C-Path Opportunities Table

In 2004, the Food and Drug Administration launched the Critical Path Initiative (CPI) to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured. In 2006, FDA issued the Critical Path Opportunities List which provided 76 opportunities divided among six topics of focus, and that, if implemented, can help speed the development and approval of medical products. More information on the CPI and the original Critical Path Opportunities List, as well subsequent updates can be found at the FDA website:

http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/default.h

Critical Path Institute (C-Path) is dedicated to developing tools and methods that address these and other opportunities, with the goals of promoting innovation, streamlining drug development and reducing the inherent risks of the drug development and regulatory review process. The work of C-Path has contributed to many of the opportunities identified by FDA. The tables below summarize the ways in which C-Path has made significant contributions to 19 of the listed opportunities, in five of the six topic areas.

TOPIC 1 Better Evaluation Tools			
Opportunity #	**Opportunity Title**	**Critical Path Institute (C-Path) Contribution**	**Status**
1	Biomarker qualification	C-Path helped pioneer the biomarker qualification process and had the first successful biomarker qualification with the FDA, EMA, and PMDA. It has been involved in working with the FDA and EMA to refine the process as C-Path has progressed several sets of biomarkers/tools through the process. C-Path received the first Letters of Support from both FDA and EMA. C-Path has also worked to help align the FDA and EMA qualification processes by requesting parallel review. C-Path is currently working with other organizations to develop a framework for considering the evidentiary standards required to qualify a biomarker depending on its type and general context of use.	Ongoing

TOPIC 1 Better Evaluation Tools			
1	Biomarker Qualification	C-Path's Arizona Center for Education and Research on Therapeutics (AZCERT) worked together with the American Medical Association on the development of a brochure for prescribers on basic concepts in pharmacogenomics and their application to the specific case of warfarin, highlighting the impact of warfarin dosing algorithms that took into account genetic variances in VKORC1 and CYP2C9. Additionally, the C-Path AZCERT team performed a concordance analysis of the drug-drug-interaction information of the FDA-approved label for warfarin sodium (Coumadin, 2007) and the information contained in three major drug compendia (Clinical Pharmacology, ePocrates, and Micromedex). Of a total of 648 entries from the four sources, only 50 were common to all. This analysis was published: **Anthony M, Romero K, Malone DC, Hines LE, Higgins L, Woosley RL. Warfarin interactions with substances listed in drug information compendia and in the FDA-approved label for warfarin sodium. Clin Pharmacol Ther. 2009;86(4):425-9.** Subsequently the C-Path AZCERT team performed a concordance analysis of the FDA-approved labels of warfarin and the 50 products common to all compendia (see above). This assessment of official US product labeling for 50 drugs, biologics, and drug classes known to interact with warfarin, comprising 73 distinct agents, found that 15% failed to mention the interaction, even though the interaction was mentioned in the warfarin labeling. This analysis was published in Clinical Therapeutics: **Hines LE, Ceron-Cabrera D, Romero K, Anthony M, Woosley RL, Armstrong EP, Malone DC. Evaluation of warfarin drug interaction listings in US product information for warfarin and interacting drugs. Clin Ther. 2011;33(1):36-45.**	Completed

TOPIC 1 Better Evaluation Tools			
18	Predicting cardiac toxicity	C-Path's Predictive Safety Testing Consortium (PSTC) has a working group focusing on biomarkers to detect drug induced cardiac hypertrophy. This work is designed to evaluate the response of N-terminal pro-atrial natriuretic peptide (NT-proANP) in rats during maladaptive left ventricular myocardial remodeling induced by pharmaceutical agents. It is hoped that NT-proANP can be used as a screening biomarker in early toxicology studies to detect candidates with the potential to cause cardiac hypertrophy. C-Path's Critical Path to TB Regimens (CPTR) is developing a torsades de pointes (TdP) quantitative platform that will serve as the foundation for supporting recommendations for the rational collection, analysis, interpretation of data, as well as decision-making related to ion channel activity, repolarization reserve information and clinical QT data throughout the development life cycle for novel TB regimens. The first pass of this effort will include collation and review of relevant data pertaining to QT changes with TB drug regimens. CPTR will then develop a quantitative risk-categorization algorithm for drug-induced cardiac arrhythmias (QT prolongation and torsade de pointes), applicable to TB drug development.	Ongoing
20	Modernizing predictive toxicology	C-Path's PSTC has six working groups looking at new approaches and new predictive biomarkers for detecting and predicting clinical drug induced toxicity. The mission of PSTC is to identify new and improved translational safety testing methods for use in nonclinical and clinical studies. Many of these approaches are subsequently submitted for formal regulatory qualification. The ultimate goal of the consortium is to improve the current approach to drug safety testing and offer assurance to drug developers that these approaches will be accepted by regulatory authorities for use in drug development programs. The current 19 corporate members of the consortium, including 250 participating scientists, share internal experience with nonclinical and clinical safety biomarkers in six working groups: Cardiac Hypertrophy, Hepatotoxicity, Nephrotoxicity, Skeletal Myopathy, Testicular Toxicity, and Vascular Injury. All research programs have a strong translational focus in order to select new safety tools that are applicable across the drug development spectrum and advance a comprehensive safety strategy. PSTC is committed to advancing novel approaches to translational safety.	Ongoing

TOPIC 1 Better Evaluation Tools			
22	Using medical imaging as a product development tool	C-Path's Coalition Against Major Diseases (CAMD) is working on imaging biomarkers for Alzheimer's and Parkinson's diseases. The Polycystic Kidney Disease Outcome Consortium (PKDOC) is advancing total kidney volume as an enrichment biomarker in polycystic kidney disease clinical trials.	Ongoing
25	Imaging biomarkers in neurocognitive disease	C-Path's CAMD is working to qualify imaging of hippocampal volume as an enrichment biomarker for Alzheimer's disease and the use of molecular neuroimaging of the dopamine transporter (DAT) as a prognostic biomarker for enrichment in trials for Parkinson's disease. FDA has acknowledged and promoted these efforts of CAMD by issuing a Letter of Support for both of these imaging biomarkers in 2015 (Link to letters: http://www.fda.gov /drugs/developmentapprovalprocess/ucm434382.htm CAMD has also been invited to participate in an effort to identify and subsequently qualify biomarkers for Traumatic Brain Injury.	Ongoing
30	Improving extrapolation from animal data to human experience	C-Path's PSTC is looking at the possible translation of their entire portfolio of preclinical toxicity biomarkers into clinical use in humans and their correlation and predictability. In 2014, PSTC received a Letter of Support from FDA encouraging the use of kidney safety biomarkers NGAL and osteopontin to be used in clinical work in order to gain necessary clinical data. A Letter of Support for three serum and one plasma biomarkers for skeletal muscle was issued by FDA in 2015. These Letters of Support can be found at http://www.fda.gov /drugs/developmentapprovalprocess/ucm434382.htm	Ongoing

TOPIC 2 Streamlining Clinical Trials			
Opportunity #	**Opportunity Title**	**Critical Path Institute (C-Path) Contribution**	**Status**

TOPIC 2 Streamlining Clinical Trials			
35	Enrichment Designs	C-Path is qualifying prognostic biomarkers in Alzheimer's, Parkinson's, and Polycystic Kidney diseases for use in clinical trial enrichment (see Opportunities #22 and #25).	Ongoing
36	Use of Prior Experience or Accumulated Information in Trial Design	The Alzheimer Disease Clinical Trial Simulation tool represents efficient use of prior randomized clinical trial (RCT) information to optimize RCT design.	Completed
38	Development of trial protocols for specific therapeutic areas	As part of CAMD's efforts to qualify imaging biomarkers, CAMD aligns with imaging biomarker experts in the field to develop trial protocols for Alzheimer's disease (e.g. Jack et al., Steps to standardization and validation of hippocampal volumetry as a biomarker in clinical trials and diagnostic criterion for Alzheimer's disease, Alz & Dem 7, 474-85, 2011).	Ongoing
40	Measuring disease related symptoms	C-Path's Patient-Reported Outcome (PRO) Consortium is working toward qualification of patient-reported outcome measures for the assessment of disease-related symptoms in six therapeutic areas. In addition, symptom-based PRO measures are being considered for development and qualification in multiple sclerosis and myelofibrosis.	Ongoing

TOPIC 2 Streamlining Clinical Trials			
41	Measuring patient centered endpoints	C-Path's PRO Consortium is working to develop and qualify patient-centered endpoint measures for mild cognitive impairment due to Alzheimer's disease, asthma, irritable bowel syndrome, non-small cell lung cancer, rheumatoid arthritis, depression, and functional dyspepsia. C-Path's CAMD is working on a performance measure of cognition and functioning for patients with prodromal Alzheimer's disease and mild cognitive impairment. The measure addresses aspects of cognition and function viewed meaningful by patients. C-Path's Multiple Sclerosis Outcome Assessments Consortium (MSOAC) is working toward qualifying a performance measure for multiple sclerosis to assess functional changes associated with MS that significantly impact patients' daily lives.	Ongoing
43	Improving efficacy endpoints in infectious diseases	CPTR is analyzing the predictive accuracy of TB time-to-positivity and 2-month culture conversion based on data from three recently completed trials to inform decisions when moving from Phase II to Phase III clinical trials.	Ongoing
44	Development of data standards	C-Path has formed a collaborative effort with Clinical Data Interchange Standards Consortium (CDISC), named Coalition for Accelerating Standards and Therapies (CFAST), to develop therapeutic area data standards. CFAST has developed and published CDISC data standards for Alzheimer's disease, Parkinson's disease, polycystic kidney disease, multiple sclerosis, tuberculosis, and influenza. C-Path is also working with TransCelerate BioPharma Inc. on many other standards that have and will be published in the coming months and years.	Completed/Ongoing
45	Consensus on case report forms	CAMD has received a pilot grant from Banner Institute Arizona Alzheimer's Consortium to evaluate and annotate case report forms in Alzheimer's disease prevention clinical trials for the purposes of harmonization and alignment with AD CDISC standards	Ongoing
TOPIC 3 Harnessing Bioinformatics			

Opportunity #	Opportunity Title	Critical Path Institute (C-Path) Contribution	Status
46	Identification and qualification of safety biomarkers	C-Path's PSTC has qualified seven preclinical kidney safety biomarkers with the FDA, EMA, and PMDA. They have received Letters of Support for additional kidney safety biomarkers skeletal-muscle safety biomarkers. PSTC is also working on safety biomarkers for liver, cardiac hypertrophy, vascular injury, and testicular toxicity.	Ongoing
51	Clinical trial simulation	C-Path's CAMD has developed and received endorsement from FDA and EMA for a clinical trial simulation tool for mild to moderate Alzheimer's disease. This represents the first-ever such regulatory endorsement for quantitative drug development platforms. Similar efforts are underway for tuberculosis. Preliminary planning has been done for a similar simulation tool to be developed for Parkinson's disease, and potentially for Duchene's muscular dystrophy.	Completed/Ongoing
TOPIC 5 Developing Products to Address Urgent Public Health Needs			
Opportunity #	**Opportunity Title**	**Critical Path Institute (C-Path) Contribution**	**Status**
67	Improving anti-microbial product testing	C-Path's CPTR initiative is evaluating and sponsoring validation of several drug development tools for tuberculosis including a hollow fiber *in vitro* testing system to measure efficacy of new combination therapies for TB, and quantifying liquid culture as prognostic indication of relapse. CPTR is launching a data platform to inform the development of new rapid drug sensitivity tests for TB to enable the implementation of new drugs and drug regimens. CPTR is also working on several models from a physiologically-based pharmacodynamic model to a population based disease progression model.	Ongoing
TOPIC 6 Specific At-Risk Populations: Pediatrics			
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TOPIC 6 Specific At-Risk Populations: Pediatrics			
72	Better extrapolation methods and best practices in pediatric trial design	C-Path is forming a new consortium to address the needs and challenges of developing drugs for a neonatal population. Developing models that can be used to extrapolate test results into pediatric and neonatal populations is high on the list of potential outcomes.	Ongoing
73	Drug metabolism and therapeutic response [pediatric population]	C-Path is in the process of forming a new collaboration directed specifically at neonatology and the challenges of drug development in this arena.	Ongoing