Patient Evaluation and OA Study Design: OARSI/Biomarker Qualification

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Received: 31 August 2011/Accepted: 31 October 2011/Published online: 22 December 2011
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Keyword biomarkers · osteoarthritis · FDA · qualification · drug development tools

Introduction

Qualification is defined as the “graded, ‘fit-for-purpose’ evidentiary process linking a biomarker with biology and clinical endpoints” [5]. As recently defined by the Federal Drug Administration (FDA), “qualification is a conclusion that within the stated context (manner and purpose) of use, the results of assessment with a drug development tool (DDT) can be relied upon to have a specific interpretation and application in drug development and regulatory decision making” [3].

Biomarkers of OA

However, currently there are no FDA-qualified osteoarthritis (OA) biomarkers. All OA biomarkers in current use are for research use only. There are two biomarkers, NTX1 and CTX1, used in osteoporosis research and clinical monitoring that are in fact in vitro diagnostics for osteoporosis. These, along with the advent, in 1979, of dual-energy photon absorptiometry as an FDA-approved method for quantifying bone mass of the spine, led to the rapid development of effective osteoporosis drugs [1]. OA currently is analogous to osteoporosis approximately 30 years ago—a disease in need of robust FDA-approved outcome measures to overcome the lack of appropriate tools for sensitively quantifying the state of

the OA joint. Some of the current critical knowledge gaps related to OA biomarkers are listed in Table 1.

The FDA recently issued guidance describing the qualification process for DDTs intended for potential use, over time, in multiple drug development programs [3]. As noted by the FDA, in the past, the qualification of DDTs was on a case-by-case basis, benefiting only the submitter of the application. The increasing complexity and cost related to development of DDTs are more likely to succeed in a collaborative setting that benefits all stakeholders and encourages participation in advance of being certain it will be of immediate value. It is believed that this approach will likely speed the process of DDT development [3]. Moreover, the new guidance is intended to provide some degree of generalizability for use of the tools such as use across multiple clinical disorders, multiple drugs, or drug classes. The pathway for DDT qualification defined by the FDA/Center for Drug Evaluation and Research (CDER) is summarized in Table 2. These particular procedures pertain to the pathway related to qualification for use by any interested party when needed for drug development.

Growing out of the OARSI/FDA Initiative biomarkers projects [2, 4] has become a major project termed the OARSI/Foundation for NIH biomarkers project to address the critical need for FDA-qualified OA biomarkers. The project will utilize already acquired images and samples from the Osteoarthritis Initiative study.

The study will encompass three main aims.

- Aim 1 To examine the relationship between efficacy markers and clinical outcomes [change in radiographic, magnetic resonance imaging (MRI), and biochemical markers over 1–2 years will predict progression to clinical outcome at 4 years]
- Aim 2 To identify the most responsive biomarkers of progression

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Table 1 Some of the current critical knowledge gaps related to OA biomarkers

1	What are the best biomarkers for predicting in the short-term and long-term clinical outcomes (pain, structure)?
2	What biomarkers are most responsive to progression?
3	Can a risk score based on baseline values of several biomarkers determine those at risk for faster progression?
4	Can OA biomarkers be FDA qualified as drug development tools?
5	Can OA biomarkers be FDA qualified as surrogate endpoints for purposes of drug approval and registration?
6	Can biomarkers assist in clinical decision making regarding OA therapy?

Aim 3 To develop a risk score based on baseline values of several biomarkers including JSN, quantitative and semiquantitative MRI measures, and biochemical biomarkers that would determine those individuals who progress to end-stage disease faster

In addition to radiographic and MRI outcomes, the study will evaluate 11 commercially available OA-related biomarkers poised to be used by any interested parties if the data justify their use in the contexts encompassed by the specific aims.

Summary and Future Initiatives

As milestones from the OARSI/Foundation for NIH biomarkers project, we expect to have a well-identified DDT concept and evidence indicating a potential to have one or more uses in drug development. We anticipate subsequent waves of qualification will involve additional biomarker candidates, e.g., based on unbiased discovery methods (such

as proteomics) and additional types of biomarkers (such as RNA) and their probable combinatorial use.

In the subsequent phases, we hope to help develop and commercialize useful custom multiplex OA biomarker panels, advance investigational and new biomarkers, tackle the difficult problem of developing means of diagnosing very early OA including susceptibility to posttraumatic OA shortly after acute injury, promote effective utilization of existing resources such as the Brandt sample repository, and encourage ongoing collection and analysis of samples from clinical studies and trials. Thus, the process will be an iterative one but hopefully one well informed by the paradigm of the OARSI/Foundation for the NIH OA Biomarker study that will rapidly lead to the first available FDA-qualified biomarkers as drug development tools.

Acknowledgments The author wishes to acknowledge NIH NIAMS PO1 AR050245, NIA Claude D. Pepper Older Americans Independence Centers 5P30 AG028716, and NIA R21 AG039782-01 for funding support.

Disclosures The author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Table 2 Pathway for drug development tool (DDT) qualification

Stage 1: consultation and advice

1. DDT letter of intent
2. DDT briefing package and initial meeting
3. DDT investigation and development by submitter

Stage 2: review for qualification decision

1. Submit a formal qualification package.
2. The QRT will review the qualification package.
3. QRT reviews will be provided to the participating CDER offices for discussion.
4. If the review and decision-making process result in a CDER decision to qualify the tool, a statement of qualification summarizing CDER's qualification determination will be issued as a draft guidance document.
5. As data from additional studies are obtained over time, submitters of DDTs will be able to continue working with the relevant Qualification Program based on the "Biomarker Qualification Program" for biomarkers or the Second Annual CDER-SEALD Endpoints for PRO and other rating scales to submit additional data and expand the qualified context of use.

QRT qualification review team, *CDER* Center for Drug Evaluation and Research, *SEALD* Study Endpoints and Labeling Development, *PRO* patient-reported outcome

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