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PART III

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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DIAGNOSTIC ULTRASOUND EQUIPMENT

Development of Action Program

[4110-03-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Subchapter J]

[Docket No. 78N-0288]

DIAGNOSTIC ULTRASOUND EQUIPMENT

Intent to Propose Rules and Develop Recommendations

AGENCY: Food and Drug Administration.

ACTION: Notice of intent.

SUMMARY: The Food and Drug Administration (FDA) is considering an action program for diagnostic ultrasound equipment, including that used to visualize and monitor the fetus during pregnancy and labor. The agency may develop recommendations or mandatory performance standards related to diagnostic ultrasound equipment or may require manufacturers to supply purchasers with performance data and other information related to safety. One or more actions could follow, including recommended user procedures, recommended training criteria for users, recommendations covering equipment performance, manufacture and test procedures, regulatory product performance standards, and/or informational requirements. Before beginning this program, the agency is requesting further information and is inviting comments on conceptual criteria for users and for manufacturers of diagostic ultrasound equipment.

DATES: Comments and data by August 13, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Melvyn R. Altman, Bureau of Radiological Health (HFX-460), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3426.

SUPPLEMENTARY INFORMATION: The Food and Drug Administration, through the Bureau of Radiological Health (BRH) and under the authority of the Radiation Control for Health and Safety Act of 1968 (Pub. L. 90-602, 42 U.S.C. 263b et seq.), administers and electronic product radiation control program. This authority provides for the protection of the public health and safety through development and administration of radiation safety performance standards and development of recommendations for controlling electronic product radiation. The Food and Drug Administration also has authority under the Federal Food, Drug, and Cosmetic Act, as amended by the Medical Device Amendments of 1976 (Pub. L. 94-295; 90 Stat. 539-583 (21 U.S.C. 360c et seq.)) regarding safety and effectiveness of medical diagnostic ultrasound equipment.

The Commissioner recognizes the demonstrated benefit of the use of diagnostic ultrasound in neurology, cardiology, obstetrics and gynecology, opthalmology, and other fields of clinical medicine. Although ultrasound is now widely accepted as an indispensable diagnostic tool, the possible risks associated with diagnostic ultrasound are not fully understood. To date there have been no reports of adverse effects associated with the clinical use of diagnostic ultrasound, but clinical impressions, although valuable, do not establish conclusively that the use of diagnostic ultrasound involves no risks. Past human epidemiological studies have yielded inconclusive evidence, and it will probably be several years before definitive data will be available from current and future epidemiological studies. Thus, laboratory studies on animals must be used as indicators of possible adverse biological effects in humans.

Many of the early animal studies utilized ultrasound intensities that were well above diagnostic intensities and examined endpoints which were often representative of only gross pathological damage. However, recent reports of biological effects in animals exposed to ultrasound have involved levels of ultrasound representative of current diagnostic ultrasound applications (Ref. 1). It may be argued that many of the studies do not represent the exact exposure conditions of the clinical situations, or that the dosimetry is imperfect, or that the data have not been verified by other investigators, or that most of the data involve continuous wave exposure. However, the Commissioner believes that not all such studies can be dismissed as irrelevant, particularly because some of the studies involve the use of clinical devices.

Because of the extent of use of diagnostic ultrasound procedures during pregnancy and the recognized susceptibility of embryonic tissue to a variety of insults, those studies indicating that ultrasound can effect the development of laboratory animals exposed in utero are of particular concern. Some of the reported effects include delayed neuromotor reflex development (Ref. 2), altered emotional behavior (Ref. 3), and fetal anomalies in rodents exposed to clinical diagnostic ultrasound devices with reported acoustic outputs ranging from 20 milliwatts per square centimeter (mW/cm^2) to 40 mW/cm^2 (spatial and temporal-average intensities) (Ref. 4).

An examination of the current literature suggests that some of the most sensitive indicators of ultrasound-induced alterations appear to be associated with the central nervous system. These reported effects include increased levels of an enzyme (glutamic oxaloacetic transaminase) in the cerebrospinal fluid of dogs (Ref. 5) and induced electrical activity in the brain (evoked electroencephalographic responses) of nonhuman primates (Ref. 6) after exposure to ultrasound from diagnostic instruments with reported acoustic spatial and temporal-average intensities of 1.5 mW/cm^2 and 3 mW/cm^2 respectively.

How the available bioeffects data translate into risk to humans exposed to ultrasound is not clear at this time. There have been attempts to use the available data, both positive and negative, to construct curves or limits that delineate threshold levels or lowest levels for significant biological effects (Refs. 7, 8, and 9). Such levels have been widely interpreted as representing "safe" levels of ultrasound. However, the Commissioner does not believe such graphic analyses of isolated bioeffect data, most of which represent studies not designed to measure threshold effects, can define a safe region. It will probably be several years before the risks of diagnostic ultrasound to humans can be established and quantified. Because human studies of adverse effects from ultrasound have been inadequate, there is no direct way at this time to establish the exposure limits that assure safety in the use of this modality. Thus, the Commissioner believes manufacturers should not state in advertising or promotional literature that diagnostic ultrasound is unequivocally safe.

In view of reports of biological effects in laboratory animals after exposure to ultrasound at intensities representative of those used in a diagnostic applications (Ref. 1) and a report of increased movement of the human fetus during examination with clinical diagnostic ultrasound (Ref. 10), the Commissioner believes an individual's exposure to ultrasound should be kept as low as practicable, consistent with obtaining essential diagnostic information. Also, ultrasound exposure of pregnant humans for commercial demonstration of equipment is not considered acceptable by most professional organizations in the field.

The Commissioner is also concerned about the rapidly growing use of this modality while definitive information on biological effects is lacking. In recent years ultrasound radiation has become a common diagnostic tool in many widely varied medical specialties. The types of devices used in diag-

nostic medicine include pulse-echo imaging devices, continuous-wave Doppler units, pulse devices, and transmission equipment. One study has advocated that diagnostic ultrasound be used as a routine screening practice in all pregnancies (Ref. 11). The Obstetrical and Gynecological Device Classification Panel recommended that physicans not use this modality indiscriminately. However, the extent to which exposure to ultrasound radiation actually occurs will depend on whether available equipment is actually used in obstetrics and whether marketing forecasts are valid.

Several investigators have measured acoustic intensity levels from commercial diagnostic pulse-echo devices. The results of these limited studies indicate that the spatial and temporal-average intensities for most available pulse-echo devices are less than 10 mW/cm^2 (Ref. 12). However, there is currently no way to assure that all equipment will operate at these levels. For example, a report submitted by a manufacturer to BRH indicates that time-average intensity output of approximately 80 mW/cm^2 can be expected from the manufacturer's pulse-echo equipment. Clearly, output levels of pulse-echo devices can vary widely without operator knowledge.

Similar variation can occur with continuous-wave Doppler devices (Ref.13). One investigator has reported that obstetrical continuous-wave Doppler devices can be designed to operate at ultrasonic intensities below 5 mW/cm^2 (Ref. 14). Here again, widely varying outputs of similar devices designed to obtain the same medical information have been observed. It may be desirable to discourage marketing of equipment with higher intensity capabilities, unless they are justified on the basis of needed improvement in diagnostic capability. With regard to Doppler units, it is important to consider that exposure times can range from less than 1 minute to periods of several hours, as in the case of fetal monitoring during labor and delivery.

From these examples, the Commissioner, in accord with recommendations of the Obstetrical and Gynecological Device Classification Panel, believes it prudent to use the lowest practical exposure levels, consistent with obtaining needed diagnostic information, and to use diagnostic ultrasound only when there is a valid medical reason. In this respect, the Commissioner believes the proposed recommendations of the Technical Committee of the Ultrasound Section of the National Electrical Manufacturers Association (NEMA) for abdominal scanning (10 mW/cm^2 for pulse-echo devices) provide reasonable guidelines for the upper limits of spatial and temporal-average intensities that should be expected from these types of diagnostic ultrasound equipment (Ref. 19).

Information on acoustic emissions and imaging characteristics should be available to the user so that the user can make informed judgments regarding the use of this diagnostic modality. The Commissioner believes disclosure of output levels, as well as imaging characteristics, would aid the user in selecting equipment that would provide the desired diagnostic information while at the same time expose the patient to the lowest levels of ultrasonic radiation. Disclosure of imaging characteristics and output information would discourage claims that higher output necessarily implies more useful equipment. The Commissioner is considering requirements that output and imaging information be provided to users by manufacturers. In addition, user training activities are needed to eliminate unproductive exposure and to assure that consistently high quality diagnostic information is produced.

Several factors, including system sensitivity, resolution, gray scale dynamic range, registration, and calibration, directly affect the diagnostic capability of Doppler and/or pulse-echo equipment. Optimizing these factors can yield superior diagnostic information with minimum ultrasound exposure. Measurement surveys by FDA and other institutions indicate these factors vary widely among commercial models of diagnostic ultrasound equipment (Refs. 15 and 16). Other reports show that in the absence of routine testing and maintenance these factors vary with time for individual devices, and the informational quality of diagnostic ultrasound equipment will deteriorate (Refs. 17 and 18). The Commissioner is considering the promulgation of recommendations to users and/or equipment performance standards to improve this situation.

Because of these concerns and unresolved issues, BRH will continue to conduct biological effects investigations, evaluate equipment performance, and support research in these areas. Also, NEMA is considering ways to support biological effects studies. As in other problem areas (e.g., effects of ionizing radiation), no single study can provide all the necessary information. A program of collaborative research including well designed and executed studies is needed to determine the extent of risk to human health posed by exposure to diagnostic ultrasound. In addition to investigating biological effects, work will continue on developing methods to measure and evaluate the acoustic emissions and the imaging characteristics of diagnostic ultrasound equipment. The BRH will continue to measure and evaluate the performance of such equipment through laboratory tests and review of reports that manufacturers are required to submit as specified in §§ 1002.10 and 1002.12 (21 CFR 1002.10 and 1002.12). Current and future data will be evaluated relative to the development of recommendations and performance standards and BRH may obtain additional performance and other technical data from manufacturers. In addition, the Commissioner encourages ultrasound users to notify BRH of accidental overexposures and adverse reactions of patients and workers.

The Commissioner recognizes and encourages the constructive efforts of the industry and others towards the development of standards for safe and effective diagnostic ultrasound equipment. A joint project by NEMA and the American Institute of Ultrasound in Medicine (AIUM) may result in a voluntary safety performance standard for this equipment. In addition, the Acoustical Society of America is actively developing standards for diagnostic ultrasound devices. The Commissioner will carefully consider the results, if timely and effective, of these and other voluntary efforts before taking further action.

The Commissioner will consult one or more of the advisory committees concerned with the safety and effectiveness of diagnostic ultrasound devices—the Technical Electronic Product Radiation Safety Standards Committee (TEPRSSC), the Medical Radiation Advisory Committee (MRAC), and appropriate medical device panels—concerning any further proposed action and any comments received in response to this notice. The TEPRSSC, is a permanent statutory advisory committee to the Secretary of Health, Education, and Welfare and must be consulted before the establishment of standards under the Radiation Control for Health and Safety Act of 1968. The MRAC advises and consults with BRH in formulating policy and developing a coordinated program related to use of radiation in the healing arts. Medical device panels have been established under section 513(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(b)) to make recommendations to the Commissioner for the classification of medical devices for human use. The MRAC and TEPRSSC considered drafts of this notice at their respective meetings on May 8 through 10 and June 1 and 2, 1978. Both committees generally supported the plan to publish a notice of intent concerning diagnostic ultrasound. Earlier, the Obstetrical and Gynecological Device Classification Panel recommended that all diagnostic and monitoring ultrasound devices be classified in class II, performance standards.

The following questions and conceptual criteria for users and manufacturers are provided for consideration and comment. Such criteria may be the subject of future proposed performance standards or voluntary recommendations under the acts administered by the agency.

QUESTIONS AND CONCEPTUAL CRITERIA RELATED TO THE CLINICAL USE OF DIAGNOSTIC ULTRASOUND EQUIPMENT

1. Diagnostic ultrasound should be used for human exposure only when there is a valid medical reason. Which of the following or what additional reasons should be considered valid (and under what conditions): medical diagnosis, patient or fetal monitoring, and educational and research applications approved by institutional review boards?

2. Users of diagnostic ultrasound equipment should have adequate training. How extensive should such training be? Should such training be only formalized training? Should it include instruction in both operator techniques and interpretation of diagnostic ultrasound information, instruction in performance measurements and procedures, and instruction in biological effects of ultrasound radiation?

3. Users of diagnostic ultrasound should implement adequate routine quality assurance programs to monitor equipment performance. What should be the elements of such programs? For example, should system sensitivity, depth calibration, and transducer resolution be periodically measured? What other measurements should be made?

QUESTIONS AND CONCEPTUAL CRITERIA RELATED TO THE MANUFACTURE OF DIAGNOSTIC ULTRASOUND EQUIPMENT

1. Manufacturer's specifications regarding ultrasound emissions as well as imaging effectiveness should be provided to the user. Which of the following or what additional parameters should be specified? (Items related to acoustic output defined in the proposed AIUM nomenclature (Ref. 20) are italicized):

a. Maximum and average ultrasound *intensity* in time and space;

b. Maximum and average ultrasound *power*;

c. Transducer pulse shape, *pulse duration*, and *pulse repetition rate*;

d. Transducer frequency spectrum information;

e. Transducer *beam pattern* (axial and transverse);

f. Transducer *focal length* and *focal zone*;

g. Area of transducer *beam cross-section* and *beam width* (at focal length, if focused);

h. Lateral resolution for each transducer;

i. Range resolution for each transducer (except for continuous-wave Doppler);

j. Sensitivity;

k. Position registration accuracy (for compound B-scan);

l. System dynamic range;

m. Range calibration accuracy (pulse-echo equipment).

2. Manufacturers should adopt quality control and testing programs adequate to assure that equipment performance specifications are met and that information provided with equipment is accurate. What are the elements of an adequate testing program for the manufacture of diagnostic ultrasound equipment?

3. Ultrasonic equipment maximum output capabilities should be as low as practical, consistent with obtaining needed diagnostic information. Should there be a specific recommended or mandatory limit on equipment output? For example, such a limit might require that diagnostic ultrasound equipment not produce spatial peak, time-average intensities in excess of 100 mW/cm^2 unless the manufacturer can strongly justify such exposures based on needed improvement in diagnostic capability. Would such a limit discourage trends to increased equipment output? Would such a limit be viewed as a "perfectly safe" level?

4. Diagnostic ultrasound should be used for human exposure only when there is a valid reason for its use. Are there any valid reasons for exposure of living humans to diagnostic ultrasound for purposes of commercial demonstration?

Persons or organizations wishing further information made public on the development of the action program for ultrasound diagnostic equipment and its use may write to the contact person whose address appears in the heading of this notice.

The following references are on file at the office of the Hearing Clerk, FDA, and may be seen in that office between 8 a.m. and 4 p.m., Monday through Friday:

(1) Stratmeyer, M. E., "Research Directions in Ultrasound Bioeffects—A Public Health View," Symposium on Biological Effects and Characterizations of Ultrasound Sources, June 2 and 3, 1977, pp. 240-245, HEW Publication (FDA) 78-8044.

(2) Murai, N., K. Hoshi, and T. Nakamura, "Effects of Diagnostic Ultrasound Irradiated During Fetal Stage on Development of Orienting Behavior and Reflex Ontogeny in Rats," *Tohoku Journal of Experimental Medicine*, 116:17-24, 1975.

(3) Murai, N., K. Hoshi, C. Kang, and M. Suzuki, "Effects of Diagnostic Ultrasound Irradiated During Fetal Stage on Emotional and Cognitive Behavior in Rats," *Tohoku Journal of Experimental Medicine*, 117:225-235, 1975.

(4) Shoji, R., E. Momma, T. Shimizu, and S. Matsuda, "An Experimental Study on the Effects of Low Intensity Ultrasound on Developing Mouse Embryos," *Teratology*, 6:119, 1972.

(5) Tsutsumi, Y., K. Sano, T. Kuwabara, T. Takakura, K. Hayakawa, T. Suzuki, and M. Katanuma, "A New Portable Echo-Encephalograph, Using Ultrasonic Transducers; and its Clinical Application," *Medical Electronics and Biological Engineering*, 2:21-29, 1964.

(6) Hu, J. H. and W. D. Ulrich, "Effects of Low-Intensity Ultrasound on the Central Nervous System of Primates," *Aviation, Space, and Environmental Medicine*, 47:640-643, 1976.

(7) Nyborg, W. L., "Physical Mechanisms for Biological Effects of Ultrasound," report based on series of lectures presented March 12 to April 2, 1976, at the Bureau of Radiological Health, HEW Publication (FDA) 78-8062.

(8) Ulrich, W. D., "Ultrasound Dosage for Experimental Use on Human Beings," Naval Medical Research Institute Research Report, Proj. M4306, 01-101-0 BXXO, Report #2, August 18, 1971.

(9) Wells, P. N. T., "The Possibility of Harmful Biological Effects in Ultrasound Diagnosis," *in* "Proceedings of Symposium on Cardiovascular Applications of Ultrasound," Beese, Belguim, May 29 and 30, 1973.

(10) David, H., J. B. Weaver, and J. F. Pearson, "Doppler Ultrasound and Fetal Activity," *British Medical Journal*, 2:62-64, 1975.

(11) Donald, I., "New Problems in Sonar Diagnosis in Obstetrics and Gynecology," *American Journal of Obstetrics and Gynecology*, 118:299-309, 1974.

(12) Stewart, H. F., G. R. Harris, and H. M. Frost, "Development of Principles and Concepts for Specification of Ultrasonic Diagnostic Equipment Performance," *Ultrasound in Medicine*, Vol. 3B, Edited by Dennis White and Ross Brown, Plenum Press, pp. 2115-2142, 1977.

(13) Rooney, J. A., "Determination of Acoustic Power Outputs in the Microwatts-Milliwatts Range," *Ultrasound in Medicine and Biology*, 1:1-4, 1973.

(14) Ziedonis, J. G., "Ultrasonic Power Levels Used in Commercial Equipment for Medical Applications and How to Control It for Patients Safety," Proceedings of the Society of Photo-Optical Instrumentation Engineers, 47:110-111, Aug. 1 and 2, 1974.

(15) Christensen, S. L. and P. L. Carson, "Performance Survey of Ultrasound Instrumentation and Feasibility of Routine Monitoring," *Radiology*, 122:449-454, 1977.

(16) Erickson, K. R., P. L. Carson, and H. F. Stewart, "Field Evaluation of the AIUM Standard 100 mm Test Object," *Ultrasound in Medicine*, Vol. 2, Edited by White and Barnes, Plenum Press, New York, 1976.

(17) Goldstein, A., "Gray Scale Shifts in Ultrasound Displays," *Radiology*, 121:175-162, 1976.

(18) Smith, S. W., H. Lopez, and H. F. Stewart, "Methods and Results of Dynamic Range Testing of Diagnostic Ultrasound Instrumentation," Proceedings of the Society of Photo-Optical Instrumentation Engineers (in press).

(19) Technical Committee of the Ultrasound Section of the Radiation Imaging Products Division, National Electrical Manufacturers Association, "Recommendations of the Technical Committee Proposed for Consideration," submitted to the Ultrasound Subcommittee of the BMD OB/Gyn

Device Classification Panel, October 22, 1976.

(20) Proposed American Institute of Ultrasound in Medicine (AIUM) Nomenclature, Fifth Draft, August 21, 1977.

This notice of intent is issued under the Public Health Service Act, as amended by the Radiation Control for Health and Safety Act of 1968 (secs. 356 and 358, 82 Stat. 1174-1179 (42 U.S.C. 263d and 263f)); the Federal Food, Drug, and Cosmetic Act as amended (21 U.S.C. 301 et seq.); and authority delegated to the Commissioner (21 CFR 5.1).

Interested persons are invited to participate in the development of an action program by submitting written comments, views, and data on the subject. Communications should reference the docket number appearing in the heading of this document and should be sent to the hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, by August 13, 1979. Timely comments will be considered in formulating the action program. Comments received after the closing date may be considered, depending on the stage of development of any standards or recommendations.

Dated: February 1, 1979.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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