IMI SAFE-T and C-Path PSTC Obtain Regulatory Support for New Liver Safety Biomarkers

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US FDA and EMA Letters of Support Pave the Way for Clinical Qualification

The Innovative Medicines Initiative (IMI) SAFE-T (Safer and Faster Evidence Based Translation) Consortium and Critical Path Institute (C-Path) Predictive Safety Testing Consortium (PSTC) announced today that the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) each issued a Biomarker Letter of Support for new liver safety biomarkers investigated by the SAFE-T Drug-Induced Liver Injury Work Package and the PSTC Hepatotoxicity Working Group. The Drug-Induced Liver Injury Network (DILIN) in the US, an expert network established by The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), contributed their expertise to the research, as well as rare samples from individuals with severe liver injury.

The liver safety biomarkers—cytokeratin 18 (CK-18), high mobility group protein B1 (HMGB1), osteopontin, and macrophage colony-stimulating factor 1 receptor (MCSFR1, or CSF1R), are proteins that can be measured in human serum. Both FDA and EMA acknowledged that higher levels of these biomarkers in patients diagnosed with Drug-Induced Liver Injury (DILI) could indicate a risk for progression toward liver failure, which may result in death or the need for liver transplantation. DILI is an adverse drug reaction that has, for decades, been a major cause for late-stage failures in drug development and post-marketing withdrawals.

In addition, EMA considered results promising for serum biomarkers total HMGB1, total and caspase-cleaved keratin 18, miR-122, and GLDH in terms of possibly improving early prediction of liver injury in clinical trials with compounds having the potential to cause intrinsic liver toxicity, similar to paracetamol (acetaminophen).

The Letters of Support indicate the new biomarkers have potential for use in humans, which warrants additional exploration and data generation, and are intended to encourage scientists to collect additional data from nonclinical and exploratory clinical studies. With this milestone, in-depth research can continue toward the qualification of the new biomarkers for use in clinical trials on top of standard safety tests.

"Many current obstacles in drug development pose substantial scientific and logistical challenges to industry and public health that are impossible to tackle by individual companies or research organizations alone. Large scale public-private partnerships are an indispensable prerequisite to solve complex tasks such as development and qualification of new safety biomarkers, as exemplified by IMI's SAFE-T and C-Path's PSTC," said Pierre Meulien, PhD, IMI Executive Director.

"The collaboration demonstrated by these specific IMI and C-Path programs has enabled this significant advance which encourages utilization of these novel liver biomarkers by sponsors. Acquiring more experience and data with these biomarkers will provide greater confidence and refinement in their utility, thereby assisting decision making within drug development programs and by regulatory authorities." Martha A. Brumfield, PhD, President & CEO, Critical Path Institute.

"The success of the SAFE-T/PSTC collaboration nicely demonstrates the benefits of working together across public private partnerships on a global scale. Shared scientific enthusiasm, persistence, and team-spirit were the key foundation for this achievement". Michael Merz, MD, Novartis Institutes for BioMedical Research, IMI SAFE-T project coordinator.

"The SAFE-T/PSTC collaboration represents the best collaborative science, bringing together experts from Europe and North America around the common goal of qualifying safety biomarkers. This relationship demonstrates how two public-private partnerships can work together in support of their members' goals and visions." John Michael Sauer, PhD, Critical Path Institute, PSTC Executive Director.

The FDA Letter of Support is posted on the FDA website, the EMA Letter of Support on the EMA website. Additionally, the documents can be accessed via the SAFE-T website, or via the C-Path PSTC website under the Regulatory Successes tab. The PSTC website includes a summary data package describing the studies that support the use of these liver safety biomarkers.

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115003, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

About the organizations:

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The Innovative Medicines Initiative (IMI) is working to improve health by speeding up the development of, and patient access to, the next generation of 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, pharmaceutical companies, other companies active in healthcare research, small and medium-sized enterprises (SMEs), patient organisations, and medicines regulators. This approach has proven highly successful, and IMI projects are delivering exciting results that are helping to advance the development of urgently- needed new treatments in diverse areas.
IMI is a partnership between the European Union and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). Through the IMI 2

programme, IMI has a budget of €3.3 billion for the period 2014-2024. Half of this comes from the EU's research and innovation programme, Horizon 2020. The other half comes from large companies, mostly from the pharmaceutical sector; these do not receive any EU funding, but contribute to the projects 'in kind', for example by donating their researchers' time or providing access to research facilities or resources.
For more information, visit www.imi.europa.eu.

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Critical Path Institute (C-Path) is an independent, nonprofit organization established in 2005 with public and private philanthropic support from the Arizona community, Science Foundation Arizona, and the US Food and Drug Administration (FDA). C-Path's mission is to catalyze the development of new approaches that advance medical innovation and regulatory science, accelerating the path to a healthier world. An international leader in forming collaborations, C- Path has established 12 global, public-private partnerships that currently include over 1,450 scientists from government and regulatory agencies, academia, patient advocacy organizations, and dozens of major pharmaceutical companies. C-Path is headquartered in Tucson, Arizona. For more information, visit www.c-path.org.

For more information:

- SAFE-T (Safer and Faster Evidence Based Translation): www.imi-safe-t.eu
- Predictive Safety Testing Consortium's (PSTC): https://c-path.org/programs/pstc
- Letter of Support on the FDA website: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM514812.pdf
- Letter of Support on the EMA website: www.ema.europa.eu/docs/en_GB/document_library/Other/2016/09/WC500213479.pdf

C-Path Contact:
Kissy Black
+1.615.298.1144
kissyblack@lotosnile.com

SAFE-T Contact:
Dominique Brees
Novartis Institutes for BioMedical Research
dominique.brees@novartis.com