FDA's New Guidance on Biomarkers and Patient Reported Outcome Qualification

PEER REVIEWED

Last fall the FDA issued draft guidance related to the Qualification Process for Drug Development Tools (DDTs). Although intended for use across a wide array of therapeutic areas, this guidance emphasises two DDTs that have special relevance to developing CNS drugs, namely biomarkers and patient reported outcome (PRO) measures. This brief review will summarise this guidance, outline the mechanism for ensuring DDT qualification, and suggest areas for further elucidation.

The Qualification Process for Drug Development Tools Draft Guidance(whichcanbefoundathttp://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf) stems from the Critical Path Initiative (CPI) which was designed to stimulate and facilitate efforts to modernise the process through which potential drugs, biological products, and medical devices are transformed from discovery into prescribed treatments. The CPI identifies and prioritises the most pressing clinical development problems, and defines the ones that may provide the greatest opportunity for rapid improvement and public health benefit. This is accomplished by directing research not only towards novel medical breakthroughs and discoveries, but also toward the creation of novel DDTs. More information on the CPI can be found at http://www.fda.gov/oc/initiatives/criticalpath/.

The intended goal of qualification is to permit the use of DDTs across multiple drug development programmes by multiple customers, theoretically speeding up the development of safer and more effective drugs for better-characterised patient populations. Once a DDT is qualified within a specific context of use, any members of the pharmaceutical industry can readily use the DDT for its qualified purpose, and Center for Drug Evaluation and Research (CDER) reviewers can be confident in applying the DDT for this qualified use without the need to reconfirm the DDT's suitability, thus expediting successful marketing applications. Thus, qualification automatically confers some degree of generalisability of the DDT's utility across multiple indications, multiple drugs, or even multiple drug classes. Given the burden of development and qualification of DDTs, in terms of both time and cost, the FDA recommends the formation of collaborative groups to undertake these efforts, providing an opportunity for meaningful industry-academia-government collaboration.

Although not intended to be inclusive, the bulk of the efforts in developing DDTs thus far has been in the area of biomarkers and PROs. Both of these areas are of keen interest to CNS drug developers who, in addition to relying on existing PROs, have led the way in the development of novel and automated/electronic PROs (ePROs), and have utilised various biomarkers (both predictive and pharmacodynamic) at all phases of psychiatric and neurologic drug development programmes.

The FDA defines a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention, and common examples in CNS research include neuroimaging, electrophysiological and CSF (cerebro spinal fluid) measures. Changes in biomarkers associated with treatment reflect the biological response to the product, and may predict or identify safety problems related to a drug, or even reveal a pharmacological activity expected to predict an eventual benefit from treatment. Importantly, if biomarkers are measured using some type of device, the review of this device and authorisation for its marketing represent an entirely separate process from DDT qualification. A PRO is defined as a means of capturing patient reported outcome data used to assess the impact of treatment as an objective of a clinical trial, which can be in the form of a rating scale composed of a subjective rating scale, or a questionnaire plus the information and documentation that support its use. PROs are widely used across a variety of psychiatric investigations, along with clinician-based measures, but are relied on almost exclusively in analgesia studies. PROs can be used as the basis for medical product approval and labelling claims if the measures are deemed to be a well-defined and reliable assessment of the study objectives, if findings are supported by appropriately designed investigations, and if the instrument measures the concept represented by the claim. Separate guidance for PRO use in medical product development can be found at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

The DDT draft guidance supplies ample information regarding the qualification process, whose goal is to reach a conclusion regarding the adequacy of the submitted data to support the DDT's qualification and context of use. The process commences with an initial stage of regulatory consultation and advice, with a subsequent stage of review for qualification determination. The consultation stage may involve multiple information-gathering and data assessment steps. The process enters the review stage only if data are thought to be sufficiently complete and adequate to allow for substantial review. It is in this stage that CDER will perform a full review of the complete data package and render a qualification decision. If a DDT is qualified, its context of use may become modified or expanded over time as additional data are collected, or even withdrawn if the growing body of scientific evidence no longer supports the context of use.

The guidance lays out a very clear process beginning with a letter of intent requesting specific context of use and a summary of studies planned to provide supporting data. This is followed by submission of a DDT briefing package. Appendices IV and V of the guidance define the contents and structure of the briefing package for biomarkers and PROs, respectively. If accepted

this leads to the formation of a Qualification Review team (QRT) composed of CDER review staff from various relevant disciplines with expertise to review of the submission. The QRT provides advice at an initial meeting, as well as continuing advice to the submitter regarding the evidence needed for qualification. Data identified during this meeting must then be acquired through DDT investigation and development, in which the submitter acquires any additional data identified during the meeting. When the submitter believes the data are satisfactorily complete (the DDT is qualified for a specific context of use) and the CDER agrees that any identified critical knowledge gaps have been addressed and official data review is warranted, a formal qualification package is submitted. If the review and decision-making process results in a CDER decision to qualify the DDT, a Statement of Qualification summarising the CDER's qualification determination will be issued as draft guidance and posted on the FDA website for comment.

Although this qualification process is very thorough, there are several areas which require further clarification, including but not limited to: data required to qualify PROs versus biomarkers; some distinction between various characterisations of biomarkers and the qualifying authority (e.g., FDA vs. EMEA); distinction between PROs (including ePROs/automated tests) and clinical rating scales which are treated like PROs in this draft guidance; the extent and type of proof needed to support qualification; the investigation and development standards of DDTs along with minimal qualifications for DDT development; the degree of generalisability of a qualified DDT across indications; the demand for proprietary versus collaborative DDTs; the involvement of other agencies and the public; and finally some notion of the anticipated timeframes and costs associated with this qualification process. Industry members, and especially CNS researchers who frequently utilise biomarkers and PROs in drug development programmes, and are looking forward to using these across programmes, should make every effort to review this draft guidance as it applies to their particular circumstances, and provide comments, questions and concerns to the FDA. Although comments can be made at any time, those received before January 24th will be given full consideration.

Henry J. Riordan, Ph.D. is Senior Vice President of Medical and Scientific Affairs at Worldwide Clinical Trials. Dr. Riordan has been involved in the assessment, treatment and investigation of various CNS drugs and disorders in both industry and academia for the past 20 years. He has been the primary author of >75 CNS protocols as well as several clinical development programs. Dr. Riordan specializes in clinical trials methodology and has advanced training in biostatistics, experimental design, neurophysiology, neuroimaging and clinical neuropsychology. He has over 65 publications including two books focusing on innovative CNS trials methods. **Email: henry.riordan@wwctrials.com**