COMMENTS OF PUBLIC CITIZEN HEALTH RESEARCH GROUP
TO THE FOOD AND DRUG ADMINISTRATION
OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Proposed Procedures for
Investigational Device Exemptions
21 CFR Parts 16, 20, and 812

5833

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I. INTRODUCTORY COMMENTS

The Health Research Group appreciates the opportunity to comment on the proposed Investigational Device Exemption (IDE) regulations. We note the express invitation in the preamble to the tentative final regulations:

> Many comments [on the original proposed regulations of August 1976] were received from industry, academic sources, and private practitioners, but none were received from public interest groups representing consumers and patient interests. The Commissioner hopes that these groups will comment on this tentative final regulation and will participate in the public hearing.
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> 43 FR 20727 (May 12, 1978).

Unfortunately, this imbalance in the comments filed in response to the August 1976 proposal apparently swayed the Commissioner's judgment. The tentative final regulations that follow his observation in the Federal Register represent a dramatic retreat at several key points from the Agency's commitment in the August 1976 proposal to the safeguarding of human subjects of medical device experiments from the risk of harm.

The Medical Device Amendments of 1976, Pub. L. No. 94-295, enacted on May 28, 1976, required the Secretary of Health, Education and Welfare to promulgate, within 120 days of the Act's effective date, regulations to

> prescribe procedures and conditions under which devices intended for human use may upon application be granted an exemption from the [other statutory] requirements... to permit the investigational use of such devices by experts qualified by scientific training and experience to investigate the safety and effectiveness of such devices.
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> 21 U.S.C. § 360j(g)(2)(A) (1976).

The Secretary issued a set of proposed regulations on the subject in August 1976. 41 FR 35299-313 (Aug. 20, 1976). These proposed regulations, while overly vague in some respects, constituted a good faith effort on the part of the Agency to carry out its statutory obligation to accord adequate protection to the people upon whom the medical device experiments would be conducted.

The Agency was then subjected to the barrage of criticism noted by the Commissioner in the Federal Register, as quoted above. Rather than follow the Act's command to put final regulations on the books in short order, the Agency delayed for two more years before publishing a set of "tentative final regulations." 43 FR 20746-57 (May 12, 1978). Not

only was this delay unauthorized by law; it resulted in a proposal that drastically weakened the protections afforded human subjects of device experiments, and did so in ways that in many respects are illegal under the Medical Device Amendment Act, as we demonstrate below.

Moreover, it is reported that the Agency is considering still further loosening of the protections for human subjects. See Devices & Diagnostics Letter, Nov. 17, 1978, at 1; Dec. 8, 1978, at 1-2. To adapt an old saw to present purposes, the Agency is caught between the devil and the deep blue sea: it will either be scorched by industry criticism or will venture again into uncharted waters, approving potentially dangerous human experiments without adequate data or scrutiny, in the field of devices as it has in the field of drugs. The Agency seems ready to take the plunge.

We are submitting our specific comments in the light of the following fundamental principles concerning medical device experiments on human beings. Both the Food, Drug, and Cosmetic Act and public policy require that "any device to be the subject of testing involving human subjects," in order to be exempted from the strict statutory requirements governing non-experimental devices, must be adequately scutinized by the Agency. FD&C Act § 520(g)(3) (emphasis added). The IDE procedure must provide for comprehensive review of the safety of all experimental protocols. We recognize the importance of keeping research and administrative expenses within reasonable limits; expedited scrutiny is appropriate for experiments involving minimal risks to human subjects. But for protocols that could involve significant risks to human health, the IDE procedure must include safeguards at each level of participation: (1) by the subject through full informed consent; (2) by the institutional review board through review of the protocol for ethical soundness and scientific merit, and through oversight of the progress of the experiment; (3) by the investigator in accordance with his or her scientific and ethical responsibilities; (4) by the sponsor through frequent and careful monitoring; and (5) by the FDA through a thorough review of the entire process. The flow of information concerning all aspects of the study must be as open to all participants in the process as possible.

A recent incident involving the only device category for which IDE procedures have been in effect, that of intraocular lenses (IOLs), illustrates the necessity of such overlapping safeguards as those described above, and of a full flow of information to key participants such as IRBs. The IOL is a plastic lens surgically implanted in the eye to replace a natural lens that has become too cloudy for normal vision. Tens of thousands are being implanted every year in the eyes of cataract patients and others.

Medical Workshop USA, Inc., an importer of IOLs manufactured abroad, submitted an application for an investigational device exemption to the Bureau of Medical Devices of FDA in early 1978. The investigation protocol failed to require the lenses to be sterilized by an ethylene oxide gas sterilization system--the most widely accepted system, and that favored in Bureau of Medical Devices guidelines. Instead, lens sterilization was to be accomplished by a liquid chemical (sodium hydroxide) system not providing adequate sterility assurance. The sodium hydroxide system had figured in previous outbreaks of contamination in IOLs, involving Luminex International (1976) and Copeland Intra-Lenses (1977), that resulted in serious vision impairment for many patients and at least five cases of removal of the eyeball.

Yet the IRBs charged with overseeing Medical Workshop's IOL experiments were apparently unaware of the previously

documented problems with the sodium hydroxide system, and had not been informed of the Bureau of Medical Devices' guidelines. Neither the sponsor, Medical Workshop, nor the IRBs carried out their function of disallowing the experimental use of this potentially dangerous device. To the contrary, after initial Bureau disapproval of the IDE application, Medical Workshop submitted, and the IRBs approved, still another unacceptable protocol. Only the multilayered structure of IDE review procedures prevented the experimental insertion of this potentially hazardous lens in the eyes of possibly thousands of unsuspecting subjects.

Against the factual background of recent experience with intraocular lens experimentation, the vacuity of the industry's self-serving hue and cry about "over-regulation" is evident. The multilayered structure of IDE review has not retarded innovation in the field. On the contrary, thousands of experiments are being carried on at this moment. And since IDE requirements were put in place, according to Bureau personnel, the greater part of the industry appears to have tightened up the sloppy manufacturing and quality control techniques that led to the Luminex and Copeland Intra-Lenses disasters. What is needed is more, not less, conscientious, informed, and focused oversight of what hitherto has been a dangerously underregulated industry.

II. SPECIFIC COMMENTS

A. The Proposed Classification Scheme

The newly proposed scheme for classifying devices for IDE purposes set out in the May 1978 tentative final regulations would expose human subjects to unacceptable experimental risks, since the Agency would lack the means to review proposed experiments adequately. Proposed § 812.20, 43 FR 20750 (May 12, 1978), would permit the sponsor of a study involving a "vital" experimental device involving "low risk" to human subjects, or a "nonvital" device involving "substantial" risk to human subjects, to employ an express notification procedure that we believe is wholly inadequate to inform FDA of the potential dangers of the study.

1. Inadequacy of the express notification procedure: The express notification procedure proposed in § 812.20 is deficient in several respects. The primary problem is that it places too much reliance on the IRBs' assessments of risk, without requiring transmittal of sufficient data from which the Agency can make an independent judgment on the issues of safety and validity of research design. The dangers of such an abdication of the Agency's responsibility are amply illustrated by the case of inadequate IRB review of Medical Workshop's intraocular lens experiment proposal, mentioned above. Examples of deficiencies in the express notification procedure are:

(a) Section 812.20(b) requires only a statement from each IRB, assessing the degree of risk to which subjects will be exposed and classifying the device as "vital or nonvital." The provision should also require an explanation of the IRB's reasoning, a summary of the evidence on which the IRB relied (including prior investigations of the device), a description of the elements of risk involved (so that the Agency could ascertain whether the IRB considered all risk parameters), and finally, but not least, a copy of any statements of dissent by IRB members. (See also our comment on § 821(b)(4)(i) and (5), page 14 below.)

(b) Neither section 812.20(b) nor Subpart F, incorporated by reference in § 812.20(e), requires submission to the Agency

of consent forms and informational materials to be given to subjects of experiments, despite the fact that such materials should be readily available at minimal cost. This omission effectively renders the IRB's informed consent determinations unreviewable by FDA at the key stage of approval. The Commissioner himself recognized the importance of Agency review of all consent materials in the preamble to the regulations. See 43 FR 20737 (May 12, 1978)(3d column).

(c) Section 812.20(b) does not require a statement about whether any other IRB has disapproved, suspended, or terminated a similar study, to the knowledge of the sponsor and the relevant IRBs. The provision should require such a statement.

(d) Section 812.20(b) does not specify what is to be included in the description of the investigational device. Unless the Agency has before it at least the information required under the normal application procedure, see § 812.21 (b)(1) & (2), well-considered independent review will be impossible. For example, the Agency might be denied information about the chemical makeup of an experimental implantable device, which could conceivably be classified by a sponsor and compliant IRB as a "low-risk vital investigational device," for which the express notification procedure would therefore by available. Cf., e.g., 43 FR 55724-26 (Nov. 28, 1978) (proposal to categorize implanted peripheral nerve stimulators and implanted spinal cord stimulators as Class II devices).

(e) Section 812.20(b) does not require submission to FDA of a description of methods, facilities, and controls used for manufacture, processing, packing, storage, and installation of the device. Again, this omission renders impossible a considered independent judgment by FDA about the safety of devices which, by definition, may be life-sustaining or may present "substantial risks" to the subject population.

(f) Section 812.20 is confusing in that it fails to specify explicitly that reports of prior investigations of the device and statements of the qualifications of investigators in the instant study must be submitted to the Agency. Sections 812.27(a) and 812.43(b), respectively, can be read to require these submissions (and of course § 520(g)(3)(A) of the statute expressly requires submission of reports of prior investigations to the Agency); but the lack of an explicit incorporation by reference in § 812.20(e) of the requirements of §§ 812.27 and 812.43 subjects the uninitiated to bafflement.

(g) Conclusion: The express notification procedure of § 812.20 as it stands will likely result in incidents of potentially dangerous experimental devices escaping adequate Agency scrutiny. Unless § 812.20 is tightened in each of the respects suggested above, the express notification procedure should be scrapped.

2. Definitional problems--assessment of risks and classification of devices: Under the May 1978 tentative final regulations, a proposal for a device experiment involving humans is automatically subject to full-fledged IDE application requirements only if the experiment both presents "substantial risk to human subjects" and involves a "vital investigational device." Section 812.21(a)(1)(i), 43 FR 20750 (May 12, 1978). The definitions of these concepts are consequently critical.

(a) "Vital investigational device": This term is defined at § 812.3(q), 43 FR 20749 (May 12, 1978), as:

> ...a device intended to support or sustain life or intended for surgical implant into the body (or a diagnostic device, e.g., an

> in vitro diagnostic product, which provides data which might reasonably by considered life supporting or vital to the care of the subject), or a device whose failure could result in permanent injury to the subject.

This definition is further explained in the preamble at 43 FR 20731. Unaccountably, part of the explanation, helpful in determining which diagnostic devices fall within the definition and which do not, has been omitted from the definition itself. We suggest inclusion of the following language from the preamble in the regulation:

> [a device that provides] significant diagnostic information about a patient which, if misleading or inaccurate, could result in significant misdiagnosis of the patient or incorrect therapeutic care of the patient.
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> 43 FR 20731 (May 12, 1978).

The Agency's intention to include such devices within the definition is not reflected in the wording of the definition itself, and a reviewing court might overlook the preamble or fail to take it adequately into account.

(a) "Substantial risk": This term is defined in § 812.3(n), 43 FR 20748 (May 12, 1978), as:

> ...a risk that may result in death or may produce morbidity (including disfigurement, permanent injury, or interference with the capacity to continue employment), require operation or reoperation, require extension of hospitalization (beyond that expected for the condition being treated), require rehospitalization, or cause increased invalidism; or, at the least, produce moderate personal discomfort and the need for extensive outpatient medical care.

With one caveat, we approve of this definition. We emphasize the importance of retaining, in the face of comments to the contrary by industry representatives, the phrase "moderate personal discomfort." The word "extensive," however, is too vague and could be used as a subterfuge for underclassifying potentially hazardous experiments. It should be deleted.

(c) Class III devices: We note that the August 1976 proposal, though overly vague in some respects, drew one eminently sensible line for classifying devices for IDE purposes. That was the requirement of a full-fledged IDE application for all clinical testing involving devices then subject to premarket approval requirements: i.e., all Class III devices (or devices then regarded as new drugs or antibiotic drugs) and their substantial equivalents. 21 CFR §§ 812.2(b), 812.2(c)(2)(ii), 41 FR 35300 (Aug. 20, 1976). This bright-line rule eliminates the administrative burdens of the "risk-and-vitality" assessment procedure for Class III devices and ensures the adequate protection of the human subjects of the experiments in question.

B. Exclusion of Diagnostic Products From IDE Requirements

Section 812.2(b)(5), 43 FR 20747 (May 12, 1978), as presently written, excludes from the requirement of Agency and IRB scrutiny certain diagnostic products which are "vital" and even "life-supporting or life-sustaining" devices. The regulation excludes:

> Devices for diagnosis of any human disease or condition (including in vitro diagnostic products) which are not invasive (e.g., do not penetrate or pierce the skin or mucus membranes of the body or the urethra, or the mouth beyond the pharynx, or the anal canal beyond the rectum, or the vagina beyond the cervical os), do not introduce energy into the subject, and are not used in the diagnosis of any disease or other condition in the subject without confirmation by use of a diagnostic device or procedure whose effectiveness for such diagnosis is established.

This exclusion seems to cover, for example, experimental electrocardiographs and electroencephalographs. Both fall within the Agency's definition of a "life-supporting or life-sustaining device":

> a device that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.
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> 21 CFR § 860.3(e), 43 FR 32994 (July 28, 1978).

For human experiments involving vital or life-sustaining devices entirely to escape FDA and IRB scrutiny is unconscionable. The exclusion for diagnostic devices in § 812.2 (b)(5) should be amended so that experiments involving all "vital investigational devices," with the definition revised as suggested above, page 5, are invariably subject to IDE requirements.

C. The Custom Device Exemption

1. General comments: The August 1976 proposal would have subjected virtually all "custom devices" to IDE application requirements. 21 CFR § 812.2(e), 41 FR 35300 (Aug. 20, 1976). The tentative final regulations proposed this year, however, exempt a broad class of custom devices from Agency and IRB scrutiny. This exemption could endanger the health and safety of innumerable patients, contains an irresolvable logical self-contradiction, and rests on highly doubtful statutory authority.

We call this the "Super Coil" exemption. In 1972 Dr. Harvey Karman habitually used the "Super Coil," which was his own invention, to induce abortions. (After Dr. Karman's initial use of the device, other practitioners also employed it.) The "Super Coil" was a plastic strip that was shoved one by one up the uterus of women three to six months pregnant until the fetuses were forced out. It was never tested properly for safety, and not unexpectedly, it caused complications in 60 percent of one group of patients; 20 percent of these patients experienced major complications. For details, see the testimony of Dr. Sidney M. Wolfe and Anita Johnson of this organization in Medical Devices: Hearings before the House Subcomm. on Public Health & Environment on H.R. 6073 et al., 93d Cong., 1st Sess., at 185-86 (Oct. 23, 1973).

Although under the tentative final regulations a device such as the "Super Coil" would be subject to IDE requirements should practitioners other than the inventor use it, the custom device exemption could leave unprotected all patients unfortunate enough to be personally treated by misguided inventors and tinkerers--the Harvey Karmans of this world.

2. Problems with the language of the regulation: The custom device exemption, as presently written, will not adequately protect the public against recurrences of the Super Coil-type travesty. Its provisions are deficient in the following respects.

(a) The regulation does not specify who is to make the determination that all the requirements listed in § 812.2(d)(1) for exemption of a custom device are met. It is absurd, of course, for the health professional to make it for himself without review. If the FDA is to make the determination, it would have to review the details of all applications for exemption--an enormous administrative burden, under a procedure that foregoes the necessary multilayered safety check of the experiments. Obviously, the interposition of IRB review is the logical step--which eliminates the rationale for the exemption of custom devices from any review.

(b) One requirement that the regulation imposes is that "the device is intended...to meet the special needs of the health professional in the course of his or her practice." Section 812.2(d)(1)(iv) (emphasis added). This undefined phrase is meaningless and open to abuse. No doubt Harvey Karman had his "special needs" too.

(c) Another requirement is that

> the device is made of safe and suitable materials (if an implant) and is not being used in an investigational study for the purpose of determining whether the device is safe or effective.

Section 812.2(d)(1)(vi), 43 FR 20747 (May 12, 1978).

The difficulties with this provision are legion. First, may devices other than implants be made of unsafe and unsuitable materials? Second, who is to determine safety and suitability, and how? Third, when a health professional starts to use such a device, by definition he is engaging in an inquiry as to its safety and effectiveness.

The logical and practical problems in excluding custom devices from IDE requirements are insurmountable. Moreover, as the following analysis shows, the Secretary lacks statutory authority to exclude custom devices from certain key IDE requirements.

3. The Secretary's lack of statutory authority: Three provisions of the statute force one to the conclusion that Congress did not intend to grant the Secretary authority to exclude custom devices from certain IDE requirements. The first is § 520(b), which excludes custom devices only from performance standard and premarket approval requirements. The second is § 520(g), which not only makes no mention of custom devices as an acceptable category for exclusion, but also specifically requires that the Secretary scrutinize "any devices to be the subject of testing involving human subjects." The third is § 519(b), which exempts certain users of custom devices from recordkeeping and reporting requirements but not from other IDE requirements such as application to the Secretary, IRB review and approval and informed consent.

(a) Section 520(b): Section 520(b) of the Act clearly specifies which other statutory requirements do not apply to custom devices. There are only two: § 514 performance standard requirements, and § 515 premarket approval requirements. Section 520(g), the investigational device exemption provision, is not mentioned. The standard method of statutory interpretation, expressio unius est exclusio alterius, dictates that when

a statute specifically applies one treatment to a discrete set of phenomena, all other treatments are excluded by implication. Hence the omission from § 520(b) of any reference to § 520(g) is a clear sign that the Secretary has no authority to exclude custom devices from at least some IDE requirements.

(b) Section 520(g): Section 520(g) of the Act prescribes conditions for exempting "devices intended for human use," § 520(g)(2)(A), or "any device to be the subject of testing involving human subjects," § 520(g)(3), from the stringent requirements of other sections of the statute. There can be no disagreement that custom devices are "intended for human use" and are "the subject of testing involving human subjects."

It is true that § 520(g)(2)(C) allows the Secretary to relax some procedures and conditions for approval of a custom device. But "variance" of procedures and conditions, to use the statutory language, does not mean their abolition. The minimum requirements of §§ 520(g)(2)(B) and 520(g)(3) are always applicable unless specific exemptions are written into the statute.

(c) Section 519(b): This section exempts from recordkeeping and reporting requirements (1) licensed practitioners who manufacture or import devices solely for use in the course of their own professional practices; (2) persons who manufacture or import devices "for...use in research or teaching and not for sale (including any person who uses a device under an exemption granted under § 520(g) [the IDE provision])" (emphasis added); and (3) other persons as to whom the Secretary determines recordkeeping and reporting requirements are unnecessary.

Admittedly the import of § 519(b), particularly in its reference to the IDE requirements of § 520(g), is obscure. If taken literally, § 519(b)(2) would entirely eviscerate § 520(g) by abolishing the recordkeeping and reporting requirements of § 520(g)(2) & (3)--an exception that swallows up the rule. In such cases of flat internal contradictions in a statute, one must turn for guidance to the principles courts use in interpreting such legislation.

The Second Circuit's standard, enunciated in a case involving medical devices, is of assistance. The court said:

> The Food, Drug, and Cosmetic Act has as its purpose the protection of the public from products not proven to be safe and effective for their alleged uses and the safeguarding of the public health by enforcement of certain standards of purity and effectiveness. The reach of the Act is broad and the provisions, touching the public interest in a direct way, are to be given a liberal construction.
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> United States v. Diapulse Corp. of America, 457 F.2d 25, 27-28 (2d Cir. 1972) (emphasis added).

Following this standard,* the provision concerned with "the protection of the public from products not proven to be safe and effective for their alleged uses"--that is, § 520(g),

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*The standard was later reiterated in essence in the Medical Device Amendments--the benchmark principles of § 520(g) itself are "the protection of the public health and safety" and "ethical standards."

regulating tests on human subjects involving experimental devices--should be read broadly. Any exceptions, such as § 519(b), should be construed narrowly.

In view of this principle, we emphasize that nowhere in the statute is there an exception made for custom devices to several key IDE requirements in § 520(g). The most important of these requirements are submission of an IDE application to the Secretary, § 520(g)(2)(B)(i); IRB review and approval, § 520(g)(3)(A) & (B); and assurance of legally effective informed consent on the part of all subjects of the experiment (except in extraordinary circumstances), § 520(g)(3)(D).

4. Conclusion: The exclusion of certain custom devices from IDE requirements in the tentative final regulation presents intractable practical and logical problems, and exceeds the Secretary's statutory authority. We urge the Secretary to return to the approach of the August 1976 proposal, which subjected virtually all custom devices to IDE application requirements. In no event does the law or HEW policy permit the exclusion of custom device experimentation from the full requirements of an IDE application, IRB review and approval, and an assurance of legally effective informed consent.

D. Export of Investigational Devices

The Agency's treatment of the regulation concerning export of investigational devices is perhaps the most appalling example in the tentative final regulations of a buckling under industry pressure. The originally proposed regulation, 21 CFR § 812.19(b)(2)(i), 41 FR 35302 (Aug. 20, 1976), would have allowed investigational devices (which by definition fail to meet performance standards or premarket approval requirements), and even banned devices, to be exported for experimentation on human beings in foreign countries--provided, inter alia, that they were subjected to the full panoply of IDE requirements in Subpart B and that sponsor responsibilities specified in Subpart C were also fulfilled. Without explanation and without even pointing out the omission in the preamble to the tentative final regulation, see 43 FR 20732-34 (May 12, 1978), the Commissioner has dropped these requirements.

All that the final regulation would require for export approval for investigational devices, in essence, is the approval of the foreign government and a vague determination that export "is not contrary to the public safety." Section 812.19(b), 43 FR 20749-50 (May 12, 1978). The Commissioner is not even required to make findings that human subjects would not be exposed to undue risk of harm and that the foreign country has adequate mechanisms to control the use of the device after export. Thus, the regulation creates a double standard--considerable protection for human subjects of device experiments if they are Americans, and minimal, perfunctory protection if they are not.

In practice, the Commissioner is unlikely to prevent export of potentially hazardous devices. As Ms. Anita Johnson pointed out earlier this year in her testimony on drug exports before the House Subcommittee on Health and the Environment, there will be no political constituency to encourage the Commissioner to stop export, and enormous pressure to permit export. But if device experimentation standards are important for the protection of Americans, they are equally important for non-Americans.

Non-objection by the foreign government is inadequate protection for citizens of developing nations. Few countries have FDAs, capable of challenging manufacturers' claims for their products. Few countries closely scrutinize claims of

safety and efficacy. Well-trained scientists and even medical libraries are a rarity.

In the past, American manufacturers have secured foreign government approvals through extra-scientific methods. For example, the Washington Post reported on February 8, 1976, that Searle Co. assured continued approval of Iran of their birth control pills by giving gifts to relatives of the decision-making official. Abbott Laboratories has admitted to the S.E.C. that it has paid foreign officials for "government action relating to the Company's business," as have Pfizer, Warner Lambert and other companies.

Companies have promoted their drugs and devices in other countries for purposes not approved in the U.S. and have failed to inform foreigners of significant side effects. Parke-Davis does not warn Latin Americans, for example, that chloromycetin can cause a fatal blood disease, although it is required to do so here. Sterling Drug promoted the hormone Winstrol (stanozolol) in Latin America for increasing appetite, strength, weight. Here, Sterling is required to warn doctors that Winstrol can stunt growth and impede normal sexual development. Dr. Harvey Karman promoted the use of his infamous "Super Coil" in Bangladesh, where it was apparently used on an unknown number of women. Similar travesties are certain to arise in the future unless device manufacturers are subjected to careful oversight. And as the Commissioner himself pointed out,

> the application of export controls to exported investigational devices serves U.S. interests by making it less attractive for firms to try to avoid the requirements of section 520(g) of the act (21 U.S.C. 352(g)) by conducting studies of investigational devices in foreign countries lacking similar requirements; reducing the unfair advantage that would accrue to such firms; and helping to ensure that data offered to FDA in support of device premarket approval applications were developed under conditions in which human subjects were protected and that ensure the collection of valid scientific data.
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> 43 FR 20833 (May 12, 1978).

We recommend a return to the approach of the August 1976 proposal: all applicants for export of investigational devices must meet all IDE requirements and must fulfill all sponsor responsibilities just as if the experiments were being conducted in the United States. All export approvals must include specific findings by the Commissioner that human subjects of the experiments will not be exposed to undue risks, and that adequate mechanisms exist in the foreign country to control the use of the device after export.

E. Waivers

The tentative final regulations contain two provisions authorizing the Agency to waive otherwise applicable requirements: a general waiver regulation, § 812.10, and a provision authorizing waiver of IRB review requirements, § 812.42(d). Both provisions are overly broad and of questionable legality.

1. The general waiver provision: Section 812.10, 43 FR 20749 (May 12, 1978), provides that "[a]ny person subject to any requirement under this part may petition the Commissioner for a waiver of such requirement" (emphasis added). We would point out that many statutory requirements are not subject to waiver, absent specific exemption in the Act: submission of an application, § 520(g)(2)(B)(i); maintaining records and making reports,

§ 520(g)(2)(B)(ii); submission of an investigatory plan and a report of prior investigations to both an IRB (if an adequate one exists) and the Agency, § 520(g)(3)(A); approval by any reviewing IRBs, § 520(g)(3)(B); submission of signed agreements to behave by all investigators, § 520(g)(3)(C); and assurance of informed consent by all subjects except under extraordinary circumstances, § 520(g)(3)(D). The existence of these non-waivable requirements should be mentioned in the regulation for the benefit of the uninitiated.

We suggest one further addition to § 812.10: that no waiver be granted that could expose any human subject to an undue risk of harm.

2. Waiver of IRB review: Section 812.42(d)(1), 43 FR 20754 (May 12, 1978), authorizes the Agency to waive IRB review "if the Commissioner determines that the requirement is not necessary either for protecting the subjects involved or for assuring the validity or reliability of the scientific data." Section 812.42(d)(2) specifies that IRB review will never be waived in three situations: when the experiment involves "institutionalized human subjects," when it is conducted "on the premises of an institution" with an adequate IRB, and when the FDA determines that the risks to the subjects justify such review.

We contend that § 812.42(d)(1) would permit waivers unauthorized by the statute, and that the statute requires the class of non-waivable IRB reviews to be drawn more broadly than the Commissioner has in § 812.42(d)(2).

Moreover, the policy recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, as well as HEW policy, militate against the waiver of IRB review. And the Agency's own experience with intraocular lens experimentation, where over a thousand IRBs are in action across the country, demonstrates that the requirement of IRB review in all cases is a feasible and necessary means of ensuring that investigational studies are safely conducted.

(a) Section 812.42(d)(1): The Act permits IRB review of the clinical testing of medical devices to be foregone in only two situations: if

> (I) no such committee [i.e., IRB] exists, or
> (II) the Secretary finds that the process of review by such committee is inadequate (whether or not the plan for such testing has been approved by such committee)...
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> Food, Drug, & Cosmetic Act § 520(g)(3)(A)(ii), 21 U.S.C. § 360j(g)(3)(A)(ii) (1976) (emphasis added).

The conclusion is cut and dried. The statute does not speak in § 812.42(d)(1)'s terms of whether IRB review is "necessary" for protection of subjects or assuring the validity of data; the question is whether an IRB exists and is adequate to fulfull its statutory function. If so, IRB review is required by the Act. Section 812.42(d)(1) must be scrapped.

(b) Section 812.42(d)(2): We have two concerns regarding this provision. First, the non-waiver requirement for studies associated with an institution with an IRB in place is drawn far too narrowly. Second, IRB review invariably should be required when subjects include particularly vulnerable individuals such as children, older people, pregnant women, or the non-institutionalized mentally infirm.

(1) Section 812.42(d)(2)(ii), 43 FR 20754 (May 12, 1978), by implication permits waiver of IRB review of investigations not "conducted on the premises of an institution that has an institutional review committee meeting the requirements of [FDA] regulations." The statute, however, does not authorize such a broad range of waivers. As noted above, the only cases where waiver is allowed are where no IRB exists or where the Secretary has specifically found that "the process of review" in a particular IRB is "inadequate." Section 520(g)(3)(A)(ii).

The statute does not explicitly define the stituations in which an IRB is deemed "not to exist" in an area. (Repeal of this exception would put to rest all doubts, and we ask the Commissioner to seek repeal of § 520(g)(3)(A)(ii)(I) by the Congress.) The law as it stands strongly implies, however, that if an adequate IRB exists within the local jurisdiction, waiver of IRB review is forbidden. Section 520(g)(3)(A)(i) speaks of a "local institutional review committee." "Local" in common parlance does not refer to a single institution, but to a territorial jurisdiction, such as a city or a county. Nothing in the statute or legislative history implies that the word is being used in other than its normal sense. Moreover, § 520(g)(3)(A)(i) goes on to specify that the "local" IRB is "to supervise clinical testing of devices in the facilities where the proposed clinical testing is to be conducted." The use of the plural "facilities" means that if an adequate IRB exists in local area, it is to review all studies in the area. Certainly Congress's use of the plural excludes the possibility of the Commissioner's interpretation in § 812.42(d)(2)(ii). Nothing in the statute permits waiver of IRB review if an adequate IRB is in place in the locality in which an investigation is to be carried out, whether the investigation is conducted "on the premises of an institution" or not.

(2) We suggest that § 812.42(d)(2)(i) be revised to prohibit waiver of IRB review of any experiment involving particularly vulnerable subjects, such as children, older people, pregnant women, or non-institutionalized mentally infirm, as well as of those involving "institutionalized subjects." This suggestion is in accordance with the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

We also suggest that the definition of "institutionalized subjects" in § 812.3(c), 43 FR 20748 (May 12, 1978), be broadened to cover patients in "outpatient surgery" or "day surgery" clinics. The "24 continuous hours" provision of § 812.3(c)(1) would exclude such patients, and thus opens the possibility of their being subjected under § 812.42(d)(2)(i) to device experiments unreviewed by IRBs. There is no reason given by the Commissioner, and indeed no reason is conceivable, to treat these patients differently from hospital in-patients for purposes of IRB review.

F. FDA Review of IDE Applications

Section 812.30, 43 FR 20752-53, sets out the procedures and standards for Agency review of IDE applications. In general, we support the § 812.30 scheme, except to the extent that it may allow the Agency to approve an investigational study despite the existence of serious deficiencies in the application.

Section 812.30(b) provides for three sorts of agency action on an application: (1) disapproval, (2) request for additional information, and (3) suggestion of revisions. The sponsor can consider any of these three actions as a "disapproval" for purposes of requesting a regulatory hearing. Section 812.30(c) sets out nine grounds for "disapproval" of an application (though it is unclear whether the word is used

in its narrow sense--(1) above--or its broad sense, encompassing (1), (2) and (3)). But § 812.30(e) provides:

> The Commissioner may, in the Commissioner's discretion, decide not to disapprove an application for which there are grounds for disapproval if the facts do not lead the Commissioner to conclude that the risks outweigh the benefits to subjects...

If "disapprove" in § 812.30(e) is given its broad meaning, encompassing requests for additional information and the suggestion of revisions, then the Commissioner would be empowered to approve applications seriously deficient in several respects--for example, where the application contains an untrue statement of a material fact or omits material information; where the investigational plan is not a reasonable plan to determine whether the device is safe or effective; where the manufacturing process, etc., does not ensure the safety and effectiveness of the device; or where the device is being commercially distributed in illegal fashion.

To clear up this problem, we suggest that § 812.30(e) be amended to read as follows:

> The Commissioner, upon finding that any of the grounds for disapproval listed in § 812.30(c) obtains, shall either disapprove the application, find it deficient and request additional information, or suggest revisions.

We would like to express our agreement with the wording of the nine grounds for disapproval, particularly § 812.30 (c)(3) & (4).

G. Withdrawal of an Exemption

Section 812.35 provides that the Commissioner may withdraw an IDE if he makes any of the twelve findings listed in § 812.35(a). Section 812.35(c), like § 812.30(e) quoted above, makes withdrawal of the exemption discretionary on the part of the Commissioner if he does not "conclude that the risks outweigh the benefits to subjects," considering the factors in § 812.35(a)(11).

Three comments are appropriate. First, the wording of § 812.35(c) appears to put the burden of proof on those asserting that the risks are unacceptably high. The burden should be reversed. Second, to avoid confusion, the safety-related grounds for withdrawal of exemptions--paragraphs 812.35(a)(2) and (a)(11) and (inasmuch as they concern safety) 812.35(a)(3), (4), and (5)--should be placed in a separate mandatory withdrawal category, distinct from the discretionary withdrawal category of § 812.35(c). Finally, the Commissioner should be required to withdraw exemptions in cases of non-safety-related deficiencies that are not corrected within a reasonable time--e.g., 60 days after notification.

H. Information Flow To IRBs

At least five provisions in the tentative final regulations should be amended to require the sponsor of a study to notify appropriate IRBs of important developments in the study.

1. When a sponsor learns of an unanticipated device-related serious adverse effect or life-threatening problem in a study, the sponsor is required by § 812.46(c)(1), 43 FR 20755 (May 12, 1978), to undertake an investigation and to notify FDA and all investigators of the results. Unaccountably

the provision does not require notification of the IRB; this omission should be corrected. Section 812.55(d) should be amended to the same effect.

2. Section 812.55(a) should be revised to require submission of the sponsor's reports on the progress of the study to the IRBs as well as to FDA.

3. Section 812.55(b) should be amended to require the sponsor to notify all relevant IRBs of the suspension, termination, completion, or discontinuance of the study, and to submit the final report on the study to the IRBs.

4. Section 812.55(c) should require notification of all relevant IRBs, as well as of FDA, of any requests to return or dispose of supplies of the investigational device.

I. Other Comments

The suggestions made above are critical to a workable regulatory scheme providing adequate protection to human subjects. A series of other minor amendments to the tentative final regulations would ensure the smooth functioning of the scheme and an adequate flow of information to all participants.

1. IRB members' dissents: Section 812.21(b)(4)(i) & (5) should require, as part of any IDE application submitted to FDA, the submission of copies of any dissents by IRB members against IRB approval of the study in question. See our comment on § 812.20(b), page 3 above.

2. Notification of suspension of other studies: Section 812.21(b)(9) should be amended to require a sponsor to state in its IDE application whether any IRB has suspended, as well as disapproved or terminated, an investigational study of the device in question. This requirement is important to bring to light device studies reviewed by IRBs before IDE rules become effective.

3. Notification of use of vulnerable subjects: Section 812.25(a)(7) & (8) should be revised to require an investigational plan to include a description of any special characteristics of the subject population that would render all or part of it particularly vulnerable. The regulation should require specific notice and justification of the fact that a study would include, for example, the institutionalized, the mentally infirm, pregnant women, or a disproportionate number of any racial or ethnic group.

4. Informed consent: An error in punctuation in § 812.42(a) may distort the meaning of the sponsor's obligations prior to allowing a human subject to consent to participation. The provision should read: "Before any human subject is allowed, or requested formally, to consent to participation..."

We will present further comments to the Agency on issues of informed consent in conjunction with our views on the forthcoming proposed general rules on informed consent.

5. Monitoring of the investigation: We suggest that § 812.46(b) be modified so that the sponsor has a definite time frame, e.g. 30 days, within which the sponsor must either secure a wayward investigator's compliance with the regulations or else discontinue shipments to the investigator or suspend or terminate the study.

We also suggest, for the sake of clarity, that § 812.46(c)(2) state explicitly that an IRB, as well as FDA, has authority to order a sponsor to suspend any study when a device-related adverse effect is regarded as presenting an

unreasonable risk. Proposed 21 CFR § 56.90(k), 43 FR 35202-03 (Aug. 8, 1978), would apparently give IRBs this power; at least a cross-reference here would be appropriate.

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