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Critical path

# The Predictive Safety Testing Consortium: A synthesis of the goals, challenges and accomplishments of the Critical Path

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**The qualification of biomarkers of drug safety requires data on many compounds and nonclinical and clinical studies. The cost and effort associated with these qualifications cannot be easily covered by a single pharmaceutical company. Intellectual property associated with safety biomarkers is also held by many different companies. Consortia between different pharmaceutical companies can overcome cost and intellectual property hurdles to biomarker qualification. The Predictive Safety Testing Consortium (PSTC) is a collaborative effort between 16 different pharmaceutical companies to generate data supporting biomarker qualification. This Consortium is coordinated through the C-Path Institute, and currently has five biomarker qualification working groups engaged in this collaboration: nephrotoxicity, hepatotoxicity, vascular injury, myopathy, and non-genotoxic carcinogenicity. These working groups are aided by a data management team and a translational strategy team. Qualification studies of promising biomarkers are already progressing in several of the working groups, and results in the nephrotoxicity working group warranted a data submission to the FDA and EMEA for regulatory qualification of new nephrotoxicity biomarkers.**

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## Introduction

The goals of the Critical Path Initiative and their successful application to improve drug development and regulatory review have required development of organizational structures reaching beyond the traditional relationship between the pharmaceutical industry and the FDA. One of these new organizational structures is the Predictive Safety Testing Consortium (PSTC), developed jointly by the FDA and the C-Path Institute. A focus on biomarker qualification and a unique genesis and membership roll make this Consortium a powerful tool in the conversion of Critical Path goals from proposals to practice.

Development of an efficient and comprehensive process for biomarker qualification is a vital element of the Critical Path. It is a key requirement for the transformation of a current process by which biomarkers reach clinical practice through exhaustive but unstructured qualification. Safety biomarkers are currently accepted through the achievement

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of professional preclinical or clinical consensus, often after many years of debate and discussions that may have been focused less on the actual scientific and clinical data supporting qualification than in the complex nuances of the organizations, scientists and clinicians proposing their use.

The PSTC emerged in an attempt to break with a passive approach to biomarker acceptance and to replace it with an active collaboration between the pharmaceutical industry, regulatory agencies, and other academic and government organizations to create an efficient framework for the generation of biomarker qualification data. The idea for the PSTC evolved from the experience of scientists and clinicians in industry and in the FDA with previous collaborations in this area. It integrates this experience into a collaboration that has learned from the past and continues to learn from the present.

## Genesis of the PSTC

Biomarker qualification and/or validation have been approached by several efforts in the past. The experience gained by these efforts has been valuable in developing the focus and organizational structure for PSTC. While it is outside the scope of this article to fully review these efforts, certain salient points are worth noting.

A model for regulatory validation of alternative test methods has been developed by the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM). ICCVAM developed to encourage the development and validation of test methods to replace animal testing in toxicology. ICCVAM developed a model for test method validation on the basis of a public process through which test method data can be shared [1]. The results of this process are communicated to the 15 Federal agencies that are currently members of ICCVAM, and these agencies are then responsible for communicating the results to their respective regulated industries.

A constraint on the ICCVAM validation model is that much of the data required for biomarker qualification in the context of drug development is actually generated by scientists and clinicians associated with the pharmaceutical industry. As a result, the direction of flow for information needed for qualification is opposite to that expected from the ICCVAM model. Regulated industries can share confidential information with their regulatory agencies, but are unlikely to share this information in a public qualification process. A second constrain on this model is its focus on test method validation rather than on a specific context associated with the use of a test measurement in drug development.

Late in 2002, the International Life Science Institute Health and Environmental Sciences Institute (ILSI/HESI) assembled a Technical Committee for the Development and Application of Biomarkers of Toxicity. Its mission is 'to advance the scientific basis for the development and application of biomarkers of target organ toxicity; to develop a systematic approach for the evaluation of biomarkers that bridge from the preclinical to clinical stages of drug development; and to provide a scientific forum for building consensus regarding how to apply biomarkers of toxicity in risk assessment' (see http://www.hesiglobal.org/Committees/TechnicalCommittees/Biomarkers/default.htm). This Committee has focused on *de novo* data generated by its members to better understand the analytical and preclinical performance of biomarkers of toxicity, with a current focus on troponins and biomarkers of nephrotoxicity. The Committee has also considered strategies for validation and regulatory evaluation of these biomarkers, and presented an update on the Committee's research programs to the FDA in April 2007.

Discussions between scientists from the pharmaceutical industry and the FDA at the Society of Toxicology Annual Meeting in 2005 underscored the need for a consortium specifically focused on the qualification of biomarkers of safety in the context of drug development and regulatory review. This consortium would be a close collaboration in the pharmaceutical industry focused on pharmaceutical applications of these biomarkers. It would be coordinated by a third party, which would provide the legal framework and functional logistics for the success of this collaboration. The Critical Path Institute (C-Path) was identified as the coordinating organization, and the Predictive Safety Testing Consortium was announced by C-Path and the FDA in March 2006 (see http://www.fda.gov/bbs/topics/news/2006/NEW01337.html). C-Path developed over the first year of this Predictive Safety Testing Consortium the legal framework needed for data sharing between its members.

## PSTC focus

Current practice in biomarker acceptance is closely associated with professional debate often initiated at the level about whether qualification for specific biomarkers should be discussed at all. This debate triggers a process by which the qualification of a biomarker in a specific application context is clouded by:

(1) *Confusion about application context definition.* While a biomarker must be defined both as a test measurement as well as a preclinical or clinical interpretation of the result from this measurement, professional debate often confounds measurement with interpretation. For example, the detection of a specific molecular species is often discussed in isolation from the interpretation of this detection in a specific preclinical or clinical context. Biomarker qualification cannot succeed if context is incorrectly defined and challenged.
(2) *Fear about the complexity of biomarker qualification.* The unstructured process by which biomarkers are currently

accepted has lead to a common perception that biomarker qualification is a process that is both hopelessly complex and poorly understood. A biomarker qualification process must be clearly defined, with explicit metrics for incremental success as qualification data are generated and interpreted.

(3) *Fear about the regulatory interpretation of a biomarker measurement*. New biomarkers cannot be efficiently developed if biomarker data introduced through and IND or an NDA can be inaccurately interpreted by regulatory reviewers. A uniform, consistent and explicit interpretation of a biomarker measurement in a specific context must be an integral part of biomarker qualification.

(4) *Fear about the cost of qualification*. Why should a pharmaceutical company work on biomarker qualification? Biomarker qualification is easily justified in drug-test co-development, but what about biomarker qualification independently of specific drugs? Efforts by individual companies to qualify biomarkers will often run into the reality of the costs associated with these efforts.

The PSTC focus has been to develop the ways and means to overcome these and other hurdles in biomarker qualification. Its goals include:

(1) *Clear definition of application context for exploratory biomarkers*. A clear definition of application context requires an accurate understanding of what a biomarker measurement is for and the scientific, preclinical or clinical evidence supporting this measurement. The PSTC will work on the accurate definition of application context for the exploratory biomarkers that the consortium is working on.

(2) *Collaboration with regulatory agencies in the development of a process for biomarker qualification*. The PSTC is working with regulatory agencies to identify structural conditions required for an efficient and comprehensive biomarker qualification process. The goal is to replace the complex, unstructured and open-ended process associated thus far with biomarker acceptance with a process that will work to qualify biomarkers in narrow contexts within drug development and regulatory review.

(3) *Uniform interpretation of biomarker qualification context by reviewers across regulatory agencies*. The biomarker qualification data generated by the PSTC is submitted at the same time to the FDA and EMEA to allow both Agencies to review and discuss the biomarker data in the context in which the biomarker was qualified. These reviews will be useful examples for a uniform and efficient biomarker qualification process.

(4) *Contribution by multiple pharmaceutical companies with data and samples for biomarker qualification*. PSTC members share data and samples to accelerate biomarker qualification by reducing the cost per company to a feasible level.

## PSTC members

PSTC members (Fig. 1) currently include 17 different organizations, with 15 pharmaceutical companies, a database provider, and a CRO. The FDA and EMEA provide representatives that serve as observers and consultants for both the PSTC steering committee as well as each of its Working Groups. These members complement each other in the information and samples they can provide for biomarker qualification through different Working Groups. The PSTC currently has Working Groups in Nephrotoxicity, Hepatotoxicity, Vascular Injury, Myopathy, and Genotoxic/Non-Genotoxic Carcinogenicity. These Working Groups are supported by teams focusing on Data Management and (Clinical) Translational Strategies. Key to the PSTC's structure is a Consortium Agreement that as a legal document addresses key concerns such as membership, anti-trust issues, governance, funding, information sharing, confidentiality, publicity and intellectual property. Project agreements represent the specific legal documents covering Working Group research projects. Governance of the Consortium is handled by an 'Advisory Committee' where each member company has one vote.

## Current PSTC progress and biomarker qualification efforts

Each of the Working Groups considers prior assay experience in developing programs to qualify promising biomarker assays, and the approach of each Group is influenced by the particular nature of the scientific question. Thus the Vascular Injury Group, in addressing the disparities between pathologies seen in various preclinical species and the absence of clear relevance to human disease [2,3] has been focusing on biomarkers that not only correlate with the observed pathology but also can be assayed in several species.

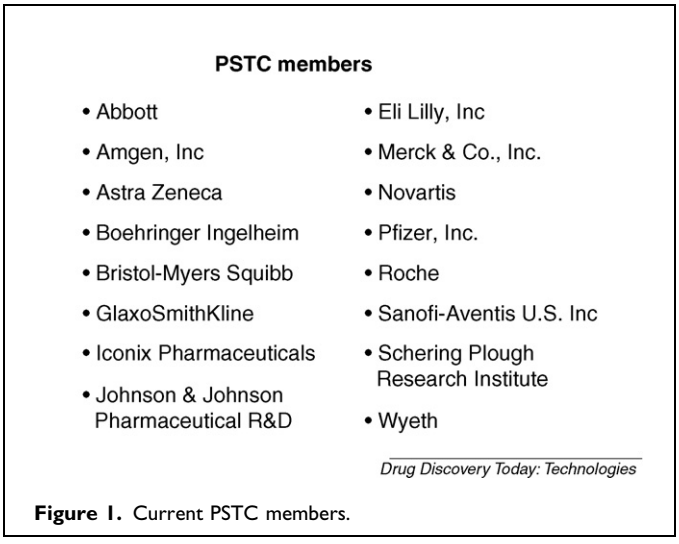


**Figure 1.** Current PSTC members.

The Carcinogenicity Working Group has critically examined certain published genomic signatures of non-genotoxic carcinogenicity [4,5] by evaluating their performance with member company genomic data. The goal in this effort is to develop a robust test that predicts the occurrence of liver tumors in the rodent 2-year carcinogenicity bioassay from gene expression measurements made on short-term (14 days or less) studies. The results of this examination have been encouraging enough to suggest that the signatures be re-assessed using a common gene expression platform (e.g. quantitative RT-PCR). The Hepatotoxicity Working Group has shared data on several assays, and is initiating a cross-qualification effort on four enzymatic assays, including glutamate dehydrogenase [6,7], where extensive internal data has indicated promise for detection of liver injury with more sensitivity and specificity than standard tests. The Nephrotoxicity Working Group has examined a panel of 23 urinary protein assays where the performance was extensively compared with that of standard markers (e.g. BUN and serum creatinine) and histopathology.

Clearly, the goal of the PSTC is to address some of the current limitations in the Critical Path to drug development. As noted above, an efficient and comprehensive process for biomarker qualification would constitute an engine for delivering new tools for both regulators and drug developers. The key to the establishment of that process is the availability of actual test cases that will allow development and refinement of robust procedures. To that end, the Nephrotoxicity Working Group of the PSTC submitted a full biomarker qualification package for seven biomarkers of nephrotoxicity to the Biomarker Qualification Review Teams at the FDA and EMEA in July of 2007. The qualification package was discussed with these regulatory agencies through a Voluntary eXploratory Data Submission (VXDS) meeting. Initial review suggested additional information might be needed for this submission, including a review of clinical studies of five of the biomarkers. Thus, the process is working as conceived, as a dialog between the regulatory agencies and the pharmaceutical industry, and it will continue to evolve as more and diverse datasets are submitted. For example, the Hepatotoxicity Working Group is considering submission of data for the qualification of biomarkers of hepatotoxicity in 2008.

## Conclusion

The PSTC represents a unique collaborative effort focused on biomarker qualification. It is a novel approach to biomarker qualification as a partnership between several pharmaceutical companies, data providers and CROs. It is anticipated that the data produced by these partners will not only lead to the availability of important novel biomarkers for the assessment of toxicity, but also be used to support regulatory agencies in the development of new, formal biomarker qualification processes. Next to its scientific impact, the PSTC is also an excellent example of how consortium efforts can further the goals of the Critical Path Initiative.

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