# Acoustic Output Upper Limits Proposition

## Should Upper Limits Be Retained?

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At the American Institute of Ultrasound in Medicine (AIUM) 2002 Annual Convention in Nashville, Tennessee, a point/counterpoint categorical course was presented on the topic of acoustic output upper limits. The course organizers were William D. O'Brien, Jr, PhD, John G. Abbott, PhD, and Mel E. Stratmeyer, PhD. The published course objective was as follows:

> The current limits on acoustic output were not derived from an analysis of health risks based on bioeffects data, nor were the limits derived from an analysis of the health benefits. Ideally, upper limits should be based on a risk-versus-benefit analysis. The speakers will explore possible impacts of removing limits, or altering current limits, on both risks and benefits. The pro and con positions were assigned to the speakers.

The course started with an overview of the regulatory background. Then the 6 speakers for the pro and con positions were given 10 minutes each to argue the proposition of whether upper limits should be retained. Three organizational views were solicited: industry, medicine, and research, with a pro and con position for each organizational view.

As a service to the medical ultrasound community, these individuals have provided the following commentaries based on their categorical course presentations. The guidelines for the pro and con commentaries were to limit their text to about 500 words. The regulatory background text was not limited to 500 words. The pro and con positions were assigned by the course organizers and do not necessarily reflect the views of the speakers or their organizations.

**Abbreviations**
AIUM, American Institute of Ultrasound in Medicine; ALARA, as low as reasonably achievable; FDA, Food and Drug Administration; NEMA, National Electrical Manufacturers Association; ODS, output display standard

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## Regulatory Background

*Gerald R. Harris, PhD*

Under the Medical Device Amendments to the US Food, Drug, and Cosmetic Act, diagnostic ultrasound is categorized as a class II device, meaning that for a new device to be marketed, the submission to the Food and Drug Administration (FDA) of a 510(k) premarket notification (named for a section of the amendments) is required. In this submission, a manufacturer must show that the device is substantially equivalent in terms of safety and effectiveness to devices marketed before May 28, 1976, the date of the amendments. Also, a class II device must not raise notable new issues regarding either safety or effectiveness. Otherwise, the device is considered class III, and a premarket approval application must be submitted.

To assist in showing equivalent safety, in 1985 the FDA established output exposure limits for both thermal and nonthermal exposure quantities in 4 application-specific categories: cardiac, peripheral vascular, ophthalmic, and fetal imaging and other.[1] These exposure limits were based on measurements of preamendment devices. A new device was considered substantially equivalent in terms of safety if its output did not exceed the relevant limits. To make this comparison fairer for devices with higher frequencies, an additional step was added of estimating an in situ (derated) value from the water-based measurements with the use of an attenuation factor of $0.3\ dB \cdot cm^{-1} \cdot MHz^{-1}$. It should be understood that this determination of device equivalence is based on an evaluation of relative, not absolute, safety, the assumption being that if new devices have outputs no greater than those of preamendment devices, then they are at least as safe.

This process of performing output comparisons of derated exposure quantities provided an effective means for making determinations of substantial equivalence based on relative safety considerations. However, in the late 1980s, the FDA was approached by the AIUM and industry with the desire to exceed the application-specific limits in some cases. An FDA 510(k) guidance document at the time stated that, "If the device is capable of employing acoustic intensities greater than pre-amendments levels, then the system must incorporate device features which will offset the question of safety raised by this capability." The FDA, the AIUM, and industry soon agreed that incorporation of an output display (via the eventual output display standard [ODS])[2,3] coupled with a user education program could serve as the "device features," and for a system incorporating these features, substantial equivalence could be established in the absence of any limits on acoustic output.

This idea was captured in the May 1990 issue of the *AIUM Reporter*, in which then President William D. O'Brien, Jr, PhD, said in his Letter from the President, "FDA is willing to remove the upper output limits (referred to as pre-Amendments levels). In return, they are requiring features on the system which provide to the user information about the output levels. The removal of the upper output limits has the potential of increasing instrumentation performance, thus resulting in better diagnostic capability, not only from improved resolution but also from new diagnostic features. But the user must become educated about the Real-Time Output Labels which are currently under active development."

At this time, the process had begun to replace the output limits with the output display–user education approach, but soon other concerns came to light that seriously compromised the agreement regarding removal of all limits. In the October 1990 issue of the *AIUM Reporter*, Robert G. Britain, manager of the Diagnostic Imaging and Therapy Systems Division of the National Electrical Manufacturers Association (NEMA), responded to President O'Brien's letter with, "As equipment manufacturers, NEMA believes that higher acoustic output will not necessarily result in either improved resolution or improved diagnostic features… Moreover, NEMA does not support unlimited acoustic output limits with the potential for a 'horsepower' race impairing ultrasound's safety record. NEMA therefore supports establishment of an overall output limit and elimination of application-specific output constraints."

Also, a letter from the president of the American Society of Echocardiography to the AIUM stated, "… because it is obviously possible to increase power to levels that can cause tissue damage, it would be imprudent and potentially dangerous for the FDA to remove controls on power output. We feel that for power output to be increased beyond present levels, manufacturers should be required to demonstrate efficacy…, necessity…, and safety…" (March 1991).

Furthermore, a similar sentiment was expressed in a letter to the AIUM from the President of the American College of Cardiology (ACC): "We believe that the consequence of no limit on power output presents a potential safety hazard for patients and cannot, therefore, adopt this document (the ODS) with a clear conscience. Based on this concern, the ACC is willing to endorse most of this information with the caveat that we feel manufacturers and users of ultrasound equipment should maintain power output limitations thereby allowing for ultimate patient safety" (July 1992).

During this time, the AIUM's concern over incorporation of an output limit was expressed in a letter from then President John C. Hobbins, MD, to the FDA: "The concern of the AIUM is that, although such a limit may appear to protect a patient from exposure to inordinately high intensities of ultrasound, it actually will suggest to a user that any setting that is below the 'upper limit' level is safe.... Additionally, this concept drastically discourages the user from adhering to the ALARA (as low as reasonably achievable) principle and sets back months of agonizing, but fruitful, discussions between AIUM, NEMA, and FDA" (September 1991).

The FDA, faced with a lack of consensus in the scientific community as to how the output display and limits should be factored into a determination of substantial equivalence, responded as follows: For devices that incorporated an output display according to the ODS, the application-specific limits would be removed, but overall upper limits would be retained equal to the highest application-specific values. In this way, the ODS in combination with user education would allow enlightened users to operate the equipment prudently at increased levels of exposure, and the overall limit would protect patients from inordinately high outputs delivered by unenlightened users. This approach was accordant with the FDA's regulatory responsibility for a class II device mentioned above, in that no notable new issues of safety would be raised, thereby justifying a 510(k) rather than premarket approval path to market.

This regulatory policy is still in effect,[4] but there are mechanisms by which it can be altered. For example, a "petition to the commissioner" can be submitted to the FDA. This is a formal procedure by which a user or an industry group could argue that raising or removing the limits would not adversely affect safety and would improve efficacy. This process is public with a public comment period. Alternatively, as part of a 510(k) submission, scientifically validated data can be presented that show the benefit and safety of an increased limit. This approach has been used to increase the field strength limit for magnetic resonance imaging applications.

There are 2 important concerns on the FDA's part with regard to a change in the output limit policy. The first is the horsepower race issue, in which increased output could be used to offset less sensitive signal processing, with no gain in efficacy and potentially compromised safety. The second is making a determination of substantial equivalence with no output limits given the generally recognized lack of success of the user education effort.[5,6] However, if it can be shown that the current output limits are imposing appreciable clinical constraints, then such evidence should be presented to the FDA so that a mutually agreeable solution can be found to meet the needs of the patients in a safe and effective manner.

## Industry: Upper Limits Should Be Retained

*John G. Abbott, PhD*

The position presented in this argument addresses the retention or existence of regulatory limits. The topic is discussed from the point of view of industry if upper regulatory limits were removed.

### *Safety*

The existence of limits provides the users with confidence that the product they are using is safe. Many desire a "safe-at-all-speeds" device, preferring not to have to consider a bioeffects risk when performing examinations. If the limits were removed, would there be enough information to make an informed risk-benefit decision? Do we effectively educate the user to balance performance versus the bioeffects risk?

### *Cost*

Changes to regulatory systems result in a finite cost to manufacturers in product design and acceptance testing. The costs from such changes will be passed on to the customer, raising the cost of the technology. Removal of limits often requires special user licensing and training, the cost of which will be partially shared by the manufacturer.

### *Liability*

Ultrasound is already a "safe" product with historically low liability. Increased outputs increase risk and therefore liability.

### *Innovation*

Many improvements to diagnostic sonography have come through addressing the image-processing path. Would techniques including harmonic imaging, pulse inversion, coded excitation, and SonoCT have been developed as early as they were had manufacturers been able to pursue a "path of least resistance" increased output option?

### *Regulatory*

Removal of the limits will only increase the regulatory load already imposed on manufacturers. Additional restrictions could include user or site licensing and reduced portability, one of the major advantages sonography has over other diagnostic imaging modalities.

### *Patient Access*

Restrictions have been proposed to the point at which much of the diagnostic power could be limited to specially trained personnel at special diagnostic centers. In many of the poorer and more remote regions of the world, where such centers are not available, the diagnostic advantages of ultrasound could be restricted.

## Industry: Upper Limits Should Not Be Retained

*Mark E. Schafer, PhD*

When the ODS was implemented within the regulatory scheme, arbitrary output limits were retained. Not only are these limits arbitrary, but work on the ODS showed that they had little relevance to patient safety. Maintaining the limits also seriously blunted the AIUM-NEMA educational program. Now, with a number of years of experience with the ODS, it is time to revisit this issue.

Implementing the current limits requires design effort during the development of new equipment, effort that could otherwise be spent on new features and capabilities made possible by higher output. Additionally, transducers are limited both by acoustic limits and by thermal limits on the temperature rise. Research into new transducer materials is hampered by the concern that even with improved thermal characteristics, there would still be a regulatory limit on the output, so why make the effort?

The notion of a horsepower race is an often-cited concern that has never materialized. Today's users are sophisticated enough to demand receiver and front-end processing capabilities, which cannot be duplicated by merely increasing the output levels.

Most importantly, removing the current limits would fulfill the original goal of providing practitioners with the control to make clinical decisions in the best interest of their patients, especially those who because of body habitus are difficult to image. Furthermore, clinical research is driving new applications of ultrasound that call for a new regulatory approach.

One possible approach is an "override" mode, in which, for limited intervals and with positive clinical control, the system exceeds the current acoustic output limits. Thus risk-benefit decisions are in the clinician's hands, who acts in the best interest of the patient on the table. Equipment with this override capability could be in a separate regulatory class, thus allowing new clinical applications to be explored in a less restrictive, yet still well-managed, situation. Sensitive applications, such as fetal and contrast-enhanced studies, would have additional "special controls." Just as the now-abandoned FDA "track 2" was a means to allow higher output in certain circumstances before the adoption of "track 3," perhaps a "track 4" could be similarly structured.

In summary, this industry's success, both now and in the future, is based on meeting the requirements of the clinician while respecting patient safety and the need for a regulated environment. However, it is time to move beyond a 25-year-old framework and use the ODS as it was originally intended. Doing so would further extend the boundaries of this incredibly valuable modality and spur innovations in transducer design, system capability, and clinical ingenuity.

## Medicine: Upper Limits Should Be Retained

*Tariq A. Siddiqi, MD*

Diagnostic ultrasound is widely used in all medical specialties, and of the 4 million infants born in the United States annually, almost all are exposed to diagnostic ultrasound in utero. When

assisted reproductive technologies are used, human embryos may be exposed as many as 4 to 6 times in the first trimester. Such exposures carry the potential for bioeffects that may not appear for decades.

One of the guiding principles of medicine is *primum non nocere* (first, do no harm). The prudent practitioner therefore always weighs risks versus benefits and acts accordingly. For diagnostic ultrasound, this approach is exemplified by the ALARA principle, i.e., the use of intensities as low as reasonably achievable for the shortest possible exposure to obtain required diagnostic information that will help guide treatment. In 1992, the FDA increased the 1976 fetal and neonatal limits to a maximal derated spatial-peak temporal-average intensity of 720 $mW/cm^2$, an almost 8-fold increase.

There are convincing data that exposure to high-intensity ultrasound can reduce birth weight in animal models and produce a host of other biological effects, including lung hemorrhage and cardiac arrhythmias, especially in the presence of gas contrast agents. In a recent meta-analysis of epidemiologic data available for in utero exposure (less than pre-1992 limits), 3 studies showed an effect on birth weight: 2, a decrease and 1, an increase. Four studies of childhood malignancies showed no effect on prevalence, whereas several studies provided reassuring data with respect to neurologic deficits. Sinistrality remains somewhat controversial, with 3 studies showing an increased rate of "non–right-handedness." Although there are no clinical data with respect to lung hemorrhage, a premature infant administered a surfactant appears theoretically vulnerable. Anecdotal data confirmed that ultrasound induced arrhythmias in human adults. These latter bioeffects have been observed with current instruments that may actually operate at higher intensities than approved by the FDA. In the case of the fetus, attenuation from the maternal abdominal wall has been shown to cause an order-of-magnitude decrease in exposure intensity.

The pre-1992 limits have served us well, and we need to collect similar epidemiologic and laboratory data for post-1992 exposure conditions before removing acoustic output limits in their entirety. There are no convincing data to suggest that removing acoustic output limits will notably improve clinical diagnostic capabilities. There are, however, credible clinical and laboratory data that suggest that higher acoustic intensities can and do cause harmful bioeffects. Thus adhering to both the *primum non nocere* and ALARA principles, I see no benefit to removing the current FDA upper limits for diagnostic ultrasound.

## Medicine: Upper Limits Should Not Be Retained

*Christopher R. B. Merritt, MD*

Today, more than ever, there are compelling arguments against the continued imposition of arbitrary limits of acoustic output for diagnostic scanners. Much of the progress in ultrasound technology over the last decade would not have occurred if earlier output limits had remained in place. It is likely that the full diagnostic potential of ultrasound will not be realized if arbitrary limits remain in place.

Limits restrict the development of new technology as well as the practice of medicine. Even if higher output levels are shown to have a risk for adverse bioeffects, their clinical value will be determined not by risk alone but by the clinician making a risk-benefit decision in an individual clinical context. Fundamental to the practice of medicine is the thoughtful assessment of the potential risks and benefits of any clinical decision. Risk-benefit assessment must be based on scientific evidence related to potential benefits, potential risks, and clinical context. Currently, the benefits of ultrasound are certain; the risks are not. There is no scientific basis relating current limits to risk. If a proven risk is identified at higher output levels, then this must be considered in the context of the potential benefit in a specific clinical setting. The mere presence of risk does not contradict the use of a potentially beneficial technique when the potential risks and benefits of alternative approaches are considered. Radiography and computed tomography subject patients to the known risks of radiation exposure and contrast agent reactions. Magnetic resonance imaging may cause considerable tissue heating and dangerous effects on ferromagnetic foreign objects. Angiography exposes patients to possible injury from not only radiation exposure and contrast reaction but also bleeding, embolization, and vascular damage.

Ultimately the physician caring for the patient is responsible for safety and successful treat-

ment. Regardless of exposure conditions, the responsibility for maintaining the excellent safety record of sonography rests with clinicians and sonographers, not regulatory agencies setting arbitrary limits. Prudent users understand the potential risks and benefits of the examination and the risks and benefits of alternative approaches. They know and monitor the output of the equipment and implement the ALARA principle. Improved diagnostic capabilities enabled by higher outputs have the potential of offering important benefits to patients. The future of ultrasound will benefit not by continuing to apply arbitrary limits to output but rather by ensuring that future generations of users understand risks and benefits and are trained to obtain the maximal benefits of their imaging tools.

## Research: Upper Limits Should Be Retained

*Francis A. Duck, PhD*

The retention of upper limits follows from past experience in development of novel clinical techniques and research findings about safety and bioeffects.

Limits have been in place for 2 decades. During this time, the following techniques have moved from research to clinic: Doppler imaging, esophageal scan heads, intravascular probes, speckle management, three-dimensional imaging, harmonic imaging, gas contrast agents, pulse coding, and elastography. In no case has development been disabled by FDA limits. Indeed, pulse coding was developed explicitly to improve resolution at depth while operating within the limits. Acoustically driven elastography is perhaps the only technique for which exposure requirements exceed limits. This single example creates a meager case for demolishing a proven safety structure. In particular, and unlike any conventional sonographic diagnostic technique, elastography includes the intention to change tissue structure ultrasonically and so deserves to be judged by different criteria. Apart from this instance, there is no evidence that the FDA limits have inhibited development of new methods or their transfer from laboratory to clinic.

Safety research provides other arguments in favor of retaining limits. Diagnostic systems, allowed by the FDA, cause tissue heating. Manufacturers can already market systems with a thermal index of greater than 6, and it can reach as high as 12. At 49°C, the time to cause permanent damage is 10 to 200 seconds depending on the tissue, and doubling power would reduce this time to less than 1 second. There is thus no meaningful scope for increasing limits on time-averaged intensity let alone removing them completely. Pulse amplitude, too, has very small scope for increase. Present clinical systems already reach 2.5 MPa at the transducer, and nonlinear propagation effects probably mean that further increases in drive will be accompanied by increasingly diminishing returns. The advisory value of on-screen indicators fails under extreme conditions of rapid heating and high nonlinearity. There are deficiencies in the safety indices as appropriate and only means to monitor safety. The physical models are simplistic; the predictive ability for a temperature rise is questionable; and the user is given no information about transducer self-heating. In addition, knowledge about the safety implications of ultrasound exposure is still limited. Thermal teratologic studies are still being reinterpreted; recent epidemiologic evidence on handedness is still under review; and there is almost no knowledge of the direct effects of radiation stress on cell behavior. It would be unethical to transfer responsibility for safety to the user on the basis of such incomplete and potentially misleading information.

## Research: Upper Limits Should Not Be Retained

*Phillip J. Bendick, PhD*

From a research and academic perspective, a risk-benefit assessment for eliminating the upper limits for acoustic output of diagnostic medical sonographic equipment offers important potential benefits with a minimum of any risk. It is a responsibility of the researcher to inform the clinician, whose primary concern is benefit for the patient, of the risks of bioeffects. Although the general nature of these bioeffects is reasonably well known, that is, thermal and nonthermal, the in vivo thresholds for these risks are largely unknown or uncertain, despite decades of bioeffects-related research. The data on bioeffects that are available show considerable scatter and very wide confidence limits for both direct measures such as tissue temperature versus time of exposure and more indirect clinical effects such as birth weight versus fetal exposure.

Raising the output limits would allow a controlled investigative environment for studying a wide range of variables in tissue phantom and animal models under clinically relevant conditions. Diagnostic ultrasound has moved beyond its early days with the use of wide-aperture, single-element transducers (early A-mode) to a time of complex beam forming and transducer excitation with scanned linear and phased array probes, yet most of the bioeffects data that do exist were acquired with A-mode systems. In the laboratory, these systems have no upper limits on output, and wide ranges of exposure can be tested. However, the characteristics in tissues of focused ultrasound beams from a single-element transducer may be quite different than the more complex beams generated by arrays. The use of clinical ultrasonic instruments for bioeffects testing is limited by their inability to generate high enough output intensities to effectively approach (much less substantially exceed) any bioeffects threshold and to establish just where that threshold might be for different tissue types.

The reality is that manufacturers will not design and build separate ultrasonic systems for clinical practice and research laboratories. With elimination of output limits, the same instruments that would be used clinically (with a strong caveat requiring education and training of the clinical users) would be available for studies in research laboratories and more relevant interpretation of the data. With that data in hand, it is more likely that the next generation of ultrasonic instruments could actually be designed to be safer, because the potential effects of the output settings would be more fully understood, and potential hazards would be brought to the immediate attention of the user.

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