



February 23, 2012

ATTN: PJ O'Brien (University College, Dublin, Ire)
WJ Reagan (Pfizer Inc, Groton, CT, USA)
MJ York (GlaxoSmithKline, Ware, Herts, UK)
MC Jacobsen (AstraZeneca, Macclesfield, UK)

RE: Biomarker Qualification Decision

Dear Drs. O'Brien, Reagan, York and Jacobsen:

This letter communicates our qualification decision, review conclusions, and recommendations for use of circulating cardiac troponins T (cTnT) and I (cTnI) in nonclinical drug development studies in rats, dogs, and monkeys.

I. Qualification Decision and Context of Use

The Biomarker Qualification Review Team (BQRT) has completed its review of your submission and concludes, as does your proposal, that in safety assessment studies in rats and dogs, serum/plasma cTnT and cTnI are qualified biomarkers for the following contexts of use:

1. When there is previous indication of cardiac structural damage with a particular drug, cardiac troponin testing can help estimate a lowest toxic dose or a highest non-toxic dose to help choose doses for human testing. In this case, cardiac troponins may serve as a clinical chemistry correlate to the histology. For example, in a safety assessment study, lower doses without increases in cardiac troponins may be used to support a no observed effect level (NOEL) identified by histology.
2. When there is known cardiac structural damage with a particular pharmacologic class of a drug and histopathologic analyses do not reveal structural damage, circulating cardiac troponins may be used to support or refute the inference of low cardiotoxic potential.
3. When unexpected cardiac structural toxicity is found in a nonclinical study, the retroactive ("reflex") examination of serum or plasma from that study for cardiac troponins can be used to help determine a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL). The results of this testing may support inclusion of cardiac troponin testing in subsequent safety assessment studies.

Because of the paucity of published data and inconsistent results, it is not possible at this time to define a qualified context of use for cardiac troponins in non-human primates (NHP). Since some individual investigators have successfully used cTn to monitor cardiotoxicity in NHP studies, we highly encourage the collection of troponin data in NHP to increase the existing database.

Although the nonclinical use of cardiac troponins within the qualified context is voluntary, all collected biomarker data must be submitted to FDA along with other data from GLP toxicology studies conducted as part of an investigational new drug (IND) development program.

II. Review Conclusions

As you have proposed, the BQRT concludes that effective implementation of cardiac troponins in nonclinical drug development studies, including gaining confidence in the validity of negative troponin data, requires:

- a) validation of the assay for the species and laboratory conditions of use
- b) sufficient knowledge of the time course of damage by the drug to allow for sampling that will accurately capture troponin elevations resulting from ongoing or active damage
- c) some understanding of the relevance of the nonclinical metabolite profile to humans

Unless these conditions are known to have been fully satisfied, the absence of an increase in cTnT and cTnI values does not necessarily demonstrate the absence of cardiac structural damage. At this time, it is not possible to make general recommendations for optimum timing of sample collection for all therapeutics.

III. Recommendations for Future Development

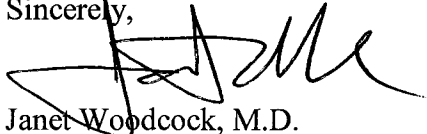
We recommend voluntary collection of cardiac troponin data to increase the database, particularly for nonhuman primates, to evaluate compounds with marked electrophysiological effects on the heart, and to address emerging technologies with improved analytic sensitivity.

When an official format for submission of biomarker data becomes available, we recommend that sponsors use this format to submit additional cardiac troponin data. The submission of troponin results in a structured format could facilitate the collection, storing, linking and analysis of troponin data with other data submitted using such standards. The analysis of standardized troponin data could stimulate a dialogue between the Agency and sponsors with respect to the enhanced use of this biomarker in drug development.

In future regulatory submissions, we recommend that sponsors indicate whether the specific use of the troponin results from nonclinical studies are intended to rely on the qualified contexts of use outlined in this letter. Sponsors may also use troponin T or I in a manner outside (or not fully conforming to the stated conditions) of the qualified contexts of uses; acceptance of such use will be subject to discussion with the appropriate regulatory review group.

We consider the qualification of biomarkers an incremental process and welcome the submission of additional animal and human data to support further application contexts for these biomarkers.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', written over a horizontal line.

Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration