DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: January 22, 2015

ATTN: John-Michael Sauer, Ph.D.
Critical Path Institute
Predictive Safety Testing Consortium
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Warren Glaab, Ph.D.
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West Point, PA 19486

Peter Burch, Ph.D.
Pfizer Inc.
Eastern Point Road, MS 8274-1237
Groton, CT 06340

Subject: Biomarker Letter of Support

Dear Drs. Sauer, Glaab, and Burch:

We are issuing this Letter of Support to the Predictive Safety Testing Consortium (PSTC) to encourage the further study and use of the following plasma or serum proteins in research, nonclinical studies, and early clinical drug development to monitor for skeletal muscle injury in an exploratory context:

- Myosin light chain 3 (Myl3)
- Skeletal muscle troponin I (sTnI)
- Fatty acid binding protein 3 (FABP3)
- Creatine kinase, muscle type (CK-M, the homodimer CK-MM)

These proteins are highly conserved and constitutively expressed in skeletal muscle. Myl3 and sTnI are components of the myofilaments. FABP3 and CK-M are expressed in the sarcoplasm and serve a role in intracellular lipid transport and metabolism, respectively. Published studies and results from unpublished studies submitted by PSTC indicate these proteins are released into the blood stream following skeletal muscle injury, defined as degeneration/necrosis.

To date, the relationship between drug-induced skeletal muscle injury and serum or plasma levels of these proteins has primarily been evaluated in rats. With further study and data collection, the intent would be to

use these biomarkers to add value to total serum creatine kinase (CK; enzymatic assay) and aspartate transaminase (AST) for monitoring skeletal muscle injury in nonclinical and clinical studies; not to replace CK and AST. Greater experience in rats and other species, including nonhuman primates, is needed to better understand the applicability of these biomarkers to drug-induced skeletal muscle injury across species, including humans.

We support PSTC's initiative to encourage the voluntary and complementary use of these serum or plasma proteins in conjunction with AST and CK as exploratory nonclinical and clinical biomarkers of skeletal muscle injury. We also support PSTC's generation of additional nonclinical toxicology data and plan for exploratory early clinical studies to potentially enable future formal qualification of these biomarkers.

We will consider data collection on these biomarkers to be exploratory in nature. If sponsors intend to include analyses of these biomarkers to support regulatory decision making for a given IND drug development program, they should actively discuss with the appropriate CDER regulatory review division.

No specific serum or plasma test system or assay validation process for these proteins is endorsed by this letter. Good scientific and laboratory practices for quality control of the assay test system are imperative. Definition of the assay platform's quantitative range and limits of detection should be established in advance of use. In addition, it is important to characterize the kinetics of changing levels of candidate biomarkers in the presence of acute self-limited as well as chronic muscle injury. Such investigations should include the study of subjects with no underlying kidney dysfunction as well as others with renal abnormalities in which biomarker clearance may be altered.

We encourage the conduct of nonclinical and exploratory clinical analyses to evaluate the translational relevance of changes in serum or plasma Myl3, sTnI, FABP3 and CKM values and the magnitude of change in serum or plasma Myl3, sTnI, FABP3 and CKM that could be considered meaningful in the determination of skeletal muscle injury when observed in an individual subject.

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Dr. John Michael Sauer (jsauer@c-path.org), the PSTC point of contact for this project, or view the Critical Path Institute website.

Sincerely,

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

U.S. Food and Drug Administration