MR as a Biomarker in Clinical Trials

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Recent advances in biomedical science have been slow to yield more effective, more affordable, and safer therapeutics for patients. This is in part because the process of developing human therapeutics has become increasingly challenging, inefficient, and costly. Both industry and regulators have recognized that a new approach taking advantage of advances in scientific and technical methods is urgently needed to improve predictability and efficiency along the path from laboratory concept to commercial product[1]. One of the key elements in this new approach is the use of biomarkers (objectively measured indicators of a biological/pathobiological process or pharmacologic response to treatment[2]). Biomarkers can provide information critical to both internal decision-making (i.e., establish presence of target, evaluate biological/clinical activity, dose selection for later phase trials, stratify study populations, conduct interim analysis of efficacy and/or safety) and establishing efficacy and/or safety for regulatory approval as a substitute for a clinical characteristic or variable reflecting patient feeling, function or survival (i.e., surrogate endpoint). Imaging is a powerful biomarker that can provide information about genetic, biochemical, physiological and anatomic processes. MR can serve as a biomarker in many diseases including multiple sclerosis, cancer, arthritis, atherosclerosis, Alzheimer's disease, and others. Several examples of how MR is used in clinical trials for development of human therapeutics will be presented.

Prior to use for decision-making at any level, it must be demonstrated that biomarkers are biologically and clinically relevant, analytically sound, operationally practical, timely, interpretable and cost effective. The graded evidentiary process linking a disease-related biomarker with biology and clinical endpoints and establishing it as suitable for the intended use is referred to as biomarker qualification.[3-5] The evidence used to qualify a biomarker for its intended use includes a combination of preclinical development, biomedical literature, technical performance, clinical trials and consensus expert panels – the amount of evidence depends on the intended use. When biomarkers are used for internal decision-making, individual companies might consider a biomarker qualified based on their own experience before the drug development community generally accepts it. However, qualification of a biomarker for regulatory licensure decisions (i.e., a 'validated' surrogate endpoint) requires evaluation by an independent panel advising the regulatory bodies. Given the relative expense of MR, the considerable technical expertise required to implement MR biomarkers in practice and the fact that development of MR biomarkers is an area of research not directly related to the development of human therapeutics, the development and evaluation of MR biomarkers beyond the initial phases should facilitated by efforts similar to the Single Nucleotide Polymorphism (SNP) Consortium.[6] Such public-private partnerships among industry, government bodies, academia and not-for-profit organizations could both reduce the cost and speed the process of developing, qualifying and validating MR biomarkers. Ongoing consortia involving MR biomarkers will be considered.

[1]FDA Critial Path Initiative (http://www.fda.gov/oc/initiatives/criticalpath/). [2]Biomarkers Definition Working Group, Clin Pharmacol Ther 69:89, 2005. [3]PhRMA Biomarker and Genomics Working Groups (www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079S2_04_Wagner.ppt). [4]Mills, G (http://www.fda.gov/cder/regulatory/medImaging/ImagingWorkshop.ppt). [5]Baker, M., Nature Biotechnology 23:297, 2005. [6]The SNP Consortium, Ltd (http://snp.cshl.org/).