

# The Predictive Safety Testing Consortium: safety biomarkers, collaboration, and qualification

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**Abstract:** The Predictive Safety Testing Consortium (PSTC) is one of nine consortia comprising the Critical Path Institute (C-Path), a non-profit organisation launched in 2005 and dedicated to playing the role of a catalyst in the development of new approaches that advance medical innovation and regulatory science. C-Path achieves this by leading teams that share data, knowledge and expertise resulting in sound, consensus-based science. PSTC is a unique, public-private partnership that brings pharmaceutical companies together to share and validate safety testing methods under the advisement of worldwide regulatory agencies, including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). The eighteen corporate members of PSTC share a common goal: to find improved safety testing methods and approaches utilizing fluid-based safety biomarkers which accurately predict drug-induced tissue injury. Specifically, the primary goal of PSTC is the qualification of novel translational safety biomarkers for use in early clinical trials in order to enable safer investigations and development of new drug candidates. This manuscript describes the critical importance of improved safety biomarkers to the drug development process and the present state of the biomarker qualification process with regulatory agencies. In addition, the work that the PSTC and its collaborative partners have done and continue to do to identify and qualify more selective and specific safety biomarkers is highlighted. Finally, successes including the recently adopted regulatory Letter of Support and ongoing efforts to better define the regulatory qualification process and an integrated translational safety strategy are also discussed.

**Keywords:** safety biomarker, biomarker qualification, letter of support, translation, target organ, therapeutic index, drug development tool, context of use

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## 1. Safety Biomarkers

Many academic and pharmaceutical industry scientists are currently involved in the discovery and biological validation of a multitude of novel biomarkers<sup>[1]</sup>. These biomarkers are intended to determine whether a patient is susceptible to a disease, already has a disease, or the extent to which a disease has progressed. In addition, biomarkers can

be used to determine whether a patient is responding to a treatment, is experiencing adverse side effects related to the treatment, or whether a treatment has worked.

While much of the data generated for these novel biomarkers will be published in the open literature, the proof required to obtain regulatory biomarker qualification, i.e. the demonstration of both the scientific utility and regulatory reliability of biomarkers in drug

development, is significantly higher than what is required for peer reviewed publication. The qualification of biomarkers is analogous to obtaining marketing authorisation for a drug product or device in that there are high scientific and regulatory expectations. However, that is where the comparison ends. The same evidentiary standards applied to drug development cannot be applied to biomarker qualification, as the ultimate scientific goal is very different.

In addition, the relationship of the stakeholders in biomarker qualification is very different to the relationship of those in drug development. When a drug candidate receives formal regulatory approval and is marketed, the drug developer stands to reap the financial rewards associated with a successful product, while the health authority takes on the potential for additional risk to public health regardless of the financial success of the drug. However, drug developers, regulators and the general public benefit when a biomarker or other drug development tool (DDT) is successfully qualified, by virtue of the accelerated process and improved probability of developing efficacious and safe drugs through use of the biomarker. Thus, the relationship between DDT qualification submitters and health authorities has to be a collaborative relationship and differs significantly from a single company investing in a drug development program. Of course, during the scientific review of qualification data supporting a novel biomarker or DDT, the regulatory agencies retain their objective and independent assessment. But all stakeholders must invest in discussion around the appropriate study design, data analysis, and level of evidence necessary to support the proposed use of a novel biomarker. The precompetitive collaborative consortia models currently being applied in the biomarker space have created these unique, collaborative relationships across health authorities, pharmaceutical companies, academia, and patient groups. This concept has allowed for the sharing of costs, risks and benefits necessary for the successful qualification of biomarkers.

The characterization and qualification of clinical safety biomarkers is a prototypical example of the benefits of this collaborative relationship. Insufficient therapeutic index is a major cause of candidate attrition in drug development. The lack of appropriate prediction of safety liabilities results in unforeseen adverse events in clinical trials or the unwarranted abandonment of potentially safe and effective therapies. Throughout the drug discovery process, thera-

peutic and toxic exposures are determined, and clinical safety biomarkers are essential for maximizing therapeutic index/clinical safety in several ways. For example, safety biomarkers can be applied to address candidate selection and manage risk by monitoring the no-observed-adverse-effect levels of exposure in preclinical and clinical studies. Safety biomarkers are also useful for assessing the human relevance of preclinical safety findings and enabling the development of safe or safer dosing paradigms. In nonclinical studies, target organ toxicity is assessed using histopathological analysis. However, in clinical trials, histopathological analysis is rarely available and biomarkers are critical to assess potential target tissue toxicity in humans. Thus, the most impactful safety biomarkers will be those used in clinical trials with direct translational ties to nonclinical safety studies.

Several consortia, primarily driven by pharmaceutical industry members and encouraged by health authorities, have been formed to evaluate and qualify safety biomarkers for use in early clinical drug development trials. In the remainder of this manuscript, we will focus on the safety biomarker qualification efforts of the Critical Path Institute's (C-Path) Predictive Safety Testing Consortium (PSTC), as well as the PSTC collaborations with the Foundation for the National Institutes of Health's Biomarkers Consortium's (FNIH BC) Kidney Safety Project (KSP) and the Innovative Medicines Initiative's (IMI) Safer and Faster Evidence-based Translation Consortium (SAFE-T). Both of these collaborations are driven by the common goal of modernizing safety science through the qualification of clinical safety biomarkers for use in drug development.

## 2. Qualification of Safety Biomarkers

Qualification is a formal regulatory review and acceptance process at the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) whereby a conclusion is reached such that within the stated context of use (COU), a biomarker or other drug development tool or novel methodology can be used with regulatory certainty. Regulatory certainty is defined as the assurance to drug developers that these approaches will be accepted by regulatory authorities. A COU is analogous to a registered drug's label. According to the FDA, a COU is a comprehensive and clear statement that describes the manner of use, interpretation, and purpose of use of a biomarker in drug development<sup>[2]</sup>. A

hypothetical COU is shown below. This COU has been proposed by the PSTC's Skeletal Myopathy Working Group (SKMWG) in response to discussions around how an ideal novel safety biomarker for drug-induced skeletal muscle injury could be most useful in drug development.

***An example COU for novel safety biomarkers for skeletal muscle injury:***

*The qualified biomarker(s) may be used to monitor for skeletal muscle safety in early clinical studies with new molecular entities (NMEs) that have been shown to cause skeletal muscle injury in animal toxicology studies. Ideally, the qualified biomarker(s) will also be translatable and will show a change in animal studies that can monitored and then used to inform skeletal muscle safety in clinical studies. The qualified biomarker(s) will be used in conjunction with conventional markers of skeletal muscle injury (e.g. serum creatine kinase (CK) activity) as a more sensitive and/or earlier biomarker of skeletal muscle injury. When a biomarker level greatly differs from a defined threshold, as seen in the absence (or presence) of an elevation of serum CK activity, this would be considered an indicator of skeletal muscle injury. For NMEs with skeletal muscle pathology in animal toxicology studies, applying the biomarker(s) in the design of the initial single and multiple ascending dose studies would enable safer progression in clinical development. Use of the biomarker(s) could also enable or restrict the planned dose escalation to higher clinical exposures, depending on risk-benefit considerations. This is because the new biomarker(s) would detect skeletal muscle injury earlier and therefore increase confidence in escalating clinical exposures up to or exceeding the nonclinical no-observed-adverse-effect level (NOAEL), provided that no change in concentration of biomarker(s) is seen in the clinical study. The absence of a significant change in the biomarker(s) in single and multiple ascending dose studies in healthy volunteers would signify no clinically relevant skeletal muscle injury at those exposures.*

Regulatory qualification at FDA and EMA generally consists of a consultation and advice phase, followed by a review phase. In the case of the EMA, the process for Scientific Advice and Opinion is uti-

lised to give Qualification Advice and Opinion. Qualification, on a fundamental level involves a submitter articulating a COU for a novel DDT or methodology which adds significant value to some aspect of drug development, and compiling the scientific data and evidence in support of that specific COU.

Following qualification, a guidance document on the uses and limitations of the biomarker, including the COU, is issued by the FDA and EMA. It is important to point out that the strategy for safety biomarker qualification utilises a translational approach. Although the primary data for clinical qualification are the biomarker performance data from clinical studies, nonclinical data are used to underpin the clinical data and anchor the biomarker's response to a defined histopathological change. A positive qualification decision by regulatory authorities ensures a more efficient implementation of safety biomarkers and encourages researchers to utilise these biomarkers in the drug development process. Thus, qualification results in both increased scientific acceptance and regulatory certainty based on a weight of evidence argument. Qualified safety biomarkers should provide a clear and easily measurable indication of organ injury, giving all parties involved a standardised, reliable tool.

### **3. Letter of Support for Safety Biomarkers**

The Letter of Support was established by the FDA and EMA in 2014 as a means to recognise the potential utility of exploratory biomarkers prior to qualification. C-Path's PSTC was the first biomarker submitter to receive a Letter of Support from the FDA and the EMA. The Letter of Support, as a regulatory outcome, resulted in part from the discussion between PSTC, EMA and FDA, and the realization that greater attention to promising biomarker programs would help facilitate the use of exploratory biomarkers.

The FDA has stated that the Letter of Support is an opportunity to recognise the potential utility of exploratory biomarkers prior to qualification<sup>[3]</sup>. A Letter of Support is issued from the FDA to a submitter who has assembled the necessary information about promising biomarkers. The letter briefly describes the views of the FDA's Center for Drug Evaluation and Research (CDER) on the potential value of a biomarker and encourages further evaluation of the biomarker. This letter does not connote qualification of a biomarker. It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies on promising biomarkers which are

not yet ready for qualification. The FDA's Letter of Support encourages the identification and qualification of new DDTs and has been recognised as an approach to overcome hurdles in drug development programs with the potential to enhance the availability of useful information about drug safety and efficacy.

The EMA has stated that based on qualification advice, the Agency may propose a Letter of Support as an option, when the novel methodology under evaluation cannot yet be clinically qualified but is shown to be promising based on preliminary data<sup>[4]</sup>. A Letter of Support from the EMA aims to encourage data sharing and to facilitate studies supporting eventual qualification for the novel methodology under evaluation. These letters from the EMA include a high-level summary of the novel methodology, COU, available data, and ongoing and future investigations. Like the FDA, the EMA publishes Letters of Support on their website, in agreement with sponsors.

In each case where both the FDA and EMA have granted Letters of Support to PSTC, the intent of the letter, as well as the basic language has been similar. However, although the goal of the Letter of Support mechanism is similar for both, the mechanism and regulatory infrastructure utilised to issue such letters differs. For the EMA, the Letter of Support is an integrated part of qualification and a result of qualification advice, while the FDA sees the Letter of Support as a product outside of the qualification process, although it may also be issued for a project pursuing qualification. While the final outcome may be the same, the process and program expectations to garner a Letter of Support are not identical between the FDA and EMA.

Regardless of its positioning, the Letter of Support is a significant step forward in helping to drive the qualification of exploratory biomarkers. This relatively straightforward approach has created numerous opportunities to share data from nonclinical and clinical studies utilising exploratory biomarkers. For example, a broad data set from an exploratory clinical biomarker with a supporting nonclinical data set could result in the qualification of the biomarker, while dedicated prospective qualification studies or other approaches could be used to expand the COU for a given biomarker. To this end, it is essential that a centralised database be established where anonymized biomarker data from global academic and industry-sponsored trials can be collected, maintained, shared and analysed. This could result not only in the

qualification of biomarkers, but could also enable COU optimization, and identify the impact of such interventions on drug safety.

In order to help drug development sponsors understand the value of including exploratory biomarkers in nonclinical studies and clinical trials, the PSTC has posted summary data packages on each of the biomarkers that have received a Letter of Support on the C-Path website<sup>[5]</sup>.

#### **4. Critical Path Institute's Predictive Safety Testing Consortium**

The PSTC is one of nine consortia comprising C-Path, a non-profit organisation launched in 2005 and dedicated to playing the role of a catalyst in the development of new approaches that advance medical innovation and regulatory science. This is achieved by leading teams that share data, knowledge and expertise, resulting in sound, consensus-based science. Although C-Path has a number of funding models for its consortia, PSTC is funded by a grant from the FDA's Center for Federal Drug Administration and Industry Collaboration (CFIC) and members' contributions. Members' contributions consist of a membership fee and in-kind contributions that support the research required to drive the objectives of PSTC's working groups. PSTC is a unique, public-private partnership that brings pharmaceutical companies together to share and validate safety testing methods under the advisement of worldwide regulatory agencies, including the FDA, the EMA, and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA)<sup>[6-9]</sup> (Figure 1). All eighteen corporate members of PSTC share a common goal: to find improved safety testing methods and approaches utilizing fluid-based safety biomarkers to accurately predict drug-induced tissue injury (Figure 2). Specifically, the primary goal of PSTC is the qualification of novel translational safety biomarkers for use in early clinical drug development trials in order to enable the safer investigation and development of new drug candidates.

As discussed above, clinical safety biomarkers for use in early drug development trials are critically important because insufficient therapeutic index is a major cause of new drug failure. However, current biomarker standards for many drug-induced tissue injuries either do not exist or have significant limitations. Thus, there is a clear need for improved safety biomarkers for each of the target organs under investigation by the PSTC. PSTC's working groups are structured

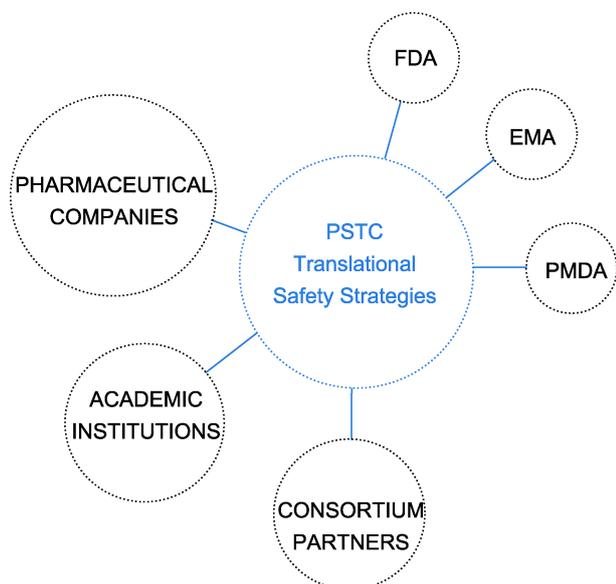


Figure 1. PSTC collaborative structure<sup>[10]</sup>.

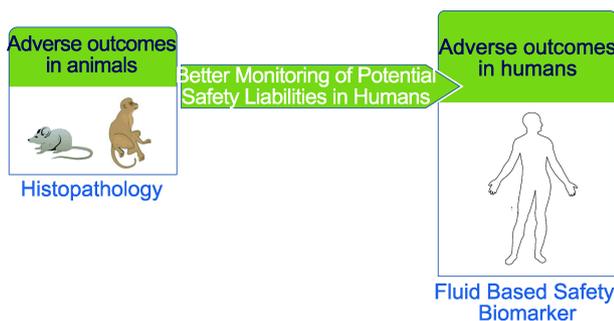


Figure 2. Monitoring drug-induced tissue injury using fluid biomarkers.

around target organs, including heart, liver, skeletal muscle, vasculature, kidney and testis, with cross-functional teams working through common approaches such as microRNA analysis, assessment and categorization of pathological lesions, and approaches to statistical analysis. Currently there are six working groups in PSTC and a brief description of their objectives is provided below.

#### 4.1 Nephrotoxicity Working Group (NWG)

Conventional biomarkers of drug-induced kidney injury (DIKI) currently used in drug development lack sensitivity. The loss of kidney function that defines acute kidney injury (AKI) is most often detected by measurement of serum creatinine, which is slow to respond even in cases of severe kidney injury. Thus, there is a clear need for biomarkers that detect early DIKI to enable earlier intervention. The NWG, in collaboration with the FNIH BC KSP and the IMI

SAFE-T DIKI work package, is working towards the clinical qualification of several urinary kidney safety biomarkers including osteopontin, clusterin, cystatin C, kidney injury molecule-1, *N*-acetyl-*beta*-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, total protein, and albumin. PSTC has already demonstrated the diagnostic utility of these biomarkers in rodents<sup>[11–25]</sup>, and has an active research program in canines and nonhuman primates.

#### 4.2 Skeletal Myopathy Working Group (SKMWG)

Drug-induced skeletal muscle toxicity is becoming more prevalent as an issue in drug development likely due to the evaluation of novel pharmacological targets and the disease populations being investigated. Aspartate aminotransferase activity (AST) and creatine kinase (CK; serum CK activity), the traditional biomarkers of skeletal muscle toxicity, lack both specificity and sensitivity. Novel skeletal muscle biomarkers show promise as more sensitive and more specific biomarkers of drug-induced skeletal muscle injury. The SKMWG is working towards the clinical qualification of several skeletal muscle safety biomarkers including plasma/serum skeletal troponin I, myosin light chain 3, fatty acid-binding protein 3, and creatine kinase muscle type. It is hoped that these biomarkers will provide greater predictive accuracy in the diagnosis and monitoring of drug-induced skeletal muscle toxicity in drug development clinical trials<sup>[26,27]</sup>.

#### 4.3 Hepatotoxicity Working Group (HWG)

Standard biomarkers of drug-induced liver injury (DILI) utilised by the clinical community for many years include alanine aminotransferase (ALT) and AST. However, both the specificity and sensitivity of these markers are limited due to lack of correlation between changes in these liver enzymes and observable histopathological damage. Although these transaminases have proven to be excellent markers of hepatotoxicity, additional biomarkers that more fully inform prediction of DILI are desirable. For instance, new markers that help predict whether ALT increases will resolve or progress to more serious DILI, and markers that can better discriminate liver and skeletal muscle injury will help in the complex assessment of DILI in drug development. The HWG, in collaboration with the SAFE-T DILI work package, is working towards the clinical qualification of several liver safety biomarkers including plasma/serum miR-122, glutamate dehydrogenase, arginase, sorbitol dehydroge-

nase and glutathione-S-transferase. Another objective of the HWG's work has been to understand the potential hepatotoxic liability of drug candidates that are potent inhibitors of the bile salt export pump (BSEP) and devise strategies to mitigate the potential risk. The PSTC hopes to clarify several aspects associated with DILI which is an important, complex issue in drug development.

#### 4.4 Vascular Injury Working Group (VIWG)

Currently, there are no biomarkers available to detect drug-induced vascular injury (DIVI) in humans. The VIWG in collaboration with the SAFE-T DIVI work package is characterizing several biomarkers that are diagnostic for inflammation, as well as endothelial cell and smooth muscle cell injury in nonclinical species and humans with the ultimate goal of qualifying these biomarkers for use in drug development. Although this group has successfully identified candidate biomarkers, differences in protein expression and function across humans and animals have limited the direct translation of these safety biomarkers. The qualification of DIVI biomarkers represents a challenge greater than that faced by other working groups due to the lack of a current clinical gold standard biomarker and the lack of direct translation of the clinical biomarkers being pursued<sup>[28]</sup>.

#### 4.5 Testicular Toxicity Working Group (TWG)

There are no biomarkers available for detecting drug-induced seminiferous tubule toxicity in the clinic, highlighting the value of work being done by the TWG. Currently, this group is focusing on the applicability of microRNA species as biomarkers of testicular injury. A focused research plan has been implemented with the ultimate goal of achieving clinical qualification of testicular safety biomarkers. The program is currently in the early discovery stage, working through much of the basic science associated with reliably quantifying microRNA in serum. Although this project's goal of providing biomarkers for drug-induced testicular injury is of significant value, the basic research around the quantification of microRNA-based biomarkers will also impact other biomarker discovery and qualification efforts.

#### 4.6 Cardiac Hypertrophy Working Group (CHWG)

Work is being completed by the CHWG to evaluate NT-proANP in rodents as a marker of drug-induced hemodynamic stress which leads to changes in cardiac

mass. The data collected indicates that NT-proANP can be used as a screening tool to identify clinical candidates with cardiac hypertrophy liabilities without resorting to ECG-gated magnetic resonance imaging (MRI) in nonclinical studies. Although NT-proANP may not be a candidate for biomarker qualification, the results of this work will have a fundamental impact on approaches used in investigational toxicology. This work points out one of the PSTC goals beyond regulatory endorsement: to impact the pharmaceutical industry's approach to toxicology (safety) in both drug discovery and development<sup>[29,30]</sup>.

#### 4.7 PSTC Regulatory Successes

Despite considerable advances in medicine and technology, many of the approaches and strategies used to evaluate drug safety have not changed in decades. The ultimate goal of the PSTC is to transform the current approach to drug safety testing and liaise with regulatory authorities to offer assurance to drug developers that these approaches will be accepted by regulatory authorities and thereby improve both the speed and precision of the drug development process. The PSTC has been successful in pursuit of this goal through the qualification of novel translational safety biomarkers.

In 2008, PSTC engaged in a joint process between the FDA and EMA to achieve the qualification of a biomarker. Utilizing this joint process, seven rodent kidney safety biomarkers were qualified by both agencies<sup>[11,12]</sup>. In 2010, these same kidney biomarkers were also qualified with Japan's PMDA<sup>[13]</sup>. Following this series of qualifications, as additional biomarker qualification requests entered the consultation (i.e. Qualification Advice at EMA) phase, the regulatory expectations for evidentiary standards evolved. This resulted in a general bottleneck in the qualification process. Therefore, for the past several years the PSTC has been working with the FDA and EMA to better define the requirements within the qualification process. An important initial step was the piloting of a mechanism by which regulatory authorities could recognise the potential utility of exploratory biomarkers prior to qualification, known as the Letter of Support. In 2014, the PSTC NWG received a Letter of Support from the FDA and EMA for two new kidney safety biomarkers<sup>[14,15]</sup>. And in 2015, the PSTC SKMWG received a Letter of Support for four new skeletal muscle injury biomarkers<sup>[26,27]</sup>. The Letter of Support represents a significant accomplishment in

the regulatory authorities' armamentarium and has been compatible with PSTC's goal to assure all stakeholders greater clarity in the path to qualification. In addition, the Letter of Support opens the door to the potential for new opportunities via broader generation of use data to further impact the qualification process.

## **5. Predictive Safety Testing Consortium and its Key Collaborations**

No single company or research organisation can independently change the approach to safety science. Thus, collaboration in pre-competitive consortia like PSTC is an effective approach to impact the scientific and regulatory landscape that governs drug development. The large number of consortia actively involved in addressing gaps in the science and practice of drug development, creates the opportunity to collaborate based on common objectives. However, it is interesting that although consortia are founded on the spirit of collaboration, cross-consortium collaborations are rare. A fundamental obstacle to collaboration appears to be "self-preservation" and the fear of losing relevance or advantage over rivals, resulting in the demise of the consortium, or the desire to be the first consortium to succeed. Luckily, in some cases the benefit of collaboration outweighs the imagined liabilities, and strong leaders find common ground to achieve even larger objectives. Although it is likely that cross-consortium collaborations will continue to expand and become the accepted norm, the establishment of functional relationships between collaborative groups can be limited by legal, logistical and cultural factors. Therefore, it is paramount that consortia organisers envision crucial collaborations at the project design stage and establish a collaborative framework at project inception.

By pooling resources and combining efforts, PSTC is working to improve the safety of newly-created therapies thereby expediting drug development and the regulatory approval process. This will have a positive, measurable impact on all stakeholders, including pharmaceutical companies, regulatory authorities and patients. Cross-consortium collaboration provides the resources to radically impact safety science in the short term. For example, while focused on nonclinical and translational aspects of safety biomarker qualification, in some cases PSTC lacks the clinical expertise required for efficient clinical qualification of translational biomarkers. Therefore, in order to achieve their primary goal of qualifying safety biomarkers, PSTC has partnered with two important consortia, FNIH BC

KSP and the IMI SAFE-T.

The PSTC collaborations with FNIH BC KSP and IMI SAFE-T are productive collaborations between consortia which share overlapping goals, as well as corporate members, in this case from the pharmaceutical industry. PSTC signed formal collaboration agreements with FNIH BC KSP on October 25, 2011 and with IMI SAFE-T on May 23, 2013. Although FNIH and SAFE-T have had a less formal relationship, PSTC's involvement with both consortia has helped enable the sharing of regulatory strategy and scientific approaches between these two groups. The following sections will discuss the collaborations that PSTC has established with the FNIH BC KSP and SAFE-T.

### **5.1 Foundation for the National Institutes of Health's Biomarkers Consortia Kidney Safety Project (FNIH BC KSP)**

FNIH was created by the United States Congress with the purpose of supporting the National Institutes of Health (NIH) in its mission and advancing collaboration between the NIH and biomedical researchers from universities, industry and not-for-profit organisations. To that end, since 1996, FNIH has raised over \$800 million and supported over 500 projects including research partnerships, scientific education and training, conferences, events and other scientific programs. One of the FNIH programs, the FNIH BC has a mission similar to that of the PSTC which is to foster the exchange of knowledge and expertise among industry, academic and government leaders to qualify biomarkers for diagnosing disease, predicting therapeutic response and improving clinical practice.

PSTC and the FNIH BC KSP initiated a formal collaboration on October 25, 2011. This \$4 million, 4-year project includes representatives from C-Path/PSTC, the pharmaceutical industry, academia, and government agencies. The project is intended to advance the acceptance of biomarkers designed to detect DIKI in clinical trials. The ultimate goal of the project is to identify novel biomarkers that are more sensitive than standard approaches and establish better criteria for when kidney safety concerns indicate the need to halt further testing of a drug in humans. This work represents the next logical step in the translational application of the rodent kidney safety biomarkers previously qualified by the PSTC<sup>[11-13]</sup>. These project objectives are being accomplished through the conduct of retrospective and prospective clinical study analyses. The learning phase portion of the project has

been completed and two prospective clinical studies are ongoing in patients who are currently being treated with cisplatin for head and neck cancer or tobramycin for cystic fibrosis with the intention of qualifying biomarkers of DIKI. The specific DIKI biomarkers include urinary osteopontin, clusterin, cystatin C, kidney injury molecule-1, *N*-acetyl-*beta*-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, total protein, and albumin.

PSTC has supported the FNIH BC KSP through financial and in-kind contributions. For example, PSTC has conducted a clinical study in healthy volunteers to aid in the selection of appropriate urinary biomarkers and to define the baseline values of the novel biomarkers in a representative Phase 1 population. With the support of C-Path's internal Submission Readiness Review Team (SRRT), PSTC is also responsible for all regulatory submissions and liaising with both the FDA and EMA in support of this joint project. C-Path, with its significant experience in data handling, storage and analysis has also implemented a nonclinical and clinical biomarker database for the program as part of its broader data platform. The ultimate goal of the project is to garner regulatory qualification of the new biomarkers in order to give confidence to drug developers that the use of these biomarkers will be accepted in regulatory submissions for new drugs. To this end, two qualification approaches are moving forward in parallel. In the first approach, data from the learning phase and urinary biomarker data from the clinical study in healthy volunteers and a cohort of mesothelioma patients treated with cisplatin are being used to derive a composite measure designed to monitor subjects for DIKI on a cohort basis in Phase 1 clinical trials. In the second approach, data from the two prospective studies and learning phase data will be used to support an expanded COU for the kidney safety biomarkers.

## 5.2 Innovative Medicines Initiative's (IMI) Safer and Faster Evidence-based Translation Consortium (SAFE-T)

IMI was launched in 2008 as part of the European Technology Platform on Innovative Medicines that was supported under the European Commission's Sixth Framework Programme for Research as a gathering of stakeholders, led by the pharmaceutical industry. IMI is a partnership between the European Union (represented by the European Commission) and the European pharmaceutical industry (represented by EFPIA, the

European Federation of Pharmaceutical Industries and Associations). IMI is working to improve health by speeding up the development of and patients' access to innovative medicines, particularly in areas where there is an unmet medical or social need. It does this by facilitating collaboration between the key players involved in healthcare research, including universities, the pharmaceutical and other industries, small and medium-sized enterprises, patient organisations, and medicines regulators. By the end of 2013, IMI had released eleven calls for proposals and committed its entire € billion budget. The success of IMI prompted the European Commission and EFPIA to take steps to continue IMI under Horizon 2020, the European Commission's framework program for research and innovation that runs from 2014 to 2020. The legislation creating 'IMI 2' was approved by the European Parliament and Member States in the first half of 2014, and IMI 2 was officially launched in July 2014. IMI 2 will run from 2014 to the end of 2024 and it will have a total budget of up to €3.276 billion.

IMI's SAFE-T consortium, initiated in 2010, is a public-private partnership that brings together pharmaceutical companies, universities, hospitals and biotechnology companies to share and validate each other's safety testing methods. With 25 cooperating consortium members, the goal of the SAFE-T consortium is to generate enough clinical evidence for qualifying new safety biomarkers for regulatory decision-making. SAFE-T is working to address a major hurdle in drug development: the current lack of sensitive and specific clinical tests to diagnose and monitor DIKI, DILI and DIVI in humans. New biomarker tests will enable studies to assess whether these drugs are safe to 'translate' into clinical use. Furthermore, the new translational safety biomarkers will allow the identification and management of side effects of drugs throughout development, helping to reduce the risk associated with developing medicines and improving the safety management of patients.

With common members and goals, the PSTC has worked closely with SAFE-T from its inception, initiating a formal collaboration on May 23, 2013 to work together in their efforts to improve drug safety for three organs in need of better clinical monitoring, including kidney, liver and the vascular system<sup>[31]</sup>. The ultimate goal of this collaboration is to identify biomarkers for monitoring DIKI, DILI and DIVI and qualify the biomarkers with regulatory authorities. The PSTC provides the nonclinical and translational

underpinning to each of the qualification efforts within SAFE-T. Although this collaboration has only been formalised for approximately two years, the PSTC has refocused its relevant working groups to support SAFE-T's efforts. The benefits of the PSTC and SAFE-T collaboration include cost sharing/cost reduction, greater speed/efficiency and sharing of the complementary strengths of the two organisations. For example, by leveraging the PSTC efforts in nonclinical studies, the clinical biomarkers being advanced by SAFE-T are adequately anchored by nonclinical translational data. The PSTC and SAFE-T partnership has also increased scientific influence and awareness through joint communication efforts and coordinated submission of new biomarker data for review by regulatory authorities. Generation of a more robust dataset with more rapid dissemination to the clinical community and patient groups in the US and Europe will also be possible with the coordinated resources of both consortia, ultimately increasing the likelihood of acceptance and application of these novel safety biomarkers for DIKI, DILI and DIVI.

## 6. Advancing the Qualification Process and Defining Evidentiary Standards

As previously stated, insufficient therapeutic index is a major cause of failure in drug development and because many current safety biomarkers lack sufficient sensitivity and specificity to adequately evaluate the therapeutic index of new drugs, there is a critical need for improved safety biomarkers. However, the adoption of novel safety biomarkers through the qualification process has been slowed for two major reasons: (1) the regulatory and scientific expectations for qualification have been evolving as more experience is gained from this relatively new program and (2) the inaccessibility of data from those using the biomarkers due to concerns over maintaining a competitive advantage and conservative legal positions around drug safety liability. Clearly defined evidentiary standards and access to appropriate data will dramatically accelerate the qualification of safety biomarkers<sup>[32]</sup>.

The articulation of evidentiary standards will allow biomarker submitters to appropriately plan their qualification strategies, and have more direct conversations with the FDA and EMA with the understanding that the level of evidence for qualification of a biomarker is directly related to factors such as the breadth of the stated COU, the implications for risk to patients if the biomarker "fails", and the predictability of the assay

performance characteristics. At this point the obvious evidentiary gaps include:

- (i) Defined expectations around clinical data generation and prospective analysis,
- (ii) Statistical methodology expectations for confirmatory data analysis,
- (iii) Biomarker assay validation and performance expectations,
- (iv) Nonclinical data expectation for (translational) qualification of clinical safety biomarkers.

The path to developing regulatory guidance on evidentiary standards for qualification of biomarkers will require involvement of all sectors of the bioscience research community including but not necessarily limited to industry, FDA, EMA, government research entities, academia, patient groups and non-profit organisations. As with the drug development and regulatory review processes, there will be a need for regulatory guidance documents focused on providing direction for critical elements of the overall biomarker qualification process. For example, there might be a guidance document specific to statistical methodology for biomarker qualification or one describing assay validation. This will be an iterative process that seeks to refine terminology, standards, language etc., in parallel with incorporating lessons learned from ongoing biomarker qualification programs. This will require science-based discussions without attribution to enable an open dialogue with exchange of various expert perspectives. Those with specific expertise in current biomarker qualification, drug development, device development, clinical trial design, statistical methodology, analytic methodology, regulatory process and strategy, regulatory decision-making, data handling, data sharing and database methodology must be included in order to ensure that information contributing to the framework for regulatory expectations and eventual guidance documents represents the application of scientific methods on the way to a regulatory outcome. Ultimately, with the attention of stakeholders, this process will provide the required underpinning to expedite the qualification of biomarkers and other DDT's and methodologies.

Several key aspects should be considered in creating scientific expectations specific to qualification of safety biomarkers. A brief list of considerations is presented below for safety biomarkers that are supported by both translational nonclinical data and clinical trial data.

- (i) Availability of sufficiently validated analytical

assays to quantify biomarkers,

(ii) Biological understanding of the biomarker including the specificity of the response to toxicological outcomes in the target tissue and other relevant tissues as well as the pharmacologic effects of agents without toxicity in the target organ,

(iii) Understanding of mechanism of the biomarker's biological response,

(iv) Correlation of biomarker response to pathology and improved performance relative to other (standard) biomarkers,

(v) Consistent response across mechanistically different compounds with similar response; similar response across sex, strain, and species,

(vi) Presence of dose-response and temporal relationship to the magnitude of response.

The second issue slowing adoption of novel safety biomarkers is inaccessibility to data from those using the biomarkers. Therefore, multiple approaches should be considered to encourage drug development sponsors and academic centres to: (1) capture data according to pre-determined standards so that data sets across multiple contributors can be aggregated and (2) share data through a protected mechanism in order to advance understanding of biomarker performance and contribute to robust decision-making about the regulatory acceptance of that biomarker. An approach being considered by C-Path is a proof-of-concept experiment whereby data from use of a pre-specified set of biomarkers can be housed in a central data repository held by a neutral, third party for the purpose of advancing the accumulation of needed evidence to enable regulatory decision about the biomarkers. This experiment should demonstrate the value of a more collaborative approach that will expedite the timeline to achieving qualification of new biomarkers.

Finally, it is critical to identify the quickest path to qualification and the implementation of safety biomarkers in well-controlled clinical trials, because the only way to understand the advantages and disadvantages of a biomarker will be through its broad application.

## 7. Defining an Integrated Translational Safety Strategy

At this point it is clear that qualification and implementation of novel safety biomarkers into the mainstream of the drug development process is only a small part of a much larger effort to modernise toxicology and clinical safety. Nearly all of the biomarker qualification efforts that PSTC is involved with are

directed at identifying drug-induced organ toxicity, a surrogate for histopathological evaluation in humans. However, what is truly needed is an integrated translational safety strategy that allows for a more predictive approach to assess clinical safety liabilities prior to introducing a new drug candidate for humans. Simply put, the application of toxicology in drug development needs to move from a descriptive science to a mechanistic science. This will require a fundamental paradigm shift and introduction of new experimental and data analysis approaches into safety assessment as well as the integration of information, traditionally viewed as non-safety data, into risk assessment.

A vision of a possible translational strategy is outlined in Figure 3; we have called this approach toxicometrics. This vision also represents a general framework to support a systems pharmacology (toxicology) approach that leverages *in vitro* and *in vivo* laboratory results, published data, and computational modelling to evaluate drug safety in order to enable a more predictive approach to translating safety information from nonclinical species to humans. Clearly there is a need to better translate whole animal data to clinical trials, but it is likely that there will be areas of understanding that cannot be extrapolated from animal studies to humans. This gap can potentially be filled with appropriate *in vitro* tools and the construction of predictive computational tools that will require mechanistic input from these same *in vitro* tools. The objective of the outlined approach is to work toward the use of computational models in the systematic evaluation of safety data from clinical trials, and the integration of mechanistic modelling with current pharmacokinetic/pharmacodynamics (PK/PD) approaches, physiologically-based pharmacokinetic modelling, and

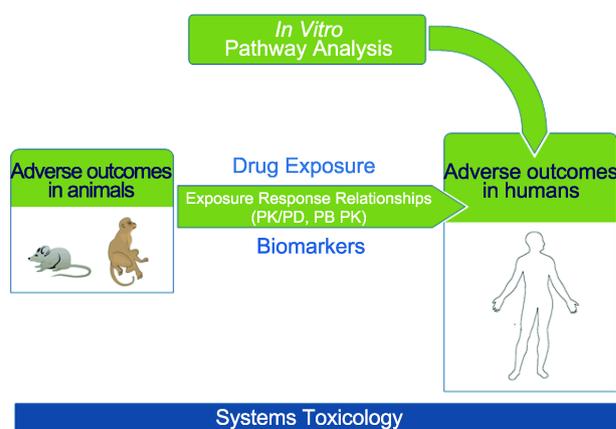


Figure 3. Vision for an integrated translational safety strategy.

mechanistic systems pharmacology approaches across multiple target organs.

## 8. Conclusion

In summary, there is a clear and critical need for the identification and regulatory qualification of improved safety biomarkers for the drug development process. C-Path's PSTC consortium is a unique public-private partnership, bringing together pharmaceutical companies to share and validate safety testing methods under the advisement of worldwide regulatory agencies. The primary goal of PSTC is to qualify novel translational safety biomarkers for use in early clinical drug development trials in order to enable safer investigation and development of new drug candidates. To this end, PSTC has established formal collaborations with FNIH BC KSP and IMI's SAFE-T, two consortia with overlapping goals and members. In addition, PSTC has worked with regulatory authorities and piloted the Letter of Support approach to help facilitate the use of exploratory biomarkers. PSTC has successfully qualified seven biomarkers of DIKI and received a Letter of Support for biomarkers of DIKI and drug-induced skeletal muscle injury. Ongoing efforts include advancing the qualification process, working with key stakeholders to define evidentiary standards for qualification, and promoting and enabling a biomarker data repository. This includes the broader goal of defining an integrated translational safety strategy that utilises computational models to evaluate clinical trial data and the integration of mechanistic modelling with PK/PD and physiologically based pharmacokinetic modelling. With insufficient therapeutic index as a major cause of new drug candidate failure, ongoing science-based efforts to improve the continued effective collaboration of all stakeholders including regulatory agencies, pharmaceutical companies, government research entities, academia, patient groups and non-profits organisations, will be utterly critical for realizing timely, transformative, science-based improvements in drug development.

## Conflict of Interest and Funding

No conflict of interest was reported by the authors.

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