

Title: Regulatory Considerations for Use of Ultra-High Field MRI

Disclaimer: Views expressed are those of Dr. Yang's, not necessarily those of the United States Food and Drug Administration.

The increasing interest in 7 T or higher MRI, particularly for neuroimaging and musculoskeletal imaging, begs the question: what are the regulatory considerations for the use of ultra-high field MRI in clinical trials? This didactic session addresses trials involving ultra-high field MRI and the use of gadolinium based contrast agents at ultra-high fields.

Clinical trials involving diagnostic and therapeutic products may be subject to oversight by several bodies, including local site Institutional Review Boards (IRBs), safety monitoring boards, the U.S. Food and Drug Administration (FDA), and international regulatory authorities. According to FDA regulations, investigational drug trials for drug development require submission of an Investigational New Drug (IND) application. Even if a drug is already approved, certain trials involving such a drug may require an IND submission. A device trial may require an Investigational Device Exemption (IDE) application approval. Trials involving an investigational device *and* an investigational drug present special challenges in regulatory oversight by virtue of having two investigational products that may be subject to different regulations.

Regarding trials involving ultra-high field MRI, the current FDA guidelines set 8T as the upper limit considered Nonsignificant Risk (NSR) (4 T for neonates) for static magnetic field strength [1]. Investigations involving only NSR devices may be carried out under the supervision of an IRB alone and do not necessitate FDA approval of an IDE application [2].

FDA approval or clearance for the marketing of drugs and devices involve unique regulations and pathways. For drugs, New Drug Applications (NDA) are reviewed whereas for devices, the review pathway may involve a 510(k) premarket notification or Premarket Approval (PMA) process. At the time of writing (December 2010), no 7 T MRI has been cleared for marketing in the United States. A magnetic resonance diagnostic device is classified as a Class II device [3] and is subject to 510(k) premarket notification requirements [4].

Most publications reporting human experience with 7 T MRI do not describe the use of a contrast agent. Some investigators have not used a contrast agent because the optimal dose for 7 T MRI is not yet known [5]. For contrast agents in which the relaxivity marginally decreases as field strength increases from 1.5 T (the majority of FDA-approved MRI contrast agents at this time) [6;7], the T1 contrast effect of the agent is likely greater at higher field strengths due to the longer intrinsic T1-relaxation time of the tissue [8;9] and consequently more significant T1 shortening after contrast administration [9]. For these approved agents, it is possible that at 7 T, a dose of contrast agent lower than that recommended in the current label may result in comparable contrast effect to the currently recommended dose used at 1.5 T. To claim efficacy of a reduced dose of contrast agent at a higher field strength in the label may

require supportive clinical trial data in a supplementary NDA submission. For the few contrast agents with particularly high relaxivity at lower field strengths due to albumin binding [6], the relaxivity of the agent can decrease as much as 50% from 1.5 T to 3 T, and even more at higher field strengths. If such agents are used at 7 T, it is conceivable that a dose higher than that currently recommended in the label may be required for optimal efficacy despite the decrease in the intrinsic tissue relaxation rate.

The rapid evolution of imaging device technology may exceed the pace of imaging drug development and drug dosage optimization. FDA encourages drug manufacturers to update their labeling to address any need for dose regimen alterations due to imaging device advances. FDA also recognizes the importance of individualizing imaging drug doses in the practice of imaging medicine, particularly in situations where imaging device advances decrease drug exposure. In light of potential adverse reactions associated with gadolinium-based MRI contrast agents in patients with difficulty eliminating the agent(s) [10], determining of the optimal dose at ultra-high field strengths appears especially important to enhance patient safety.

Reference List

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