

Non-Imaging Biomarkers and Regulatory Aspects of Imaging Biomarkers

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Issues:

What exactly is a biomarker and what are the regulatory implications of biomarkers? For the purposes of this presentation I will focus on FDA regulatory implications although similar regulations are in place in the EU and the rest of the world. While my expertise and experience is primarily with US regulations there are common threads with respect to the EU, Japan, Australia, New Zealand and other countries with respect to therapeutics and biomarkers.

- The official NIH definition of a biomarker is: "***a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.***"ref: BIOMARKERS DEFINITIONS WORKING GROUP: BIOMARKERS AND SURROGATE ENDPOINTS: PREFERRED DEFINITIONS AND CONCEPTUAL FRAMEWORK. CLIN PHARMACOL THER 2001;69:89-95."

- A recent search of the FDA website for the term 'biomarker' yielded over 1800 hits. The FDA has 'encouraged' the use of biomarkers through the 'Critical Path Initiative' (<http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm>)

- If you 'Google' biomarker definitions' you will get nearly 400,000 hits with one recent hit being an article by VO Puntman entitled "How-to guide on biomarkers: biomarker definitions, validation and applications with examples from cardiovascular disease" (*Postgrad Med J* 2009 85: 538-545)

Clearly, there is a great deal of interest in biomarkers, whether 'wet' (e.g. proteomics) or 'dry' (e.g. imaging) in the biomedical research community as well as in the pharmaceutical industry. There is a draft guidance for image based biomarkers expected from the FDA in 2011. A recent publication by Steiger ("Use of Imaging Biomarkers for Regulatory Studies" *J Bone Joint Surg Am.* 2009;91:132-136) provides an excellent overview of the regulatory implications of using biomarkers in both IDE (device) and IND (new drug) activities.

In any case, a biomarker can be simple a marker of disease progression or a marker of therapeutic intervention (and in some cases a biomarker could address both issues). This is in contrast to a 'clinical end point' which describes how a 'patient feels, functions or survives.' The 'ultimate' biomarker would be one that could substitute for the clinical endpoint, in other words, act as a surrogate for the clinical end point. Short of surrogacy there are other levels of biomarker 'qualification' and 'validation' that may still provide important information regarding the action of a therapeutic intervention or the progression of disease. A biomarker at baseline may provide predictive or prognostic information about the disease progression or even the response to treatment (e.g. baseline intra and extra cellular pH in tumors or phospholipid metabolism in tumors).

It is also likely that biomarkers will be used as clusters of information rather than relying on single biomarkers and that imaging markers may be combined with 'wet' markers from 'omics and other biochemical analyses. Ultimately the analysis of such markers will need to consider the issues of 'how good' is the treatment as well as issues related to positive and negative responses (both true and false).

In all cases there will be regulatory 'hurdles' that will need to be met for implementation of a biomarker or biomarker cluster at each of the levels that are being addressed by any number of regulatory guidance documents.