

Biomarkers and the FDA—Are We There Yet?

By Christine King

The burden of renal disease is continuing to increase not only in the U.S. population but worldwide, as comorbidity factors such as obesity and diabetes become more prevalent (1). This year, the CDC estimates that more than 10 percent of adults in the United States, approximately 20 million people, may have chronic kidney disease (CKD) in varying degrees of severity, with many people being unaware that they either have CKD or are at increased risk of developing it (2).

The prevalence of CKD, now and in the future, truly represents a public health challenge. The area of renal biomarker research holds much promise for providing better tools to meet the challenge of predicting and identifying renal injury, staging it, and monitoring the effectiveness of therapies. However, innovators often feel stymied by the regulatory requirements in obtaining clearance or approval for new devices. So, perhaps a more appropriate question for renal biomarker researchers and manufacturers is not “Biomarkers and the FDA—Are we there yet?,” but rather “Biomarkers and the FDA—Where do we start?”

The regulatory process and criteria used by the Center for Devices and Radiological Health/Office of In Vitro Diagnostics and Radiological Health (CDRH/OIR) for evaluating the safety and effectiveness of biomarker devices are the same as with any diagnostic device. The FDA classifies all devices by risk. In other words, what is the impact of an incorrect result on the intended use population?

The amount of risk associated with a new device is dependent on its intended use. The intended use should state the purpose of the device, such as diagnosis, prognosis, monitoring, stratifying, or identifying specific populations. It should also specify the targeted population for the biomarker test such as renal allograft recipients, diabetics, or patients on certain drug therapies. The intended use and its designated population can be specific or broad depending on the purpose of the biomarker assay. The intended use should be formulated after the basic research and feasibility of the new biomarker and its assay has been completed and evaluated. These initial studies should be robust for characterizing the biomarker as “fit for purpose” by defining the clinical conditions under which the biomarker is to be used, and for the analytical validation of the assay used to measure the biomarker.

Feasibility studies should be designed to test the clinical hypothesis for the validity of the biomarker test in a small sampling of the proposed intended use population. It is during this phase of development that any applicable clinical cutoffs or algorithms are tested and then “locked” prior to commencing the pivotal clinical trial. The pivotal trial should validate the performance of the locked cutoffs and/or algorithms in the intended use population. If the data from the pivotal trial indicate that the cutoff(s) or algorithm(s) need to be modified to meet the intended use of the device, then a new pivotal study will need to be performed to validate the new cutoff/algorithm.

Analytical validity means that the device per-

formance is reproducible over time (precision), specific for the target biomarker, and accurate. Analytical validity also could encompass linearity; detection limits (e.g., limit of the blank, limit of detection, and limit of quantitation); stability of the sample, reagent, controls and calibrators; and definition of a measuring range. The final submission to the FDA should include validation of analytical validity in addition to the clinical validity of the biomarker assay.

The pivotal clinical study to support the indications for use should be well designed to ensure that the right data, rather than just more data, is collected. The study populations should be appropriate for the intended use of the biomarker test, whether the use is diagnostic or prognostic, and should include individuals who represent the intended test population, including those who have or are at risk for developing the disease or condition. Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) should be evaluated to determine how well the biomarker test is able to distinguish between those who have or are at risk for developing the disease or condition and those who are not.

Study end points also need to be considered in pivotal studies. The selection criteria should include how measurable or definable the end point is, and whether the intended use for the biomarker should be supported by a single, or multiple end points. Regardless of the number of end points, the acceptable performance criterion for the biomarker device and its ability to meet the end point(s) should be established prior to beginning the pivotal study. Also, if multiple end points are used, each end point should be distinguishable from the others in the study in order to prevent “double counting” of results and reduce variability or bias in outcome reporting.

Correlation with clinical diagnosis is one example of an end point. This end point is often used for diagnostic biomarker tests where the results of the device are compared to diagnosis of a disease or condition in the study population per current clinical practice or guidelines. Ideally, this type of study should include several different test sites—large and small, urban and rural—to account for variability in clinical practice, comorbidities, and patient demographics.

Longitudinal end points or outcomes may be appropriate for pivotal studies, especially for prognostic biomarkers. However, duration of the study and participant dropout are factors to be considered in this type of study design.

Studies may be performed prospectively or retrospectively. There are advantages and disadvantages to each type of design. The advantage to a prospective study is that the study conditions can be well defined for the particular intended use of the biomarker device. A disadvantage is that it may be difficult to determine the disease/condition prevalence in prospective studies so that there is adequate statistical power. It may also be difficult to estimate the length of time needed for the subject to reach the end point.

Retrospective data or samples may be used; however, the study protocol under which the samples were collected and stored needs to be well

documented. The patient population, disease prevalence, and study population in a retrospective study needs to be the same as that specified in the intended use of the new biomarker device to avoid bias in the data, such as selection bias. Biomarker stability in the stored samples must be validated prior to beginning the pivotal study to determine whether retrospective testing will adequately substitute for prospective testing.

Some pitfalls to avoid when using retrospective study samples include the following: 1) the retrospective inclusion/exclusion criteria may not be appropriate for the intended use of the new biomarker; 2) samples or data may be missing; 3) the patient demographics may not mimic or match the intended use population; and 4) the biomarker recovery between the retrospective study and the intended use population may not be same, or the prevalence of the disease or condition as defined by the intended use may not be the same. The impact of the differences may prevent accurate calculations of PPV and NPV, or determination of risk. Additional information on FDA’s current thinking on clinical study design for in vitro diagnostic devices can be found in FDA guidance documentation (3).

This has been only a brief discussion of “Where do we start?” for biomarker tests and the FDA. There is a mechanism for early interaction between the FDA and sponsors called the “Pre-Submission” process. Sponsors may submit their proposed study design to FDA for feedback (4). The process is informal and flexible and the FDA encourages this interaction early in the biomarker test development so that safe and effective new biomarkers for renal disease may soon be available to the public. ●

Christine King, MS, MT(ASCP), is affiliated with the Division of Chemistry and Toxicology, Office of In-vitro Diagnostic and Radiological Devices, Center for Diagnostic and Radiological Devices, at the U.S. Food and Drug Administration, in Silver Spring, MD.

References

1. Smyth S, Heron A. Diabetes and obesity: the twin epidemics. *Nat Med* 2006; 12:75–80.
2. Centers for Disease Control and Prevention. 2014 National Chronic Kidney Disease Fact Sheet. <http://www.cdc.gov/diabetes/pubs/factsheets/kidney.htm>.
3. U.S. Food and Drug Administration. Design Considerations for Pivotal Clinical Investigations for Medical Devices; Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff. <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373750.htm>.
4. U.S. Food and Drug Administration. Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administrative Staff. <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>