provided that unapproved drugs could be made available to humans for investigational use only. Section 505(i) of the act further provided for the issuance of regulations which condition the investigational use, in part, on:

*** the manufacturer *** requiring that experts using such drugs *** certify *** that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible, or in their professional judgment, contrary to the best interests of such human beings.

This provision created the general requirement of informed consent for investigations conducted under sections 505(i) and 507(d) of the act.

The Medical Device Amendments of 1976 revised FDA's authority to regulate medical devices and, in part, set up a statutory scheme under which devices would be classified and subjected to varying degrees of regulatory control according to classification. Section 520(g) of the act created a system under which the safety and effectiveness of new medical devices could be investigated by qualified experts.

Among other requirements, section 520(g)(3)(D) of the act provided that the sponsor of clinical investigations must: *** assure that informed consent will be obtained from each human subject (or his representative) *** except where subject to such conditions as the Secretary may prescribe, the investigator conducting or supervising the proposed clinical testing of the device determines in writing that there exists a life threatening situation involving the human subject of such testing which necessitates the use of such device and it is not feasible to obtain informed consent from the subject and there is not sufficient time to obtain such consent from his representative. Section 520(g)(3)(D) of the act further provided that this determination:

*** shall be concurred in by a licensed physician who is not involved in the testing of the human subject with respect to which such determination is made unless immediate use of the device is required to save the life of the human subject of such testing and there is not sufficient time to obtain such concurrence.

Sections 505(i) and 507(d) of the act permit waiver of informed consent either when "it [is] not feasible" or when it is "contrary to the best interests of such [subjects]." Section 520(g) of the act permits waiver of informed consent in life-threatening situations which "necessitates the use of such device and it is not feasible to obtain informed consent ***."

In 1979, following the enactment of the Medical Device Amendments, FDA proposed rules revising its regulations governing informed consent (44 FR 47713, August 14, 1979). FDA issued final regulations governing informed consent in the Federal Register of January 27, 1981 (46 FR 8942). Those regulations, codified in part 50 (21 CFR part 50), apply to any clinical investigation subject to regulation by FDA under sections 505(i), 507(d), and 520(g) of the act, as well as to clinical investigations that support applications for research or marketing permits for products regulated by FDA. The agency explained its reasons for revising its regulations governing informed consent in the preamble to these final regulations. These reasons included, among others: (1) The desire to address the informed consent provision included in the device amendments; (2) the need to create a uniform set of agency-wide informed consent standards for more effective administration of the agency's bioresearch monitoring program; (3) implementation of recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; and (4) harmonization of FDA rules with those of the HHS.

Some comments on the proposed regulations questioned whether the regulations met the statutory requirements of sections 505, 507, and 520 of the act, but all comments approved of the elimination of regulatory confusion and the enhancement of human subject protections. In responding to public comments, the agency stated its belief that the standard regarding informed consent expressed in the 1962 Drug Amendments was the standard of its time, but that it was no longer the current standard of practice, given progress in the understanding of ethical principles and their relevance to biomedical research. The preamble went on to express the agency's intent to adopt a single standard that reflected both the most current congressional thinking on informed consent and the important ethical principles and social policies underlying the doctrine of consent. (See 46 FR 8942 to 8944, January 27, 1981.) In the preamble to the August 14, 1979, proposed rule, FDA further explained the requirement that a determination be made as to lack of an available alternative method of therapy that may save the life of the subject. FDA stated that this requirement:

* * * has been added to prevent routine reliance on the exception. This additional requirement should provide guidance to

investigators regarding those exceptional situations in which informed consent need not be obtained. As noted above, obtaining informed consent has come to be a standard of practice for professional clinical investigators. Defining those circumstances when informed consent need not be obtained should provide a clearer understanding of how to determine when informed consent is "not feasible." (44 FR 47713 at 47720).

In § 50.23(a) of the 1981 rule, FDA required informed consent except when obtaining informed consent is determined not to be feasible for the emergency use of an investigational article, where:

* * * both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: (1) The human subject is confronted by a life-threatening situation necessitating the use of the test article. (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject. (3) Time is not sufficient to obtain consent from the subject's legal representative. (4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the investigational product is, in the investigator's opinion, required to preserve the life of the subject, and there is not sufficient time to obtain an independent physician's determination in advance of using the product, the use of the product is to be reviewed and evaluated in writing by a physician who is not participating in the study within 5 working days after its use (46 FR 8951, January 27, 1981).

On December 21, 1990, FDA published an interim rule in the Federal Register (55 FR 52814), amending these informed consent regulations to permit an exception from the general requirements for informed consent in certain military combat circumstances. As codified in § 50.23(d), the Commissioner of Food and Drugs (the Commissioner) is permitted to make a determination that obtaining informed consent from military personnel for the use of an investigational drug or biologic is not feasible in certain battlefield or combat-related situations. The Commissioner is authorized to make such a determination when the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) named in the investigational new drug application (IND) provide written justification for their conclusions that, in the use of specific investigational drugs or biologics in a specific combat-related situation, obtaining informed consent is not feasible and withholding treatment

would be contrary to the best interests of the military personnel because of military combat exigencies and that the waiver of informed consent is ethically justified (52 FR 52814, December 21, 1990). This exception was upheld in the United States Court of Appeals for the D.C. Circuit in 1991. (See *Doe v. Sullivan*, 938 F.2d 1370 (D.C. Cir. 1991), affirming 756 F. Supp. 12 (D. D.C. 1991)).

In June 1991, the Office of Science and Technology Policy published the common Federal Policy for the Protection of Human Subjects (common rule) in the Federal Register. (56 FR 28002, June 18, 1991.) Issuance of the common rule was the result of more than a decade of work by Federal agencies and departments that conduct, support, or regulate research involving human subjects. The common rule implemented a recommendation of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (President's Commission). This recommendation was included in the December 1981 report of the President's Commission, entitled, "First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and their Implementation, for the Protection of Human Subjects in Biomedical and Behavioral Research, Protecting Human Subjects," which stated:

The President should, through appropriate action, require that all federal departments and agencies adopt as a common core the regulations governing research with human subjects issued by the Department of Health and Human Services (codified at 45 CFR 46), as periodically amended or revised, while permitting additions needed by any department or agency that are not inconsistent with these core provisions. (56 FR 28004, June 18, 1991)

In May 1982, the Chairman of the Federal Coordinating Council for Science, Engineering, and Technology appointed an Ad Hoc Committee for the Protection of Human Subjects. The Ad Hoc Committee agreed that uniformity was desirable among departments and agencies and worked to develop a model Federal policy, which became the common rule, to "eliminate unnecessary regulation and to promote increased understanding and ease of compliance by institutions that conduct federally supported or regulated research involving human subjects." (56 FR 28004, June 18, 1991.) Section xx.116(d) of the common rule described the conditions under which an Institutional Review Board (IRB) was authorized to waive some or all of the elements of informed consent. This section was adopted unchanged into the HHS regulations (45 CFR part 46). (56 FR

28022, June 18, 1991.) The HHS regulations apply to research supported or conducted by HHS; they are implemented under the direction of the Office for Protection from Research Risks (OPRR) at the National Institutes of Health (NIH).

Although FDA concurred in the common rule and amended its regulations in 21 CFR parts 50 and 56 to conform them to the common rule to the extent permitted by the act, FDA regulations diverged from section xx.116(d). (56 FR 28025, June 18, 1991.) In describing the reason for this divergence, FDA stated as follows:

The act requires that informed consent be obtained from all subjects of clinical investigations except in very limited circumstances (see, e.g., 21 U.S.C. 355(i), 357(d)(3), and 360j(g)(3)(D), which establish requirements for the conduct of clinical investigations for drugs, antibiotic drugs, and medical devices, respectively). FDA does not have the authority under the act to waive this requirement.

(53 FR 45679, November 10, 1988).

Thus, FDA retained its exception language dealing with individual emergency use which was contained in FDA's 1981 regulations (§ 50.23(a) through (c)); this exception remains applicable today. FDA modified other aspects of parts 50 and 56 (21 CFR part 56) in the Federal Register on June 18, 1991, in order to bring them into harmony with the common rule (56 FR 28025).

IRB's that are subject to both the HHS and FDA regulations have had to ensure that both the criteria in the common rule as set forth at 45 CFR part 46 and in FDA's regulation at 21 CFR part 50 are met in order to permit research to be approved.

On many occasions IRB's, functioning under HHS regulations, have been unable to approve research that required use of the waiver allowed by 45 CFR 46.116(d) because the risk involved in emergency research activities was thought to be greater than minimal and therefore the condition that the research activity "involve no more than minimal risk" could not be met. (See 45 CFR 46.116(d).)

Similarly, FDA has permitted only a very limited number of controlled trials involving investigational drugs to be conducted without informed consent under its current exception provisions. This is because § 50.23(a) permits the use of an investigational product without consent only in order to save the life of a patient, and if there is no other approved or generally recognized alternative therapy available that provides an equal or greater likelihood of saving the life of the patient. In other words, the investigator and the

independent physician have had to determine that the investigational product represented the best available treatment for the patient.

The agency has permitted limited trials involving investigational drugs to be conducted by interpreting § 50.23(a) as describing the general state of circumstances that must exist as a threshold to determining that informed consent is not feasible (Refs. 1 and 2). The term "human subject," defined in § 50.3(g) as one who participates in research either as a recipient of the test article or as a control, supports the interpretation that this provision was intended to be used in the setting of an investigation conducted in accordance with principles of good clinical design, including blinding, randomization, and, where appropriate, use of a placebo as a control.

III. Background on Current Practices in the Research Community

Most therapeutic intervention in acute care and emergency research must be initiated immediately to be life-saving. For victims of heart attacks or head injuries, for example, this intervention often must be instituted in the field, prior to hospital admission, when the individual is usually found to be unresponsive and unable to communicate and where there usually is no authorized representative of the subject available to give surrogate consent.

In 1993, the agency became aware that certain IRB's were approving research involving interventions in acutely life-threatening situations by invoking a "deferred consent" procedure. This term was used to describe a procedure whereby subjects or representatives of subjects are informed, after the fact, that the subject participated, unknowingly, in a clinical investigation of an experimental product, and was administered a test article in the course of the investigation. Subjects or their representatives were then asked to ratify that participation retroactively, and to agree to continuing participation (Refs. 3 through 6). As described, "deferred consent" is nothing other than post-hoc ratification. Post-hoc ratification is not genuine consent because the subject or representative has no opportunity to prevent the administration of the test article, and cannot, therefore, meaningfully be said to have consented to its use (Ref. 7).

In August 1993, IRB chairs at institutions with written assurances of compliance with HHS regulations were sent a letter by NIH's OPRR reiterating the mandate for obtaining legally effective informed consent

prospectively and reminding them that the only deviation allowed by the HHS regulations is contained in 45 CFR 46.116(d), its waiver provision. The letter indicated that "deferred consent" or "ratification" fails to constitute informed consent under the HHS regulations (Ref. 8).

During the summer of 1993, the Commissioner of Food and Drugs received a number of letters from the neurology and emergency medicine communities, including the Society for Academic Emergency Medicine, the National Coalition for Research in Neurological Disorders, and the National Head Injury Foundation, expressing concern about their continued ability to conduct placebo controlled research in subjects unable to provide informed consent if FDA did not permit "implied" or "deferred consent." The Commissioner responded to these letters on September 14, 1993, indicating that FDA did not agree that "deferred" consent constituted true consent; he stated further that:

While we recognize that it is not always possible to obtain informed consent from subjects prior to the administration of an investigational drug, we believe that it is critical to define and seek some consensus on how, precisely, patients who cannot give consent can be enrolled in such trials * * *. Before establishing new policy in this area, the Agency believes that it needs broad public and scientific input in order to determine how to balance the need for well-controlled studies with the protection of subjects' rights. Therefore, we are in the early stages of planning a workshop that will be co-sponsored by NIH to obtain necessary advice on this topic. * * * * (Refs. 9 through 12)

Thus, although the research community is now aware that "deferred consent" does not meet the requirements of either HHS or FDA rules, and does not constitute valid informed consent, it has been given no alternative procedure, under which it may conduct emergency research under the FDA and HHS regulations, other than the limited exceptions and exemptions described previously.

IV. Patients and Research Community's Support for Change in Regulation and Congressional Interest

In correspondence, at meetings, and in published articles, the IRB and research communities have expressed their frustration at the difficulties they faced in interpreting existing regulations to fit the needs of emergency research. They have identified the need for FDA and NIH to reach a decision concerning the conduct of these studies that would result in a harmonization of the FDA and HHS regulations. Patient advocacy

groups and researchers have stressed that the research at stake is of great importance to patients and the health of the nation and care must be taken to ensure that the agencies' regulations do not inappropriately disrupt access to, or prevent the development of, potentially life-saving treatments for serious illnesses and injuries (Refs. 13 through 20). The IRB and research communities have stressed that a common position adopted by both FDA and NIH will help eliminate confusion concerning which regulations, FDA or HHS or both, need to be followed and will eliminate conflicting requirements that must be met in order for the research to proceed. This is especially true in cases where a majority of the study sites are subject to both sets of regulations. Finally, they have argued that it is appropriate that FDA and NIH agree on the basic conditions and the ethical conduct of acute care research in order to carry out PHS's dual leadership responsibility to promote sound biomedical research while helping to protect the rights and welfare of human subjects (Refs. 21 through 25).

The research addressed by this proposed regulation is believed to constitute a small fraction of all clinical research. This is because, in some instances, an individual may be unconscious or incompetent to give informed consent, but immediate involvement in research is not needed to promote healing or to prevent death. In those instances, it may be possible to delay participation in research until consent from a legally authorized representative can be obtained. There are also medical conditions that predictably occur in given identifiable patient populations. In such cases, prior informed consent can be obtained from potential future subjects before the intervention occurs because the patient will understand the likelihood of the future need to participate in research when consent cannot be obtained. In other cases, such as events that occur regularly in already hospitalized, acutely ill patients, the majority of subjects will have a legally authorized representative readily available to provide surrogate consent. In these instances, the research may, in accord with the provisions of the law of the jurisdiction, proceed without invoking a waiver of informed consent. In those cases that remain, research can only be conducted in the absence of informed consent.

A May 23, 1994, hearing of the Subcommittee on Regulation, Business Opportunities, and Technology, House Committee on Small Business, then chaired by Representative Ron Wyden,

addressed problems encountered in securing informed consent of subjects in clinical trials of investigational drugs and medical devices (Ref. 26). In Representative Wyden's opening remarks, he acknowledged that while informed consent is an essential component of biomedical research, there are certain conditions under which obtaining informed consent in the classic sense may not be possible, and it is imperative that testing of potentially life-saving therapies go forward. He further asserted that contradictory and confusing Federal policies on informed consent have fostered inconsistent application of the Federal requirements on the part of investigators and IRB members. Representative Larry Combest, in his opening statement, expressed his desire for HHS Secretary Donna Shalala to establish consistent Federal rules related to obtaining informed consent during research on unapproved drugs and medical devices. He emphasized the need to harmonize HHS and FDA regulations while streamlining the approval process.

Researchers, IRB members, device and drug manufacturers, and ethicists testified about the state of emergency research and the negative impact current regulations have had on the ability of such research to proceed; the ethical issues surrounding the conduct of emergency research in situations where human subjects are not competent to give informed consent; and the need for better guidance from Federal agencies. Representatives from NIH and FDA testifying at the hearing acknowledged the need to further examine the issue of circumstances under which research activities may go forward when informed consent cannot be obtained.

On October 25, 1994, persons associated with several professional organizations, institutions, patient advocacy groups, and the bioethics community met at the Coalition Conference of Acute Resuscitation and Critical Care Researchers (the Coalition) to discuss the current Federal regulations regarding informed consent for participation in research. Observers from the legal community, congressional and senate offices, FDA, and the NIH's OPRR also attended.

The Coalition conference was convened under the joint sponsorship of the American Heart Association and the Society for Academic Emergency Medicine and included representatives from the American Academy of Clinical Toxicology, the American Association for the Surgery of Trauma, the American College of Cardiology, the American

College of Emergency Physicians, the Applied Research Ethics National Association, the Emergency Nurses Association, the Joint Section on Neurotrauma and Critical Care, the National Head Injury Foundation, and the Society of Critical Care Medicine.

Following this Coalition conference, the Coalition developed a consensus document to offer recommendations to help resolve some of the issues concerning informed consent and waiver of consent in emergency research. The American Heart Association and the Society for Academic Emergency Medicine submitted the consensus statement to FDA. The consensus document has been endorsed by a number of professional organizations, including the American Academy of Clinical Toxicology, the American Academy of Pediatrics' Pediatric Emergency Medicine Collaborative Research Committee and Section on Emergency Medicine, the American Association for the Surgery of Trauma, the American Autoimmune Related Diseases Association, the American Brain Injury Consortium, the American College of Emergency Physicians, the Applied Research Ethics National Association, the Emergency Nurses Association, the Medical Device Manufacturers Association, the National Head Injury Foundation, the New England Biomedical Research Coalition, the Society for Pediatric Emergency Medicine, the Society for Critical Care Medicine, and the National Association of EMS Physicians.

The consensus document described the importance of emergency research, provided background on the current regulations that govern waiver of consent in clinical research trials, and reviewed current issues arising from the use of waiver of consent in emergency research. The consensus document concluded that there are circumstances under which it is not feasible to obtain consent for enrollment into a protocol involving emergency research; and that, in these circumstances, patients are vulnerable both to risks associated with research, but also to being denied benefits offered by research interventions when no effective standard treatment is known. The consensus document contained recommendations "which should be met when the critical nature of the illness or injury, or the need for rapid treatment intervention, precludes prospective consent for participation in emergency research" (Ref. 22).

On January 9 and 10, 1995, FDA and NIH cosponsored a Public Forum on Informed Consent in Clinical Research Conducted in Emergency

Circumstances, as was proposed by the Commissioner of Food and Drugs in his letters of September 14, 1993 (Refs. 9 through 12 and Refs. 23 and 24). The Coalition consensus document was presented and discussed as well as other models for changing the regulatory paradigm (Ref. 25). Participants at that public forum affirmed the need to protect research subjects while allowing clinical research to proceed if the research subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and immediate intervention is necessary if the intervention is to be of benefit (Refs. 25 and 26). Many participants expressed concern that the current regulations value individual autonomy and the right to informed consent at the expense of the principles of beneficence and justice. They argued that when the expected outcome of standard therapy is poor, and a promising research intervention is available, the principle of beneficence should be permitted to take precedence over the principle of autonomy (Ref. 23). A minority view expressed was that one cannot ethically assume that acutely ill, incompetent patients would, if they were able, choose to participate in a research protocol. Those supporting this view believed that to exclude these patients from a research protocol did not discriminate against them, but rather respected their autonomy (Refs. 24, 27, and 28).

Forum participants discussed the ethical, regulatory, and operational challenges faced by IRB's and by emergency and acute care researchers, as well as ideas for resolving those dilemmas in an ethical way. Speakers emphasized that the "golden hour" or the "window of opportunity" following acute injury is a concept on which modern trauma care is based. "Nearly all patients who die from injury in the first 24 hours do so from processes set in motion at the time of injury. Any therapeutic intervention must [therefore] be begun immediately to interrupt the injury-induced cascade of body reactions leading to death. That is, intervention must be instituted in the field by the first response team of paramedics, in the trauma room in the operating room, and in the surgical critical care unit" (Ref. 23, p. 277).

Participants agreed that current resuscitation modalities are only minimally effective in saving lives and improving outcome and quality of life. Trauma and acute care physicians reported frustration in employing time-honored treatments that provide little benefit to their patients. Many

expressed concern that, because of the current Federal regulations, emergency care professionals are hesitant to conduct appropriately designed clinical trials which are needed to validate or discredit current or innovative treatments. During the Public Forum, participants provided numerous examples of the chilling effect that the current regulations have had on the conduct of clinical research, including cardiopulmonary resuscitation (CPR) studies, and studies of acute trauma, overdose, acute asthma exacerbations, cardiac arrest, head injury, seizures, and stroke (Refs. 23, 24, and 25).

Representative of the studies discussed was one in the area of sudden cardiac arrest. Each year, approximately 350,000 people in the United States suffer a sudden cardiac arrest. Most die, while many others are irreversibly harmed by complications such as brain damage. In the cases of patients who survive, the risk of recurrence is high and the protection offered by easily implantable cardioverter-defibrillators exemplifies the important successes that can be achieved. One of the most critical challenges is to find ways to improve the initial survival rate of individuals who are typically unresponsive and unable to communicate. Currently, despite efforts to instill basic life support education (i.e., standard CPR techniques), only a small percentage of individuals who suffer sudden out-of-hospital cardiac arrests are resuscitated by bystanders. Few survive to leave the hospital. This percentage may be as low as 1 to 3 percent in some large metropolitan areas, with the best results estimated to be only in the 25 percent range. Given the large number of sudden cardiac arrests annually in the United States alone, even small improvements in care offer enormous life-saving potential (Ref. 29).

Standard CPR methodology was largely developed on a mechanistic and theoretical basis. Improvement or rigorous challenge of the methodology is complicated by the difficulty in obtaining approval to undertake studies in out-of-hospital cardiac arrest victims. The inability of most cardiac arrest victims to provide the requisite informed consent has proved a significant barrier to evaluating either treatment options available in other countries, or new techniques devised in the United States (Ref. 29).

Participants asserted that, without validation of standard treatment, many patients are now essentially participants in uncontrolled "experiments" when they receive emergency care. These "experiments," however, do not yield data on which progress in rational

medical decisionmaking can be based. For example, one IRB would not approve a protocol for a randomized clinical trial of high dose versus standard dose epinephrine in cardiac arrest, even though some clinicians at that institution used high dose epinephrine in some cases and others did not. The ultimate result was that patients were not allocated randomly to high or standard dose (Ref. 30). The scientific question of which dose was better could be realistically addressed only in a controlled trial with subjects randomly allocated to each dosage level in order to assure that multiple variables caused by differences in physicians or other features of resuscitation technique did not confound the data.

The majority of participants in the Public Forum recommended that NIH and FDA change their regulations so that they are clear and consistent and that NIH and FDA develop a new section in the regulations to clearly permit the waiver of informed consent for acute care research if certain defined conditions and safeguards are met. Participants recommended that a short- and long-term solution be sought which would permit this research to proceed. The short-term solution would be needed if a change in the regulations could not be accomplished quickly.

Since the time of the Public Forum, the Assistant Secretary for Health, the NIH Director, and the Commissioner of FDA have received a number of letters urging NIH and FDA to clarify their regulations to allow for waiver of informed consent in appropriate emergency research circumstances. On March 31, 1995, the Coalition of Acute Resuscitation and Critical Care Researchers submitted a statement containing over 1,300 signatures requesting that NIH and FDA: (1) Recognize the need for clinical research in emergent circumstances where informed consent may not be feasible; and (2) issue an interpretation of the existing Federal regulations to allow the performance of this research.

V. Statutory Basis for These Regulations

Sections 505(i), 507(d), and 520(g) of the act direct the Secretary (and, in accordance with section 903 of the act (21 U.S.C. 394), FDA) to issue regulations establishing conditions under which investigational use of drugs and devices by qualified experts will be permitted. For drugs (including biological drugs and antibiotics) and devices, the statute specifies that the agency must include among these conditions that the product manufacturer or sponsor require the

expert studying the product to obtain informed consent from the subjects or their representatives.

The only exceptions from the informed consent requirement for drugs are where the investigators "deem it not feasible or, in their professional judgment, contrary to the best interests" of the subjects (sections 505(i) and 507(d) of the act). The language of these provisions makes it clear that Congress contemplated that informed consent could be waived in the context of placebo-controlled drug trials: "[the investigators] will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered * * * and will obtain the consent of such human beings or their representatives, except where [not feasible or contrary to their best interests]" (emphasis added). The 1962 Drug amendments, which included section 505(i) of the act, added the requirement that drugs be shown to be not only safe, but also effective through "adequate and well-controlled investigations, including clinical investigations," by experts qualified to evaluate effectiveness (section 505(d) and (e)). Section 505(i) of the act, then, authorized FDA to establish the conditions for the conduct of these required studies in humans. (See also section 507(d) of the act.)

The 1962 amendments were adopted following the thalidomide tragedy, in which women were given the drug without being informed that the drug was experimental, or that they were research subjects, or that the safety of the drug had not been established. (See generally legislative history discussion at 44 FR 47714-47715, August 14, 1979.) Although the House bill would have required informed consent in all clinical trials of drugs, the version reported out of Conference allowed the exceptions that became law (H.R. Rept. No. 2526, 87th Cong., 2d sess., October 3, 1962, pp. 4 and 5). Professional responsibility, based on "the greatest exercise of conscience," was accepted in permitting administration of investigational drugs without informed consent (108 Congressional Record 22038, 22042-43, 87th Cong., 2d sess., October 3, 1962).

The only exceptions from the informed consent requirements for devices are where the investigator determines "there exists a life threatening situation involving the human subject of such testing which necessitates the use of such device and it is not feasible to obtain informed consent from the subject and there is not sufficient time to obtain such consent from his representative" (section

520(g)(3)(D) of the act). In addition, "unless immediate use of the device is required to save the life of the human subject," and there is insufficient time to obtain the concurrence of a licensed physician not involved in the testing, such a physician must concur in the determination (section 520(g)(3)(D) of the act). The exceptions to require informed consent are "subject to such conditions as the Secretary may prescribe."

The context of this provision also is a statutory amendment allowing exemptions to permit investigational use to study the products' safety and effectiveness (section 520(g)(2)(A) of the act). The Medical Device Amendments of 1976, which included section 520(g), added a system of classifications and premarket approval for certain devices (section 513 of the act (21 U.S.C. 360c)). The amendments contemplated that, with certain exceptions, effectiveness would be determined based on "well-controlled investigations, including clinical investigations where appropriate," by experts qualified to evaluate effectiveness (section 513(a)(3) of the act).

Congress was explicit about the purpose of section 520(g) of the act: "to encourage to the extent consistent with the protection of the public health and safety and with ethical standards, the discovery and development of useful devices intended for human use and to that end to maintain optimum freedom for scientific investigators in their pursuit of that purpose" (section 520(g)(1)). The conditions required by section 520(g), then, are to be interpreted within the context of this stated general purpose of providing freedom to the investigators within ethical standards and health and safety protections.

Both the House report on the bill containing the language that became law in section 520(g) of the act and the Conference report refer to the study by the National Commission on the Protection of Human Subjects concerning informed consent. (See H.R. Rept. No. 853, 94th Cong., 2d sess. 44 (1976); H.R. Rept. No. 1090, 94th Cong., 2d sess. 64 (1976).) This Commission, established by the National Research Act in 1974, was to study the basic ethical principles underlying the conduct of biomedical and behavioral research involving human subjects. Congress clearly intended HHS to act in response to the Commission's efforts (id.). The Commission issued numerous reports, including a report on Institutional Review Boards. (See generally 44 FR 47716, August 14, 1979 for a listing of the reports.) This IRB

report stated that "investigators should not have sole responsibility for determining whether research involving human subjects fulfills ethical standards. Others, who are independent of the research, must share this responsibility, because investigators are always in positions of potential conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of human subjects of their research" (43 FR 56174, November 30, 1978).

The Commission's articulation of the basic ethical principles that should underlie the conduct of biomedical research involving human subjects is the Belmont Report, which was prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979 (44 FR 23192, April 18, 1979). In proposing its informed consent regulations in 1979, FDA noted the congressional purpose reflected in both the Drug Amendments of 1962 and the Medical Device Amendments of 1976, to require that biomedical research be conducted "in accordance with the highest contemporary ethical standards" (44 FR 47718, August 14, 1979). In interpreting sections 505(i), 507(d), and 520(g) of the act in 1995, it remains consistent with congressional intent to apply the principles of the Belmont Report in their applications by ethicists to current research issues. As discussed in detail in the following section, this proposed rule to provide an exception from the requirement of informed consent is supported by contemporary application of the ethical principles of the Belmont Report.

Congress did not specifically address the fact that the statutory language containing the informed consent exemption requirements for investigational devices differed from those for investigational drugs enacted 14 years earlier. However, as the agency discussed in proposing its informed consent regulations in 1979, the actual policy followed by FDA regarding the drug informed consent exception was very similar to the policy being proposed for devices (44 FR 47718). In originally promulgating its regulations in part 50 on the protection of human subjects, FDA chose to apply the same standards to drug and device research. In order to preclude confusion that might result from different systems for informed consent for drug and device research and to implement congressional purpose reflected in both the Drug Amendments of 1962 and the Medical Device Amendments of 1976 (i.e., to require conduct of research in accordance with contemporary ethical

standards), FDA is again proposing to apply the same standards to drug and device research.

Sections 505(i), 507(d), and 520(g) of the act authorize the agency to establish the conditions for investigational use. In the proposed rule, FDA would establish conditions that satisfy the statutory criteria for exceptions from the informed consent requirement and allow for safe use under ethical standards for research.

Under sections 505(i) and 507(d) of the act, a showing that obtaining informed consent is not "feasible" is alone sufficient to permit an exception to the requirement. Research without informed consent is also authorized in drug studies based upon professional judgment regarding the "best interest" of the subjects. Under section 520(g), informed consent is required unless there is a written determination that (1) "There exists a life threatening situation involving the human subject of such testing which necessitates the use of such device," (2) "it is not feasible to obtain informed consent from the subject," and (3) "there is not sufficient time to obtain such consent from his representative." In addition, a licensed physician who is not involved in the testing must agree with this three-part determination unless there is not sufficient time to obtain such concurrence. Consequently, circumstances that satisfy the statutory informed consent exception criteria for investigational devices will also satisfy the criteria for investigational drugs.

The exception from the informed consent requirement permitted by the proposed rule would be conditioned upon various findings by an IRB. First, the subjects must be in a situation that is: (1) Life-threatening, (2) where available treatments are unproven or unsatisfactory, and (3) the collection of valid scientific evidence is necessary to determine the most beneficial intervention (§ 50.24(a)(1)). In addition, the opportunity to be in the study must be in the interest of the subject because the life-threatening situation necessitates intervention and the risk of the study is reasonable in light of the medical condition and what is known about the risks and benefits of current therapy and of the investigational intervention (§ 50.24(a)(3)). With regard to the study itself, it must be research that could not practicably be carried out without the informed consent waiver (§ 50.24(a)(4)).

These conditions satisfy the criterion included in sections 505(i) and 507(d) of the act regarding the best interest of the subject. They also satisfy the criteria in section 520(g) of the act that the subject

be in a "life threatening situation" which "necessitates the use of such device." The proposed rule would limit the exception to the narrow circumstance in which both (1) intervention is needed because of the subject's medical condition, and (2) the collection of valid data is needed because of the absence of proven satisfactory available treatment for the condition. The proposed rule thus gives double weight to the statutory "necessitates" criterion.

The agency's proposed implementation of the "necessitates" criterion also would permit administration of either the test product or a control product, in keeping with the legislative intent to permit scientific investigation to demonstrate safety and effectiveness. Randomized placebo-controlled or active-controlled studies may be needed to demonstrate the effectiveness of products for life-threatening, as well as nonlife-threatening, conditions. As discussed in more detail below, this interpretation is also consistent with the ethical principles in the Belmont Report. For example, the principle of beneficence supports research that ultimately "makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous" (Belmont Report, 44 FR 23192 at 23194, April 18, 1979).

In issuing current § 50.23(a), permitting exceptions from obtaining informed consent, the agency included an additional criterion not required by section 520(g)(3)(D) of the act (44 FR 47720, August 14, 1979). This provision of the regulation, codified at § 50.23(a)(4), was added "to prevent routine reliance on the exception" (44 FR 47720, August 14, 1979). In final form, this subsection required that "[t]here is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject." The proposed new § 50.24(a) would permit use of the test product when there is an alternative unproven or unsatisfactory therapy in general use that may be equally likely to save the subject's life. Section 50.24(a)(3) would allow for "reasonable" risk, given what is known about the risks and benefits of the test product, the alternative therapy, and the medical condition. The narrowly circumscribed situation described in § 50.24, as well as additional safeguards, such as public disclosure prior to beginning the study, protects against "routine reliance" on this exception to

conduct research without informed consent.

Section 50.24 also would require, in accordance with the criterion in sections 505(i), 507(d), and 520(g) of the act, that obtaining informed consent not be "feasible." This regulation would restrict determinations of infeasibility to those situations in which: (1) The subjects are unable to give consent because of their medical condition, (2) the product must be administered before it is feasible to obtain consent from legally authorized representatives, and (3) individuals likely to be eligible cannot reasonably be identified prospectively (§ 50.24(a)(2)). Thus, section 50.24(a)(2) also incorporates the required criterion of section 520(g) that there be insufficient time to obtain consent from a representative.

Section 50.24 would require approval of the protocol by an IRB, which is also required to have at least one member who is a licensed physician not otherwise involved in the research protocol (or such a consultant) who concurs with the protocol. That physician's concurrence is in keeping with the provision of 520(g)(3)(D) for concurrence by such an individual that the criteria for testing without informed consent have been satisfied. In most, if not all, instances under § 50.24 there will be a need for "immediate use" to save the subject's life and not sufficient time following the onset of the life-threatening condition to obtain the concurrence by an independent physician and, therefore, there will be no statutory requirement for such concurrence. Nevertheless, the agency believes that concurrence with the protocol by an independent physician associated with the IRB is another valuable protection for the subject and additional assurance that the statutory intent of independent physician concurrence will be satisfied.

For the reasons discussed above, the provisions of § 50.24 satisfy all of the statutory criteria of sections 505(i), 507(d), and 520(g) of the act for permitting exceptions to the informed consent requirements for investigational drug and device uses.

Section 50.24 also contains additional protections for the health and safety of the research subjects (e.g., establishment of an independent data and safety monitoring board), as authorized by, and in keeping with the purposes of sections 505(i), 507(d), and 520(g) of the act. This proposed regulation is also authorized by section 701(a) of the act, which provides general authority to issue regulations for the efficient enforcement of the act.

The conforming amendments to regulations governing drug and device investigations and marketing are authorized by sections 502, 503, 505, 506, 510, 513, 514, 515, 516, 518, 519, 520, 701, and 801 of the act and section 351 of the Public Health Service Act (21 U.S.C. 352, 353, 355, 356, 360, 360c, 360d, 360e, 360f, 360h, 360i, 360j, 371, and 381, and 42 U.S.C. 262)

VI. Ethical Basis for These Regulations

In developing this proposed regulation, FDA has carefully considered the basic ethical principles that underlie research to ensure that it is consistent with those principles. The agency is convinced that the research described in this section is ethically permissible.

The current FDA and HHS IRB and informed consent regulations are based, in large part, on the ethical principles discussed in the Belmont Report. As discussed in that report, the three basic ethical principles that are relevant to research involving human subjects are the principles of respect for persons, beneficence, and justice.

The principle of respect for persons incorporates two general rules of ethical behavior: (1) Competent individuals must be treated as autonomous agents, that is to say, persons who are legally and morally competent to understand the risks and benefits of a proposed research activity must provide prior, uncoerced informed consent before they may be enrolled as research subjects; and (2) persons whose autonomy is absent or diminished may participate in research only if additional protections are provided for them. The proposed rule recognizes that subjects who are candidates for emergency research will not meet the condition of being fully competent. In many cases, they will be totally incompetent. Such potential subjects, if they are to be enrolled in research, must be provided with special additional protections. The special protections proposed in this rule for subjects of emergency research include prior FDA and community consultation on the research, public disclosure, and careful mandatory oversight of the welfare of subjects by a data and safety monitoring board. These special protections are described below.

The principle of beneficence requires that the risks associated with a research activity are reasonable in the light of expected benefits and it also requires that the chance for benefits from participation be maximized, and the risk of possible harms be minimized, consistent with sound research design.

The principle of justice requires that the burdens and benefits of

participation in research be equitably distributed across the entire population in the place or region where the research is conducted. That means, in general, that racial, ethnic, gender, and economic status should not be used as exclusion criteria for participation in research. It further means that persons who are eligible for participation in the research because of their disease or condition, should be provided reasonable opportunity to participate in research until the research cohort is fully recruited. Experience has repeatedly shown that requiring surrogate consent from legally authorized representatives tends to inhibit equitable inclusion in the study because surrogate consent is more easily obtained from family members of Caucasians than from family members of minorities, and it is more easily obtained from family members of middle and upper income persons than from persons of lower income (Ref. 31). Waiving the requirement for informed consent from potential subjects and their surrogates helps to provide for an equitable distribution of both burdens and benefits of emergency research in a manner that meets the requirements of justice.

The Belmont Report notes that “[t]hese principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.” (44 FR 23193, April 18, 1979.) The Belmont Report did not, therefore, address resolution of conflicts among these ethical principles that might be occasioned by a particular research protocol, but it did provide a framework within which conflicts among the principles could be resolved.

The National Commission did not explicitly address the issue of research involving the comatose patient. However, in March 1983, the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research issued its “Second Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and of their Implementation, for the Protection of Human Subject.” In its report, the President’s Commission identified research on the comatose as an issue worthy of further consideration. In its discussion, it noted that

It is settled law that physicians and hospitals may assume that an emergency patient would consent to life-saving treatment; such treatment may therefore be initiated without express consent. The legal

principle is based, however, on the provision of standard care. It is not so clear, however, whether one should assume that an emergency patient would consent to participation in research on new or experimental treatment. (Ref. 32)

The agency has considered the ethical principles set forth in the Belmont Report in the formulation of this rule. It has also engaged in extended public dialogue to resolve the difficulty noted by the President’s Commission. The exception from informed consent for investigations involving life-threatening conditions would apply only to subjects not in a position to exercise autonomy. These subjects will be in a life-threatening situation which necessitates emergency intervention. Thus, in accord with the principle of respect for persons, persons in these situations are entitled to special protection.

In emergent situations, protection is provided and the principle of respect for persons is satisfied if, in circumstances of clinical equipoise, either the test therapy or its historic alternative is provided, even without specific consent. When the relative benefits and risks of the proposed intervention, as compared to standard therapy, are unknown, or thought to be equivalent or better, there is clinical equipoise between the historic intervention and the proposed test intervention. Clinical equipoise would exist, according to testimony presented at the January 1995 FDA/NIH Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances, whenever at least a reasonable minority of medical professionals believe the experimental treatment would be as good as, or better than, the standard treatment (Ref. 23).

This proposed rule is also consistent with the principle of beneficence. The principle of beneficence maximizes possible benefits and minimizes possible harms. In order to avoid harm, one must know what is harmful. In emergency medicine, the standard of care may not have been validated—it may be beneficial or it may be harmful. The principle of beneficence dictates that knowledge be gathered when there is clinical equipoise between established and proposed interventions, through the conduct of research. Beneficence can be assured by the collection of valid scientific evidence, including evidence derived from randomized controlled clinical trials, in order to determine whether the particular intervention is beneficial. Harms are minimized, in part, by careful monitoring of the study by an independent data and safety monitoring board that regularly compares study

data with preestablished "stopping rules" designed to terminate the study before any serious harm occurs.

The principle of justice is also pertinent to this proposed rule. Systematically excluding persons who are unable to give informed consent and who have no surrogate to consent for them from research may be discriminatory, as noted above. An inability to consent, or lack of an authorized representative, should not in itself be a reason for excluding persons from participating in potentially beneficial and scientifically well-designed, controlled, studies (Refs. 33 and 34).

VII. Description of the Proposed Rule

A. Introduction

Section 50.24 will be applicable only to that limited subset of research activities that involve individuals who are in a life-threatening situation and for whom available treatments are unproven or unsatisfactory (e.g., have poor clinical outcome or leave individuals with substantial mortality or major morbidity). FDA believes that evidence submitted at the Public Forum on the chilling effect of current regulations on the care and medical management of such persons in life-threatening situations, including impairing their access to potentially life-saving therapy, justifies the prompt issuance of regulations governing research on such subjects. Thus, FDA intends to issue a final rule, responding to comments received on this proposed rule, promptly following the 45-day comment period.

B. Scope

Section 50.24(d) will require that all protocols that involve a product regulated by FDA and that involve the possibility of invoking an exception under this section are to be performed under a separate IND or a separate Investigational Device Exemption (IDE).

For medical devices, this means that a sponsor may not submit the investigation to an IRB as a nonsignificant risk device (21 CFR 812.2(b)). All device investigations are to be submitted to the agency as separate IDE's, prominently identified as IDE's that propose to invoke the exception in this rule. If the sponsor has already submitted an IDE to the agency for the medical device, the sponsor may cross-reference information in that IDE. The purpose of proposing to require a separate IDE is to ensure that there are 30 days before commencement of the trial in order to permit agency review of

the protocol and supporting information.

For drugs, this means that the exemptions from the requirement to submit an IND, contained in 21 CFR 312.2(b), may not be invoked for investigations of a drug product that is lawfully marketed in the United States if the investigation involves potential invoking of § 50.24. The agency believes that investigations that propose to involve individuals who are unable to give informed consent do not meet the requirements of § 312.2(b)(iii), i.e., the use in this subject population would increase the risks or decrease the acceptability of the risks associated with the use of the drug product and, therefore, agency review of the IND is appropriate. All drug investigations will be submitted to the agency as separate IND's, prominently identified as IND's that propose to invoke the exception in this rule. If the sponsor has already submitted an IND to the agency for the drug product, the sponsor may cross-reference information in that IND. The purpose of proposing to require a separate IND is to ensure that there are 30 days before commencement of the trial in order to permit the agency to review the protocol and supporting information.

C. IRB Responsibilities

Section 50.24(a) gives the IRB the primary responsibility for determining that the research meets the requirements of this proposed rule. In the Coalition's consensus statement, the Coalition recommended that the interests, rights, and welfare of subjects in emergency research trials be protected by special safeguards applied by IRB's. It recommended further that because IRB's have good insight into local practice, subject populations, and the capabilities of researchers, institutions and resources, that IRB's should be the primary unit responsible for maintaining oversight of these clinical trials. The majority of participants at FDA/NIH Public Forum also expressed support for this responsibility being placed on IRB's.

At the congressional hearing and at the Public Forum, some individuals expressed concern about placing this responsibility with IRB's that charge for their services and that are not physically located where the research is to be conducted, so called, "independent IRB's." The agency has considered these concerns, but believes that duly constituted IRB's that fulfill the requirements of part 56 (21 CFR part 56) and § 50.24, including paragraph (a)(5) which will require consultation with the communities from which the subjects

will be drawn and public disclosure, will ensure that the rights and welfare of research subjects are protected. The agency has permitted independent IRB's to review research since 1981. The agency has acknowledged that independent IRB's that lack members from the area of the research site may have difficulty acquiring knowledge of community attitudes, information on conditions surrounding the conduct of the research, and the continuing status of the research. FDA has advised these IRB's, at conferences and in written educational materials, to be particularly sensitive to meeting all requirements of the regulations.

This regulation would permit the IRB to approve research without requiring that informed consent be obtained if the IRB determines and documents that it is approving such research for the reasons given in § 50.24(a).

D. IRB Documentation

This regulation will require the IRB to document that it considered each element in § 50.24(a) and found that each element was met by the proposed research. The agency believes that this documentation is necessary to ensure that the IRB is adequately protecting the rights and welfare of human subjects.

Under § 50.24(e), an IRB would be required to document its findings when it cannot approve the research either because the research does not meet the criteria in § 50.24 or because of other relevant ethical concerns. The IRB is to provide this information in writing to the research sponsor. The sponsor of the research must share this information with FDA, and investigators, and other IRB's that are asked to review this or a substantially equivalent trial. FDA believes that sharing IRB information with these entities concerned with the study will enhance the protection provided to research subjects by establishing communication among IRB's on this important issue. IRB concerns about the approvability of studies may identify to the sponsor and FDA issues that need to be addressed in the research such as the need to alter the study design to better protect the rights and welfare of research subjects. The sponsor's sharing of these concerns with other investigators and IRB's that are asked to review this or substantially equivalent research, assures that all relevant IRB's and investigators will be aware of concerns noted by other IRB's and will have the opportunity to assess those concerns in their review of the research activity.

Because IRB's that review FDA-regulated research may be institutionally-based, independent of an

institution, commercial, established by the sponsor of the research, or established by a group of investigators, it is possible for an investigator to seek approval of an investigation from more than one IRB. Thus, if the study is disapproved by one IRB, it is possible for the investigator to seek approval from another. The agency believes that the provision requiring the sharing of information will enable any IRB that is asked to review the study to take into account relevant ethical concerns raised by another IRB.

This requirement would not add an additional documentary burden to IRB's because under § 56.115(a)(2), the IRB is required to document the basis for disapproving any proposed research and to prepare a written summary of the discussion of controverted issues and their resolution. The proposed requirement in § 50.24(c), for IRB retention of records and for their availability during an inspection, is identical to that required for records maintained pursuant to part 56.

E. Criteria for IRB Approval

Section 50.24(a)(1) would require that the IRB determine that:

* * * the human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo controlled trials, is necessary to determine what particular intervention is most beneficial.

The agency believes that an IRB can determine that the subjects are in a life-threatening situation if it determines that the medical condition being treated by the proposed intervention poses an imminent risk of loss of life. FDA considers treatments to be unproven when, for example, their safety and effectiveness have not been established in adequate and well-controlled clinical trials. FDA believes that unsatisfactory treatments include those treatments which fail to prevent a significant proportion of deaths or permanent disabilities in the population of interest. As discussed earlier, in order to learn what is harmful or beneficial, the intervention or activity must be subjected to adequate and well-controlled trials, including, where appropriate, trials involving a placebo. Determining the risks and benefits of intervention for potentially life-saving therapies will enable physicians to better evaluate the appropriate treatment for individual patients.

As the Coalition noted in its consensus statement:

Patients deserve and expect modern, safe, and effective medical care when they are acutely ill or injured. We believe the public

desires advances in acute emergency and critical care and understands that research is required to improve medical care. The benefits of emergency research include potential improvement in survival and the quality of life following many life threatening conditions that otherwise would have dismal outcomes. The risk of not doing emergency research is denying promising new treatments to individual patients with conditions that currently have no effective therapy, or to future patients with the same devastating condition. (Ref. 22.)

Section 50.24(a)(2) defines when obtaining informed consent is not feasible. The agency believes that the first criterion (§ 50.24(a)(2)(i)) generally will be met if, once the medical condition develops, the potential subjects would not be able to give informed consent as a result of the medical condition. Examples of situations in which obtaining informed consent from the subject may not be feasible include individuals who have suffered a cardiac arrest, severe head injury, or other catastrophic medical or traumatic event.

Section 50.24(a)(2)(ii) would require the IRB to determine that it is necessary to administer the intervention before it is feasible to obtain informed consent from a legally authorized representative. It would require the IRB to consider the consequences of waiting to administer the intervention until a legally authorized representative can consent on behalf of the subject. This criterion recognizes the Coalition's concern that "the test therapy for these catastrophic conditions must be given immediately after the acute injury or illness to have any possibility of benefit." If the window of time is narrow, it will be difficult or impossible to identify a legally authorized representative especially for patients whose identities are unknown at the time of presentation.

Section 50.24(a)(2)(iii) would require the IRB to determine that there is no reasonable way to identify prospectively the individuals likely to become eligible for the research because the emergence of the condition to be studied cannot be predicted reliably in particular individuals. The agency believes that when there is a reasonable way to prospectively identify such individuals, that efforts should be made to obtain prospective consent for the particular protocol from those subjects.

Section 50.24(a)(3) describes why the research intervention is in the best interests of subjects. As discussed earlier, the agency expects clinical equipoise to exist in protocols that would be approved under this section. Clinical equipoise exists when the relative benefits and risks of the

proposed intervention are unknown, or thought to be equivalent or better than standard therapy. Clinical equipoise has been described as existing when at least a reasonable minority of medical professionals believe the test article is as good as or better than the standard treatment or that the standard treatment to be tested is no better than placebo. The agency expects that evidence from animal studies, previous use in humans (for other indications), similarity to other products used in humans, and other evidence, could be used to document clinical equipoise.

Section 50.24(a)(4) would require the IRB to determine that the study could not practicably be conducted without the waiver. This regulation will not permit waiver of informed consent in instances in which an individual may be unconscious or otherwise incompetent to give informed consent, but immediate intervention is not needed in order to prevent death because there is sufficient time to locate, and obtain consent from, a legally authorized representative. In those instances, it may be possible to delay treatment until a court appointed patient-advocate is arranged, the consent of a family member can be obtained, or some other procedure for a surrogate can be followed. There are also medical conditions that predictably occur in given identifiable subject populations. In those cases, it is possible to obtain advance consent before the intervention is required. In other cases, such as events that occur regularly in already hospitalized, acutely ill patients, the majority of subjects will have a family member or a legally authorized representative readily available to provide consent. In these instances, the research may, in accord with the provisions of the law of the jurisdiction, proceed without invoking a waiver of informed consent. In cases such as these, it will be inappropriate to invoke this exception.

The agency recognizes that there may be situations where research studies that would be conducted under § 50.24(a) may include a limited number of subjects for whom a representative is able to provide surrogate consent for the subject, and the treatment window may be such to permit such consent to be obtained. In anticipation of this possibility, the IRB will be required to have reviewed and approved an informed consent document in accord with § 56.109(b), so that surrogate consent can be obtained for those subjects.

Section 50.24(a)(5) describes four "additional protections" that would have to be provided for each protocol:

consultation with representatives of the communities from which the subjects will be drawn; public disclosure prior to the commencement of the study sufficient to describe the study and its risks and benefits; public disclosure of sufficient information following completion of the study to apprise the community and researchers of the study and its results; and the establishment of an independent data and safety monitoring board. In addition to these protections, the IRB should consider whether there are other appropriate additional protections that should be included to protect the rights and welfare of these subjects.

In order to provide for consultation with representatives of the communities from which the subjects will be drawn, and to supplement the information available for review by the IRB, all IRB's should consider, for example, having the clinical investigator or sponsor convene a public meeting in the community on the protocol; establishing a separate panel of members of the community from which the subjects will be drawn; including consultants to the IRB from the community from which the subjects will be drawn; enhancing the membership of the IRB by adding additional members who are not affiliated with the institution and are representative of the community; or developing some other mechanism to ensure community involvement and input into the IRB's decisionmaking process.

In order to provide for public disclosure, the IRB should consider how best to publicly disclose, prior to the commencement of the study, sufficient information to describe the study's risks and benefits, e.g., relevant information from the investigator's brochure or study protocol. Public disclosure following IRB review should be sufficient to disclose information concerning the IRB's resolution of issues and final decisions; this disclosure should provide community confidence in the role of the IRB and in its decisionmaking capability. Disclosure following completion of the study should provide sufficient information to the community about its results and sufficient information to researchers, which would include the underlying data, to be able to assess the results of the study.

The agency recognizes that the level of disclosure to representatives of the community and to researchers that would be required by § 50.24(a)(5) would require sponsors to disclose information about an investigation which they might not otherwise publicly disclose. FDA would require

sponsors to provide copies to FDA of the publicly disclosed information for any investigation which proposes an exemption from the informed consent requirement. The agency believes that by disclosing the information described in this paragraph, the community will better understand the nature of the research and the rights and welfare of subjects will be better protected. By broadly sharing the results of the research with the scientific community, there may be less need to replicate the research; therefore, fewer subjects may be needed to obtain the same level of scientific knowledge and to advance emergency medicine.

Requiring an independent data and safety monitoring board would help ensure that if it becomes clear that risks are greater than anticipated, or that the benefits do not justify the risks of the research, the IRB is informed and can act on the information. For multi-center studies, the agency generally would expect the sponsor of the research, rather than the IRB, to establish the independent data and safety monitoring board. By "independent," the agency intends that the board be composed solely of individuals who have no financial interest in the outcome of the study, and who have not been involved in the design or conduct of the study. Section 56.111(a)(6) currently requires the IRB to determine that, where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. As discussed in the preamble to the January 27, 1981, regulations, in response to comments questioning the meaning of § 56.111(a)(6) and requesting guidelines for determining at what point in each experiment one treatment is shown to be safer and more effective than alternative treatments or no treatments, FDA responded:

This [data monitoring] procedure might be an appropriate requirement in large scale clinical trials or in studies with a high degree of risk. The IRB may require the use of data safety monitoring boards in order to meet the requirements of this provision. Thus, if it becomes clear that risks are greater than anticipated, or that the benefits do not justify the risks of the research, the IRB is informed and can act on the information. This provision matches the HHS requirement * * * IRB's generally will not have the scientific competence to make such a judgement [at what point in each experiment one treatment is shown to be safer and more effective than alternate treatments or no treatment]. The determination whether and at what point in an investigation a test article has been shown to be safe and effective in accordance with the requirements of the act is a determination that must be made by the investigator, the sponsor, and, ultimately, FDA. (46 FR 2869, January 27, 1981)

Section 50.24(b) describes a hierarchy of persons who should be informed of the subject's inclusion in the study, about the details of the study, and that the subject can discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The hierarchy is, first, the subject; if the subject remains incapacitated, then a legally authorized representative of the subject; if the representative is not available, a member of the subject's family is to be informed. The agency has included the phrase "without penalty or loss of benefits to which the subject is otherwise entitled" to ensure, in part, that a subject who is withdrawn from a study is provided with appropriate alternative medical care consistent with that person's medical condition.

The definition of "family members" in § 50.3(n) was taken from the Federal Government's Office of Personnel Management's final rule which relates, in part, to the use of sick leave to care for family members. That rule implements the Federal Employees Friendly Family Leave Act (Pub. L. 103-388), and was published in the Federal Register of December 2, 1994 (59 FR 62266). The definition has been modified by the phrase "legally competent" to acknowledge that family members must be not only of legal age, but also possess appropriate mental capacity, to have this information meaningfully conveyed to them.

F. Preemptive Effect

In developing these proposed rules, FDA considered whether there were existing State or local legal requirements governing informed consent that might limit or preclude participation in research in circumstances that otherwise could be authorized by IRB's acting in accord with these proposed rules. FDA believes that it is important that informed consent requirements governing this type of research be nationally uniform, particularly in light of the current confusion created in the research community by differing Federal regulations. FDA recognizes, however, that the existing Federal Policy for the Protection of Human Subjects, which governs much of this type of research, currently provides that it does not affect any State or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects. Accordingly, FDA specifically invites comment on whether there are existing State or local legal requirements that might limit or preclude participation in research in circumstances that otherwise could be

authorized by IRB's acting in accord with these proposed rules and whether any such requirements should be preempted by Federal requirements.

VIII. Effective Date

FDA is proposing to make these regulations effective on the date of publication of the final rule in the Federal Register because of the urgent need to permit emergency research to proceed. The agency believes that it is in the public interest to have a final rule in place as quickly as possible. By permitting certain controlled clinical trials to be conducted with the involvement of human subjects who are confronted by a life-threatening condition and who are also unable to give informed consent because of that condition, the agency expects to provide individual access to potentially beneficial treatment. The agency also expects that research to result in advancement and improvement of therapies used in emergency medicine situations that currently have poor clinical outcome. As a result of this rule, many individuals confronted by life-threatening situations will benefit immediately. Survival of these individuals may be enhanced by their participation in controlled trials. Therefore, FDA tentatively concludes that there is good cause to dispense with the normal 30-day period between publication of a final rule and its effective date.

IX. Request for Comments

Interested persons may, on or before November 6, 1995 submit to the Dockets Management Branch (address above) written comments regarding this proposal. Comments are also solicited regarding the need for Federal preemption (see sections VII.F. and XI.B. of this document) and information collection requirements subject to Office of Management and Budget (OMB) approval under the Paperwork Reduction Act of 1995 (see section XIII. of this document). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Comments on information collection requirements should be directed to FDA's Dockets Management Branch (address above) and to OMB's Office of Information and Regulatory Affairs (addressed below in section XIII. of this document).

FDA believes that a comment period greater than 45 days would be contrary

to the public interest for the reasons given above. In addition, FDA is taking this action in response to the congressional hearing, the Consensus Conference, FDA/NIH Public Forum, and to public and professional concerns that not all of what has become standard and accepted medical therapy for use in acute or resuscitation care has been subjected to controlled clinical trials to establish its safety or effectiveness.

Currently, there are some investigations ongoing involving life-threatening conditions which enroll only subjects able to consent; other investigations are on hold pending issuance of this regulation. In those trials that are ongoing, accrual of subjects is exceedingly slow. Further delay could cause sponsors and funding institutions to cease support of such research, resulting in the research being stopped before sufficient data is gathered to demonstrate efficacy. FDA believes that extending the comment period would delay implementation of this rule and would result in the cessation of some of these studies or in the diversion of emergency research resources to other activities. As a result, potential subjects would be deprived of the opportunity to obtain potentially life-saving treatment. In addition, society would suffer as a result of this discontinuity in research by not being able to determine the effectiveness of potentially life-saving therapies.

Because of these public health concerns, FDA does not intend to extend the comment period beyond that date. Also, the agency is advising that it may not be able to consider any comments received at the Dockets Management Branch after the close of business on November 6, 1995. Although FDA is providing 45 days, rather than 90 days, for comments on this subject through the routine notice and comment procedures, it has received much input through the various conferences and congressional hearings discussed above and in correspondence. This input has come from IRB's, sponsors, investigators, ethicists, patient groups, etc.

The agency considered whether a reinterpretation of its existing regulations would meet the needs of persons in life-threatening situations and the research community. It concluded against such a reinterpretation for a number of reasons, including: it would not make the FDA regulations and the HHS regulations congruent; it would not provide prospective protections to subjects participating in such research; it would be difficult if not impossible to enforce additional safeguards that the agency

believes are essential to protect subjects involved in such research activities; and it would not adequately eliminate the confusion that currently exists within the research community as to the standards that must be applied to this research. The sole benefit of a reinterpretation of existing regulations would be to permit this limited class of research to move forward quickly, rather than delaying until a new regulation could be written. The agency has, thus, placed priority on developing this proposed regulation in order to permit the ethical conduct of a limited class of emergency research.

X. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XI. Executive Orders

A. Executive Order 12606: The Family

Executive Order 12606 directs Federal agencies to determine whether policies and regulations may have a significant impact on family formation, maintenance, and general well-being. FDA has analyzed this proposed rule in accordance with Executive Order 12606, and has determined that it has no potential negative impact on family formation, maintenance, and general well-being.

FDA has determined that this rule will not affect the stability of the family, and particularly, the marital commitment. It will not have any significant impact on family earnings. The proposed rule would not erode the parental authority and rights in the education, nurture, and supervision of children.

B. Executive Order 12612: Federalism

Executive Order 12612 requires Federal agencies to carefully examine regulatory actions to determine if they would have a significant effect on federalism. Using the criteria and principles set forth in the order, FDA has considered the proposed rule's impact on the States, on their relationship with the Federal Government, and on the distribution of power and responsibilities among the various levels of government. FDA concludes that this proposal is consistent with the principles set forth in Executive Order 12612.

Executive Order 12612 states that agencies formulating and implementing

policies are to be guided by certain federalism principles. Section 2 of Executive Order 12612 enumerates fundamental federalism principles. Section 3 states that, in addition to these fundamental principles, executive departments and agencies shall adhere, to the extent permitted by law, to certain listed criteria when formulating and implementing policies that have federalism implications. Section 4 lists special requirements for preemption.

Section 4 of Executive Order 12612 states that an executive department or agency foreseeing the possibility of a conflict between State law and federally protected interests within its area of regulatory responsibility is to consult with States in an effort to avoid such conflict. Section 4 also states that an executive department or agency proposing to act through rulemaking to preempt State law is to provide all affected States notice and opportunity for appropriate participation in the proceedings. As required by the Executive Order, States have, through this notice of proposed rulemaking, an opportunity to raise the possibility of conflicts and to participate in the proceedings (section 4(d) and (e)). Consistent with Executive Order 12612, FDA requests information and comments from interested parties, including but not limited to State and local authorities, on these issues of federalism.

XII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-395). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule is a deregulatory action insofar as it will permit research to proceed which could not proceed under existing regulations, and because relatively few research projects will need to meet the requirements of this rule, the agency certifies that the proposed rule will not have a significant economic impact on

a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

XIII. Paperwork Reduction Act of 1995

This proposed rule contains only information collection requirements which are subject to review by the OMB under the Paperwork Reduction Act of 1995 (Pub. L. 104-13), and which are already approved under Protection of Human Subjects—Recordkeeping Requirements for Institutional Review Boards, part 56 under OMB Control No. 0910-0130; Investigational New Drug Application under OMB Control No. 0910-0014; and Investigational Devices Exemption Reports and Records, part 812 under OMB Control No. 0910-0078. Modifications to these approved information collection requirements are underway.

For Protection of Human Subjects—Recordkeeping Requirements for Institutional Review Boards (IRB) under OMB Control No. 0910-0130, FDA has calculated the existing recordkeeping burden on IRB's based on the estimated number of IRB's and the estimated annual number of hours each IRB spends in recordkeeping activities. FDA does not believe that this rule will increase the number of IRB's. However, the agency estimates that the number of hours for recordkeeping related to studies which propose to invoke this exception from informed consent will increase for an estimated 200 IRB's by 5 annual hours per record-keeper. This will change the estimated recordkeeper burden from 65 to 70 hours annually.

The newly redesignated and revised § 56.109(e) proposes to require that an IRB notify in writing the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under § 50.24(a) of this chapter or because of other relevant ethical concerns. In accord with the Paperwork Reduction Act of 1995, this proposal discloses the agency's intent to require this third party notification.

For Investigational New Drug Application under OMB Control No. 0910-0014, the agency estimates that sponsors will submit an average of 20 studies a year, with an average of 20 clinical investigators each, that propose to invoke this exception from informed consent. Currently, the agency estimates the reporting requirements contained in part 312 to average 123.34 hours per respondent annually. FDA estimates that respondents will increase by 400 annually, resulting in an increase of 49,336 hours over that currently estimated. The reporting burden for

respondents will, as a result, increase from an estimated 3,926,308 hours annually to 3,975,644 hours annually.

New § 312.54(b) proposes to require the sponsor to provide information when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. This information is to be provided promptly in writing to FDA, investigators who are asked to participate in the trial or a substantially equivalent trial, and other IRB's that are asked to review the trial or a substantially equivalent trial. In accord with the Paperwork Reduction Act of 1995, this proposal discloses the agency's intent to require this third party notification.

For recordkeeping, the agency estimated that an average of 165.13 hours were spent per respondent. For the estimated additional 400 recordkeeping respondents invoking this rule, this would result in approximately 66,072 hours annually. The recordkeeping burden for respondents will, as a result, increase from an estimated 2,244,090 hours annually to 2,310,162 hours annually.

For Investigational Devices Exemption Reports and Records under OMB Control No. 0910-0078, the agency estimates that 10 studies proposing to invoke this exception will be submitted to the agency annually. The number of studies upon which the current paperwork reporting burden is estimated may, therefore, increase from 244 original submissions to 254 original submissions, increasing the number of hours by 800 for respondents (estimated at 80 hours per submission), from a total of 19,520 to 20,320 hours annually.

New § 812.47(b) proposes to require the sponsor to provide information when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. This information is to be provided promptly in writing to FDA, investigators who are asked to participate in the trial or a substantially equivalent trial, and other IRB's that are asked to review the trial or a substantially equivalent trial. In accord with the Paperwork Reduction Act of 1995, this proposal discloses the agency's intent to require this third party notification.

The number of recordkeepers is currently estimated at 700; this number is not expected to change. The estimated number of annual hours for recordkeeping requirements is expected to increase by 100 hours. The agency had estimated that original submissions

require 10 hours annually of recordkeeping per submission; recordkeeping related to protocols invoking this rule are expected to increase the submissions from 244 to a total of 254.

As required by section 3507(d) of the Paperwork Reduction Act of 1995, FDA has submitted a copy of this proposed rule to OMB for its review of these previously approved information collection requirements. The agency solicits comments on the information collection requirements in order to: (1) Evaluate whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) enhance the quality, utility, and clarity of the information to be collected; and (4) minimize the burden of the collection of information on those who are to respond, including through the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, e.g., permitting electronic submission of responses. Organizations and individuals desiring to submit comments on the information collection requirements should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, rm. 10235, New Executive Office Bldg., 725 17th Street, N.W., Washington, DC 20503, Attention: Desk Officer for FDA.

XIV. Conforming Amendments

This proposed rule would necessitate a number of changes to the regulations for human drugs, biologics, devices, and institutional review boards so that those regulations are consistent with this rule.

A. Amendments to Regulations for IRB's

FDA is proposing to amend § 56.109(c) to expressly recognize that IRB's may approve studies for which informed consent is not obtained when the requirements in § 50.24 are met. FDA is also proposing to amend § 56.109 to specify in the IRB regulations the requirement to notify sponsors when an IRB determines it cannot approve such studies and to notify sponsors when public disclosure of these studies has occurred. In addition, FDA is proposing to revise § 56.111 to reference the IRB's need to find that the criteria set forth in § 50.24

are met before approving investigations involving an exception from informed consent under § 50.24.

B. Amendments to Regulations for Human Drug Products

The proposed amendment to § 312.2(b) (21 CFR 312.2(b)) makes clear that these studies are not exempt from the requirements of part 312 (21 CFR part 312). Proposed § 312.20(a) and the amendments to § 312.30 would codify in the IND regulations the requirement for a separate IND for studies under § 50.24. Proposed new § 312.23(f) contains the requirement referenced in § 50.24(d) that sponsors prominently identify these studies in separate IND's. FDA is proposing to add new § 312.54 to specify the need for sponsors to actively monitor the progress of proposed investigations so that appropriate public disclosure can occur and so that other IRB's, investigators, and FDA are notified of an IRB determination that it cannot approve the investigation. Section 312.60 would be amended to reference the exception from informed consent in § 50.24. The amendment to § 314.430(d) (21 CFR 314.430(d)) would acknowledge that studies involving § 50.24 will not proceed without public discussion. Section 314.430(d) would be amended to codify that sponsors identify the information publicly disclosed.

C. Amendment to Biologics Regulations

FDA is proposing to amend 21 CFR 601.51(d) for the reasons set forth above for § 314.430(d).

D. Amendment to Device Regulations

FDA is proposing to amend §§ 812.20 and 812.35(a) (21 CFR 812.20 and 812.35(a)) to codify in the IDE regulations the requirement for filing a separate IDE for studies under § 50.24. Section 812.20(b)(13) would be amended to codify the need to clearly identify in the IDE submission that the study involves an exception from informed consent under § 50.24. The amendment to § 812.38(b)(2) would acknowledge that studies involving § 50.24 will not proceed without public discussion. Section 812.38(b) would be amended to codify that sponsors identify the information publicly disclosed.

New § 812.47 would specify the need for the sponsor to actively monitor proposed investigations so that appropriate public disclosure can occur and so that other IRB's, investigators, and FDA are notified of an IRB determination that it cannot approve the investigation. FDA is proposing to amend 814.9(d) (21 CFR 814.9(d)) to

codify the need for sponsors to identify information publicly disclosed consistent with the requirements of § 50.24(a)(5)(ii) and (a)(5)(iii).

XV. References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Prentice, E. D., et al., "IRB Review of a Phase II Randomized Clinical Trial Involving Incompetent Patients Suffering from Severe Closed Head Injury," *IRB A Review of Human Subjects Research*, 15:1-7, 1993.
2. Prentice, E. D., et al., "An Update on the PEG-SOD Study Involving Incompetent Subjects: FDA Permits an Exception to Informed Consent Requirements," *IRB A Review of Human Subjects Research*, 16:16-18, 1994.
3. Fost N., and J. A. Robertson, "Deferring Consent with Incompetent Patients in an Intensive Care Unit," *IRB Review of Human Subjects Research*, 2:5-6, 1980.
4. Beauchamp, T. L., "Commentary: The Ambiguities of 'Deferred Consent'," *IRB Review of Human Subjects Research*, 2:6-9, 1980.
5. Levine, R. J., "Commentary: Deferred Consent," *Controlled Clinical Trials*, 12:546-550, 1991.
6. Olson, C. M., "Editorial: The Letter or the Spirit; Consent for Research in CPR," *Journal of the American Medical Association*, 271:1445-1447, 1994.
7. Abramson, N. S., and P. Safar, "Deferred Consent: Use in Clinical Resuscitation Research," *Annals of Emergency Medicine*, 19:781-784, 1990.
8. "Informed Consent—Legally Effective and Prospectively Obtained," OPRR Reports-Human Subject Protections, Number 93-3, 1993.
9. Jane, J. A., June 28, 1993, letter to D. A. Kessler and September 14, 1993, response.
10. Herr, D. L., July 23, 1993, letter to D. A. Kessler and September 14, 1993, response.
11. Binder, L. S., and M. H. Biros, July 23, 1993, letter to D. A. Kessler and September 14, 1993, response.
12. Zitnay, G. A., June 22, 1993, letter to D. A. Kessler and September 14, 1993, response.
13. Abramson, N. S., and P. Safar, "Response to Commentary," *Controlled Clinical Trials*, 12:551-552, 1991.
14. Parrillo, J. E., "Special Article: Research in critical care medicine: Present status of critical care investigation," *Critical Care Medicine*, 19:569-577, 1991.
15. Halperin, H. R., et al., "A Preliminary Study of Cardiopulmonary Resuscitation by Circumferential Compression of the Chest with Use of a Pneumatic Vest," *New England Journal of Medicine*, 329:762-768, 1993.
16. Cohen, T. J., et al., "A Comparison of Active Compression-Decompression Cardiopulmonary Resuscitation with Standard Cardiopulmonary Resuscitation for Cardiac Arrests Occurring in the Hospital," *New England Journal of Medicine*, 329:1918-1921, 1993.

17. Lurie, K. G., et al., "Evaluation of Active Compression-Decompression CPR in Victims of Out-of-Hospital Cardiac Arrest," *Journal of the American Medical Association*, 271:1405-1411, 1994.

18. Schwab, T. M., "A Randomized Clinical Trial of Active Compression-Decompression CPR vs Standard CPR in Out-of-Hospital Cardiac Arrest in Two Cities," *Journal of the American Medical Association*, 273:1261-1268, 1995.

19. Olson, C. M., "Editorial: Plungers and Polemics: Active Compression-Decompression CPR and Federal Policy," *Journal of the American Medical Association*, 273:1299-1300, 1995.

20. Levine, R. J., "Editorial: Research in Emergency Situations; The Role of Deferred Consent," *Journal of the American Medical Association*, 273:1300-1302, 1995.

21. Marwick, C., "Research in Emergency Circumstances," *Journal of the American Medical Association*, 273:687-688, 1995.

22. "Informed Consent in Emergency Research," Consensus from the Coalition Conference of Acute Resuscitation and Critical Care Researchers, 1994.

23. "Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances," transcript of January 9, 1995.

24. "Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances," transcript of January 10, 1995.

25. "Report of the Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances," FDA and NIH, May 1995.

26. "Problems in Securing Informed Consent of Subjects in Experimental trials of Unapproved Drugs and Devices," Hearing before the Subcommittee on Regulation, Business Opportunities, and Technology of the Committee on Small Business, House of Representatives, Washington, DC, Serial No. 103-85, 1994.

27. Miller, B. L., "Philosophical, ethical, and legal aspects of resuscitation medicine," *Critical Care Medicine*, 16:1059-1062, 1988.

28. Miller, B. L., "The Ethics of Cardiac Arrest Research," *Annals of Emergency Medicine*, 22-118-124, 1993.

29. "Waiver of Informed Consent: A Critical Issue for Improving Treatment of Emergent Medical Conditions," North American Society of Pacing and Electrophysiology Government Relations Committee Position Statement, Testimony presented at FDA/NIH Public Forum, 1995.

30. Wears, R. L., Written testimony presented at FDA/NIH Public Forum, 1995.

31. McCarthy, C. R., "To Be or Not to Be: Waiving Informed Consent in Emergency Research," *Kennedy Institute of Ethics Journal*, 5:155-162, 1995.

32. "Implementing Human Research Regulations; Second Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and of their Implementation, for the Protection of Human Subjects," President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 1983.

33. Fost, N. C., "Part 3; Human Subjects in Cardiopulmonary Resuscitation Research," in

"Ethics in Emergency Medicine," Edited by Iserson, K. V., et al., Williams & Wilkins, Baltimore, pp. 77-81, 1986.

34. Sprung, C. L., and B. J. Winick, "Informed Consent in Theory and Practice: Legal and Medical Perspectives on the Informed Consent Doctrine and a Proposed Reconceptualization," *Critical Care Medicine*, 17:1346-1354, 1989.

List of Subjects

21 CFR Part 50

Informed consent, Prisoners, Reporting and recordkeeping requirements, Research, Safety.

21 CFR Part 56

Human research subjects, Reporting and Recordkeeping requirements, Safety.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

21 CFR Part 814

Administrative practice and procedure, Confidential business information, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 50, 56, 312, 314, 601, 812, and 814 be amended as follows:

PART 50—PROTECTION OF HUMAN SUBJECTS

1. The authority citation for 21 CFR part 50 continues to read as follows:

Authority: Secs. 201, 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 379e, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b-263n).

2. Section 50.3 is amended by adding a new paragraph (n) to read as follows:

§ 50.3 Definitions.

* * * * *

(n) *Family members* means the following legally competent persons: Spouses; parents; children (including adopted children); brothers, sisters and their spouses; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

3. Section 50.24 is added to subpart B to read as follows:

§ 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent be obtained if the IRB (with a concurring licensed physician member or consultant) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo controlled trials, is necessary to determine what particular intervention is most beneficial.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give consent as a result of their medical condition; and

(ii) The intervention under study must be administered before consent from legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for the research because the emergence of the condition to be studied cannot be predicted reliably in particular individuals.

(3) The opportunity for the subjects to participate in the research is in the interest of the subjects because:

(i) A life-threatening situation necessitates intervention, and

(ii) The risk of the investigation is reasonable in light of what is known about the medical condition and the risks and benefits of current therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The research could not practicably be carried out without the waiver.

(5) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (which may include consultation carried out by the IRB itself) with representatives of the

communities from which the subjects will be drawn;

(ii) Public disclosure prior to the commencement of the study sufficient to describe the study and its risks and benefits;

(iii) Public disclosure of sufficient information following completion of the study to apprise the community and researchers of the study and its results; and

(iv) The establishment of an independent data and safety monitoring board.

(6) The IRB has reviewed and approved an informed consent document for use with subjects or legal representatives in situations in which obtaining such consent may be feasible for some subjects.

(b) When possible and at the earliest possible opportunity, each subject (or, if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member) will be informed of the subject's inclusion in the research study, the details of the research study, and that the subject (or, if the subject remains incapacitated, a legally authorized representative of the subject or, if such a representative is not reasonably available, a family member) may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraphs (d) and (e) of this section are to be retained by the IRB for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under an investigational new drug application (IND) or investigational device exemption (IDE). FDA requires clear identification of protocols that would include subjects who are unable to consent, and submission of those protocols in a separate IND/IDE (even if an IND for the same drug product or an IDE for the same device already exists). Applications for investigations under this section may not be submitted as supplemental applications under §§ 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve this research because the research does not meet the criteria in the exception provided under paragraph (a) of this section or because of other

relevant ethical concerns, the IRB must document its findings and provide these findings in writing to the sponsor of the research. The sponsor of the research must share this information with FDA, researchers/clinical investigators who are asked to participate in this or a substantially equivalent trial, and to other IRB's which are asked to review this or a substantially equivalent clinical trial.

PART 56—INSTITUTIONAL REVIEW BOARDS

4. The authority citation for 21 CFR part 56 continues to read as follows:

Authority: Secs. 201, 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371, 379e, 381); secs. 215, 301, 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b–263n).

5. Section 56.109 is amended by revising paragraph (c), by redesignating paragraphs (d) and (e) as paragraphs (e) and (f), by adding a new sentence to the end of newly redesignated paragraph (e), and by adding new paragraphs (d) and (g) to read as follows:

§ 56.109 IRB review of research.

* * * * *

(c) An IRB shall require documentation of informed consent in accordance with § 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context, or

(2) The IRB may, for some or all subjects, find that the requirements in § 50.24 of this chapter for an exception from informed consent for emergency research are met.

(d) In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(e) * * * For studies involving an exception to informed consent under § 50.24 of this chapter, an IRB shall notify in writing the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under § 50.24(a) of

this chapter or because of other relevant ethical concerns.

* * * * *

(g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under § 50.24 of this chapter a copy of information that has been publicly disclosed under § 50.24(a)(5)(ii) and (a)(5)(iii). The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. The sponsor shall provide copies of the information disclosed to FDA.

6. Section 56.111 is amended by adding new paragraph (c) to read as follows:

§ 56.111 Criteria for IRB approval of research.

* * * * *

(c) When the research involves an exception from informed consent for emergency research under § 50.24 of this chapter, the IRB finds and documents that the safeguards set forth in § 50.24 are included.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

7. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec 351 of the Public Health Service Act (42 U.S.C. 262).

8. Section 312.2 is amended by adding paragraph (b)(6) to read as follows:

§ 312.2 Applicability.

* * * * *

(b) * * *
(6) A clinical investigation involving an exception from informed consent under § 50.24 of this chapter is not exempt from the requirements of this part.

* * * * *

9. Section 312.20 is amended by adding paragraph (c) to read as follows:

§ 312.20 Requirements for an IND.

* * * * *

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter.

10. Section 312.23 is amended by adding paragraph (f) to read as follows:

§ 312.23 IND content and format.

* * * * *

(f) If the investigation involves an exception from informed consent under § 50.24 of this chapter, prominent

identification on the cover sheet that the investigation is subject to the requirements in § 50.24.

11. Section 312.30 is amended by adding a new sentence to the end of the introductory text to read as follows:

§ 312.30 Protocol amendments.

*** Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in § 50.24 of this chapter, the sponsor shall submit a separate IND for such investigation.

* * * * *

12. New section 312.54 is added to subpart D to read as follows:

§ 312.54 Emergency research under § 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all proposed investigations involving an exception from informed consent under § 50.24 of this chapter. The sponsor shall determine when the public disclosures required by § 50.24(a)(5)(ii) and (a)(5)(iii) of this chapter of the proposed investigation have occurred and promptly shall submit to the IND file and to Dockets Management Branch copies of the information that was disclosed.

(b) The sponsor also shall monitor such proposed investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent trial, and other IRB's that are asked to review this or a substantially equivalent trial.

13. Section 312.60 is amended by revising the second and third sentences in the text as follows:

§ 312.60 General responsibilities of investigators.

*** An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in § 50.23 or § 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

14. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

15. Section 314.430 is amended by adding two sentences to the end of paragraph (d) to read as follows:

§ 314.430 Availability for public disclosure of data and information in an application or abbreviated application.

* * * * *

(d)*** For applications concerning investigations involving an exception from informed consent under § 50.24 of this chapter, sponsors are required to submit copies of information that has been publicly disclosed under § 50.24(a)(5)(ii) and (a)(5)(iii) to the IND file and to Dockets Management Branch. Copies of this information will be available to the public from the Dockets Management Branch.

* * * * *

PART 601—LICENSING

16. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381); secs. 215, 301, 351 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263).

17. Section 601.51 is amended by adding two sentences to the end of paragraph (d) to read as follows:

§ 601.51 Confidentiality of data and information in applications for establishment and product licenses.

* * * * *

(d)*** For applications concerning investigations involving an exception from informed consent under § 50.24 of this chapter, sponsors are required to submit copies of information that has been publicly disclosed under § 50.24(a)(5)(ii) and (a)(5)(iii) to the IND file and to the Dockets Management Branch. Copies of this information will be available to the public from the Dockets Management Branch.

* * * * *

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

18. The authority citation for 21 CFR part 812 continues to read as follows:

Authority: Secs. 301, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701, 702,

704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381); secs. 215, 301, 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b–263n).

19. Section 812.20 is amended by revising paragraph (a)(1) and adding paragraph (a)(4) to read as follows:

§ 812.20 Application.

(a) *Submission.* (1) A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation, intends to conduct an investigation that involves an exception from informed consent under § 50.24 of this chapter, or if FDA notifies the sponsor that an application is required for an investigation.

* * * * *

(4)(i) A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter, and

(ii) If the investigation involves an exception from informed consent under § 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in § 50.24.

* * * * *

20. Section 812.35 is amended by adding a sentence to the end of paragraph (a) to read as follows:

§ 812.35 Supplemental applications.

(a)*** Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in § 50.24 of this chapter, the sponsor shall submit a separate IDE for such investigation.

* * * * *

21. Section 812.38 is amended by adding two sentences to the end of paragraph (b)(2) to read as follows:

§ 812.38 Confidentiality of data and information.

* * * * *

(b)***
(2)*** If a device is subject to an investigation that involves an exception from informed consent under § 50.24 of this chapter, sponsors are required to submit copies of information that has been publicly disclosed under § 50.24(a)(5)(ii) and (a)(5)(iii) to the IDE file and to the Dockets Management Branch. Copies of this information will be available to the public from the Dockets Management Branch.

* * * * *

22. New section 812.47 is added to subpart C to read as follows:

§ 812.47 Emergency research under § 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all proposed investigations involving an exception from informed consent under § 50.24 of this chapter. The sponsor shall determine when the public disclosures under § 50.24(a)(5)(ii) and (a)(5)(iii) of this chapter of the proposed investigation have occurred. The sponsor promptly shall submit copies of the information that has been publicly disclosed to the IDE file and also to the Dockets Management Branch.

(b) The sponsor also shall monitor such studies to determine when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to

participate in this or a substantially equivalent trial, and other IRB's that are asked to review this or a substantially equivalent trial.

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

23. The authority citation for 21 CFR part 814 continues to read as follows:

Authority: Secs. 501, 502, 503, 510, 513–520, 701, 702, 703, 704, 705, 708, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 352, 353, 360, 360c–360j, 371, 372, 373, 374, 375, 379, 379e, 381).

24. Section 814.9 is amended by adding two sentences to the end of paragraph (d) to read as follows:

§ 814.9 Confidentiality of data and information in a premarket approval application (PMA) file.

* * * * *

(d) * * * For applications concerning investigations involving an exception from informed consent under § 50.24 of this chapter, sponsors are required to submit copies of information publicly disclosed under § 50.24(a)(5)(ii) and (a)(5)(iii) to the IDE file and to the Dockets Management Branch. Copies of this information will be available to the public from the Dockets Management Branch.

* * * * *

Dated: August 31, 1995.
David A. Kessler,
Commissioner of Food and Drugs.
Donna E. Shalala,
Secretary of Health and Human Services.
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