Thomas Jefferson University | **Jefferson Medical College**

June 18, 2003

2999 '03 JUN 19 A9:17

Dockets Management Brach (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room #1061
Rockville, Maryland 20852

Re: Docket No. 98D-0785: Revised Draft Guidance for Industry on Developing Medical Imaging Drugs and Biologics (June 2000)

Dear Sir or Madam:

These comments on Food and Drug Administration's (FDA's) May 2003 Draft "Guidance for Industry: Developing Medical Imaging Drugs and Biologics" (hereinafter the "Draft Guidance") represent our personal opinions and are based on our extensive experience in diagnostic imaging including all applications in diagnostic ultrasonography, as well as extensive clinical research and the use of ultrasound contrast agents in animal and clinical models. We have had the opportunity to review the detailed comments submitted to you by the Committee on Health Care of the Council on Radionuclides and Radiopharmaceuticals (CORAR) and by the Medical Imaging Contrast Agent Association (MICAA) in their letter of 6/18/2003. In both the draft guidance for industry, as well as in the comments submitted by CORAR and MICAA, our attention has been directed to part II related to indications, clinical usefulness, and review of medical literature. We share the concerns expressed by CORAR and MICAA with respect to part II and are in agreement with the recommended changes incorporated in their response to the May 2003 draft.

As physicians experienced in diagnostic ultrasonography and its applications, and being committed to the improvement of patient care and safety, we believe that reasonable means to facilitate the approval of ultrasound contrast agents are in order. We strongly urge the FDA to incorporate the recommendations of CORAR and MICAA in the final Guidance for Industry.

Sincerely,

Barry B Goldberg, MD
Professor of Radiology, Thomas Jefferson University
Director, Division of Diagnostic Ultrasound
Past Present of the American Institute
of Ultrasound in Medicine

Christopher Merritt, MD
Professor of Radiology, Thomas Jefferson University
Past Present of the American Institute
of Ultrasound in Medicine

Alfred B. Kurtz, MD
Professor of Radiology, Thomas Jefferson University
Past Present of the American Institute
of Ultrasound in Medicine

98D-0785 C 26

Ultrasound Contrast Agent FDA Evaluation Procedures

Ultrasound has established itself as an important imaging modality throughout the United States and the world. The World Health Organization has designated ultrasound as the most important imaging procedure after basic x-ray and it is estimated that almost 25% of all imaging procedures are performed by ultrasound. Every Radiology Department has ultrasound as an integral part of its imaging capabilities. Ultrasound is integrated into the residency programs not only in radiology but in obstetrics and gynecology, cardiology, internal medicine, surgery, emergency medicine, neurology, endocrinology and, most recently, in orthopedics. One of its most important uses is in the evaluation of solid organs throughout the body. The ability of ultrasound to detect the presence of masses in such organs as the liver, kidney, thyroid and testes, just to name a few, has been established. While there are other competitive modalities such as CT and MRI, their additional costs and decreased accessibility compared to the widespread availability of ultrasound equipment makes it, in many cases, the initial study that is performed in the evaluation of these organs. Thus, in such areas as the thyroid and testes it is usually the first study performed. In other areas such as the breast it is recognized to add important information after mammography, particularly in dense breasts. It is used routinely as the initial study in evaluation of the kidney. In the area of the liver, patients who have either vague symptoms, elevated liver function studies, or pain related to the right upper quadrant, ultrasound is the procedure most often used. While it is true that CT and MRI with contrast can detect masses within the liver, these examinations are usually performed when there is suspicion for metastatic disease. Even in the cases of patients with chronic hepatitis ultrasound is often used as the first study of choice in the evaluation of the liver and the uniformity of the parenchyma in an attempt to evaluate for possible tumors. Whenever ultrasound is performed and there is suspicion of liver irregularity, CT or MRI is often performed. However, if a mass or masses are present it may lead directly to biopsy under ultrasound guidance or if staging is important patients are referred to CT or MRI.

However, it has long been established that the use of a contrast agent in CT and MRI leads to increased detection of masses and also aids in their characterization by allowing for the study of blood flow through and around these tumors. Without contrast, masses are often not seen with CT and MRI since the attenuation of the mass may be similar to the normal parenchyma. When contrast is given, however, the differential uptake of contrast between the tumor and normal tissue often allows it to stand out. With CT sometimes lesions may appear to vanish when contrast is given because the differential uptake is such that it makes the attenuation differences between tumor and normal tissue disappear. Ultrasound, up until the last decade, has not had available to it a contrast agent. However, a number of researchers and companies have produced agents which have been evaluated here in the United States and elsewhere in the world in both animals and humans showing that the contrast effect is similar to that which has long been established in CT and MRI; that is, the differential uptake of contrast allows for significantly improved visualization of tumors and also, like with contrast in CT and MRI, it can be used for characterization of the lesion by evaluating blood flow differences and patterns. It is clearly established that there is significant improvement in the visualization of tumors post-contrast compared to pre-contrast using ultrasound. This is becoming particularly important with the increasing utilization of ultrasound as a guide for treatment, monitoring and follow-up examination of patients with tumors who are undergoing a variety of therapies including

chemotherapy and thermal ablation to name just a few. The ability of ultrasound with contrast to more clearly define the lesion and to define its borders shows promise of improving the accuracy of these treatment techniques in which needles or treatment instruments are guided to the area for proper localization, as well as showing promise for better identification of lesions helping to guide the surgeon during open biopsy or resection. Ultrasound with contrast should be valuable for the follow-up of post surgical effects or post treatment effects looking for residual tumor or for re-growth of tumor. It is difficult as well as expensive to use CT or MRI for guidance for treatment and certainly this is even more so when used in the operating room. Ultrasound has long been established as the study of choice, with multiple papers confirming its usefulness in the staging of colon cancer and other cancers in which there is suspected spread to the liver. It is possible in the operating room to identify masses within the liver which were not detected with standard ultrasound, CT with contrast or MRI with contrast. The addition of an ultrasound contrast agent should allow for even greater detection of masses in the liver avoiding, in many cases, unnecessary surgery and speeding up the decision-making process as to the most appropriate treatment.

The desire for the FDA to require that ultrasound with contrast be at least equal to the results of CT and/or MRI with contrast is not appropriate. I, in a busy practice of ultrasound, have had many cases in which ultrasound has found lesions even without contrast not seen with CT as well as, of course, the reverse with CT and MRI showing lesions not detected by ultrasound without contrast. However, the referring patterns of physicians is to send the majority of patients who have right upper quadrant symptoms such as pain or elevated liver function tests initially for an ultrasound study for triaging and then go on to other studies such as CT or MRI if indicated. Our experience demonstrates that the use of an ultrasound contrast agent in the evaluation of the liver as well as other organs would lead to improved visualization of masses over a non-contrast ultrasound examination. This should decrease the number of other studies required as well as allow the clinician to more rapidly make a clinical decision reducing hospital stays and/or costs for additional studies. The ability of one modality to detect 5 lesions, another 8 lesions, another 12 lesions, or some of which may or may not be the same lesions is not the major concern for the referring clinicians. Ultrasound is currently used for evaluation of the liver and other organs and, with the introduction of contrast, will be used with greater efficacy to detect the presence or absence of tumors. This will often lead to a more thorough investigation such as a biopsy under ultrasound guidance. The use of an ultrasound contrast agent should make that biopsy procedure more accurate by delineating those areas which are vascularized as opposed to those being necrotic leading to an increased positive biopsy rate. In other cases, the clinicians may send the patient to have a CT or MRI for a tumor staging process in order to fully delineate the extent of tumor as well as spread of tumor to adjacent lymph nodes or organs. The use of ultrasound contrast in the O.R. evaluation of tumor spread to the liver from primary bowel tumors will greatly aid in the decision-making process avoiding over treatment by surgical resection in those patients in which there is more extensive involvement of the liver than was thought prior to surgery. This will also prove useful when resection of portions of liver for removal of what are initially thought to be solitary lesions turn out to be multiple lesions in more than one lobe. Finally, the use of ultrasound contrast in the evaluation of hepatomas in patients with chronic hepatitis has long been the focus of ongoing research in Asia, particularly in Japan. With the increasing incidence of hepatitis in this country the need for a screening procedure has long been established. In fact today, ultrasound is frequently used without contrast in an attempt to image

these lesions. It is quite obvious from animal experiments and from human evaluations that the ability to detect masses will improve significantly with the use of ultrasound contrast. It is much too costly to perform routine studies every 6 to 12 months with CT or MRI and at the present time not being allowed to use ultrasound contrast agents is a disservice to our patients.

In conclusion, there is no question in the minds of ultrasound imagers and, particularly, those who have had the opportunity to use a variety of ultrasound contrast agents that there is a significant improvement in the detection of masses in the liver and other structures using ultrasound contrast agents when compared to non-contrast ultrasound imaging. Ultrasound contrast will allow us to improve our diagnostic capabilities and decrease the chances of a misdiagnosis. There is no need to compare the contrast enhanced ultrasound to CT and MRI. The key is to compare the difference between ultrasound with and without a contrast agent. It is well understood by physicians in the United States and around the world that there are differences between CT, MRI and ultrasound. These differences can be an advantage when CT and MRI with contrast are used after ultrasound to provide additional information when this is needed. The established patterns of using ultrasound for evaluation of the right upper quadrant of the abdomen, particularly the liver, can only be reinforced with the use of an ultrasound contrast agent. The techniques for imaging with ultrasound are totally different than those with CT and MRI. It is extraordinarily difficult and, in my opinion, impossible to obtain a direct comparison between these imaging modalities on a lesion to lesion basis. In fact, the limitations imposed by the FDA requiring scanning in one plane so that one can compare ultrasound to CT and MRI is totally misconceived. Ultrasound scanning incorporates real-time imaging, which is not available with CT or MRI. It also incorporates scanning in multiple planes in real-time, also not possible with CT and MRI. The ability to easily turn on a lesion allowing for a 360-degree analysis at the time the mass is seen during scanning adds additional information not possible with CT or MRI. Without this information the ability to interpret with ultrasound is severely handicapped. Thus, the requirements currently in effect for comparison of contrast enhanced CT and/or MRI with ultrasound with contrast makes it impossible to have an outcome that would prove that ultrasound with contrast is comparable to contrast enhanced CT or MRI. The FDA has missed the point of how ultrasound is used and how it would significantly improve the diagnostic capabilities of those performing ultrasound if they were allowed to use an ultrasound contrast agent as is the case with CT and MRI.