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Qualification of cardiac troponins for nonclinical use: A regulatory perspective

E.A. Hausner [a,*], K.A. Hicks [a], J.K. Leighton [b], A. Szarfman [c], A.M. Thompson [a], P. Harlow [a]

[a] Division of Cardiovascular and Renal Products, Center for Drug Evaluation and Research, Office of New Drugs, US Food and Drug Administration, United States
[b] Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, Office of New Drugs, US Food and Drug Administration, United States
[c] Division of Biometrics VI, Center for Drug Evaluation and Research, Office of Biostatistics, Office of Translational Sciences, US Food and Drug Administration, United States

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ABSTRACT

The US Food and Drug Administration (FDA) Biomarker Qualification Review Team presents its perspective on the recent qualification of cardiac troponins for use in nonclinical safety assessment studies. The goal of this manuscript is to provide greater transparency into the qualification process and factors that were considered in reaching a regulatory decision. This manuscript includes an overview of the data that were submitted and a discussion of the strengths and shortcomings of these data supporting the qualification decision. The cardiac troponin submission is the first literature-based biomarker application to be reviewed by the FDA and insights gained from this experience may aid future submissions and help streamline the characterization and qualification of future biomarkers.

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1. Introduction

Drug-induced cardiac toxicity has impeded drug development and has resulted in the withdrawal of marketed drugs (Newby et al., 2011). To address the need for better tools to detect drug-induced cardiac damage, PJ O'Brien (University College, Dublin), W Reagan (Pfizer Inc), M York (GlaxoSmithKline), and M Jacobsen (AstraZeneca) submitted a "Request for Qualification by FDA of Circulating Cardiac Troponins as a Translational Biomarker for Nonclinical Toxicology Studies." On February 23, 2012, the US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) qualified the context of use as proposed by the submitters.[1]

Arguably, the history of both skeletal and cardiac troponins began over 60 years ago with attempts to understand muscle contraction (Szent-Gyorgi, 1946). The cardiac troponin literature focused on mechanistic understanding until Cummins et al. (1987) described a radioimmunoassay for cardiac troponin I and Katus et al. (1989) announced an ELISA (enzyme-linked immunosorbent assay) for cardiac troponin T. These assays facilitated both clinical and nonclinical research. Data supporting the non-clinical qualification of cardiac troponins accumulated over the subsequent years as the result of work performed by independent investigators. In the latter portion of the timeline, more rapid advances were made through the combined, focused efforts of groups of investigators or research consortia, including the ILSI/HESI[2] consortium.

The cardiac troponin qualification submission was the first literature-based biomarker application received by CDER. That is, the submitters did not conduct studies specifically for the purpose of this submission, although the submitters had contributed significantly to the published literature. Instead, after conducting an exhaustive literature search, they summarized the published literature supporting nonclinical qualification of cardiac troponins. The depth and scope of the compiled data make it an excellent case study of the data needed to support a biomarker context of use. This successful use of publicly available data also demonstrates a path to reduce and refine animal experimentation in biomarker qualification by decreasing redundant studies and by designing

Abbreviations: BQRT, Biomarker Qualification Review Team; CDER, Center for Drug Evaluation and Research; CLSI, Clinical and Laboratory Standards Institute; DDT, Drug Development Tool; ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug Administration; H&E, hematoxylin and eosin; HESI, Health and Environmental Sciences Institute; ILSI, International Life Sciences Institute; IND, Investigational New Drug; LOD, limit of detection; LOI, letter of intent; NDA, New Drug Application; NOAEL, no observed adverse effect level.

* Corresponding author. Address: 10903 New Hampshire Avenue, Building 22, Room4145, Silver Spring, MD 20993-0002, United States. Fax: +1 301 796 9841.
E-mail address: Elizabeth.hausner@fda.hhs.gov (E.A. Hausner).

[1] (www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentTools-QualificationProgram/ucm284076.htm).

[2] ILSI Health and Environmental Sciences Institute.

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focused studies to address issues already apparent in the existing data or to fill data gaps. Therefore, these publicly available data may help to facilitate and streamline the qualification process.

Here, the Biomarker Qualification Review Team (BQRT) provides its perspective on the data supporting the nonclinical qualification of cardiac troponins, summarizes the factors considered in the regulatory decision and gives a brief history of the evolution of cardiac troponins into translational biomarkers. Finally, we discuss how the experience derived from the cardiac troponin submission might be applied to future biomarker efforts.

2. Biomarker background

2.1. Critical path biomarker qualification

The cardiac troponin qualification proposal was submitted under the Critical Path Initiative, a CDER strategy for transforming the way FDA-regulated medical products are developed. One of the Critical Path Initiative's principal mechanisms for advancing drug development is the regulatory qualification of Drug Development Tools (DDT), including biomarkers, animal models, and clinical outcome assessments. "Qualification" is a conclusion that, within the stated context of use, the results of DDT measurements have specific interpretation and application in drug development and regulatory decision making. "Context of use" is a statement that describes the manner of use, interpretation, and purpose of use of a biomarker in drug development.[3]

2.2. Brief history of the cardiac troponins in clinical use

The first *in vitro* diagnostic assay for cardiac troponin was approved by the FDA Center for Devices and Radiological Health in 1994[4]. Clinical evaluations of circulating cardiac troponins T and I began prior to that, however, and were conducted to determine sensitivity and specificity in diagnosing and monitoring myocardial infarction (Mair et al., 1991; Larue et al., 1993) and peri-operative myocardial damage (Katus et al., 1991). Nine years later, the abundance of clinical data and experience supported the European and American cardiology communities' designation of cardiac troponins as the preferred clinical chemistry diagnostic gold standard for myocardial infarction (Alpert et al., 2000).

The widespread clinical measurement of cardiac troponins produced data for many different situations. Investigators reported increases in circulating cardiac troponin concentrations after rigorous exercise (Mair et al., 1992), cardiac transplantation (Zimmerman et al., 1993), cardiac by-pass (Mair et al., 1993), cardiac dysfunction (Kollef et al., 1997), congestive heart failure (Missov et al., 1997), and other conditions (Khan et al., 1999). Some interpreted these elevated cardiac troponin concentrations as nonspecific to a particular organ system (Khan et al., 1999), while others interpreted the data as evidence of previously unrecognized cardiac damage (Guest et al., 1995). The current understanding is that increased circulating cardiac troponins may indicate myocardial damage secondary to non-cardiac causes and the biomarker may provide prognostic information in these situations (Vasile et al., 2010; Nikolaos et al., 2011).

2.3. Cardiac troponins in nonclinical safety assessment

It was widely recognized that better tools were needed to evaluate drug-induced cardiac toxicity in nonclinical safety assessment. In 2000, the Nonclinical Studies Subcommittee of the CDER Advisory Committee for Pharmaceutical Science requested nominations for an Expert Working Group to focus on biomarkers of cardiac toxicity. Beginning in 2001, the Cardiotoxicity Biomarker Expert Working Group examined the suitability of cardiac troponins for nonclinical safety assessment and concluded that cardiac troponins I and T were sensitive and specific biomarkers of myocardial damage in animals in reporting the extent of irreversible myocardial cell injury following both natural and drug-induced causes (Wallace et al., 2004). The paper also noted several opportunities for future research. Some of these questions were subsequently explored by a separate ILSI/HESI consortium, a collaboration of 15 pharmaceutical companies. The consortium conducted studies to address the suitability of different commercially available cardiac troponin assays for use in nonclinical species. The group also explored the temporal correlation of cardiac troponin release into circulation relative to the evolution of morphologic damage (Apple et al., 2008; Clements et al., 2010). Of note, all of these efforts were initiated prior to the establishment of the DDT qualification program at CDER.

3. The qualification

3.1. The O'Brien submission

In 2008 O'Brien et al. submitted a "Request for Qualification by FDA of Circulating Cardiac Troponins as a Translational Biomarker for Nonclinical Toxicology Studies." The literature-based submission was a synthesis of the large body of data that had been generated by independent researchers/groups over many years. The cardiac troponins qualification package cited 240 peer-reviewed publications, 90 of which were considered central to the proposed context of use. In addition to this, CDER had already used the cardiac troponins in regulatory decision making. There were existing Investigational New Drug (IND) and New Drug Application (NDA) files where cardiac troponins had been used nonclinically and/or clinically. This case by case use of cardiac troponins was sometimes initiated voluntarily by drug sponsors and sometimes requested by CDER. The totality of the submitters' cited publications and the internal, non-public experience contributed to the FDA's decision to qualify cardiac troponins for nonclinical use. In addition, the pharmaceutical industry conducted nonclinical cardiac troponin validation studies, which, although not available to the BQRT, helped to define the proposed context of use and recommendations for validation.

In their submission, O'Brien et al. proposed that in appropriately designed and conducted nonclinical studies, circulating cardiac troponins could be used to show that myocardial damage has occurred and to estimate the extent of this damage. The qualification submitters outlined several possible scenarios for use:

1. A drug in development has a history of a signal for cardiac damage that requires further exploration. In this situation, circulating cardiac troponins may be used in several ways, including characterization of the time course of damage and identification of a No Observed Adverse Effect Level (NOAEL). Reflex testing[5] of reserved serum or plasma samples from a study may be appropriate when a new or unexpected signal is indicated. Histopathology is typically used as the indicator of the dose(s) where damage occurs. However, an increase in circulating cardiac troponins with no histopathology finding may indicate that a lesion or

[3] www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm.

[4] Search troponin at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

[5] Reflex testing is a follow-up test automatically initiated based on specific algorithms (Srivastava et al., 2010). Used to clarify or elaborate on primary test results, reflective testing is a procedure in which additional tests are added to the originally enumerated list of tests after inspection or reflection of the results by a laboratory professional (Verboeket-van de Venne et al., 2012).