Cardiac Safety Research Consortium Conference Papers

New precompetitive paradigms: Focus on cardiac safety

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For the last several years, there have been a decreasing number of new innovative medical therapies approved for use in the United States despite an increasing expenditure on medical product development.[1,2] This situation has been compounded by an increasing awareness of safety issues arising from these approved drugs as well as from medical devices that have resulted in medical product discontinuations or recalls.[3]

With the heightened awareness of medical product safety issues and, in particular, cardiovascular safety, the Cardiac Safety Research Consortium (CSRC) was formed in 2006 to formulate paths forward to address these public heath concerns. The CSRC is a public-private partnership consisting of members from academia, industry, and various governmental agencies such as the US Food and Drug Administration (FDA) and Health Canada, which have organized as a group with the goal of identifying mechanisms to improve cardiovascular safety of medical products, while at the same time, encouraging more effective and more efficient medical product development. The Cardiac Safety Research Consortium has adopted this approach from the FDA's Critical Path Initiative (www.fda.gov/oc/initiatives/criticalpath) that was set forth to foster the evaluative sciences behind both safety and efficacy surrounding medical product development. This is critical because, as the safety hurdles for new approvals and marketed products have been raised, medical product development timelines have increased with the potential to impede innovation and limit the availability of needed therapies for patients.

The primary goal of the CSRC is to bring together diverse organizations to collaborate on primary research that will address specific questions regarding cardiovascular safety that directly impact drug and medical device development. By sharing data across industry, academia, and government agencies, large exploratory research projects of mutual interest become feasible because the costs can be shared. The research will be published and made available for public use without proprietary considerations. Using this "precompetitive" approach, the topics of interest can then be used to foster safer and more streamlined drug and device development.

A major component of the CSRC's initial effort has focused on generating white papers, which can serve dual roles as follows: (1) to serve as an expert consensus describing what is known, unknown, and controversial regarding an issue and propose paths forward to address key knowledge gaps or (2) to describe how the fruits of targeted research projects can be practically applied to cardiac safety evaluations. These white papers are not formal regulatory recommendations or policies nor are they meant to substitute for these. However, these white papers can provide a useful and accessible starting point from which to develop reasonable approaches or points to consider related to cardiovascular safety issues for specific new therapeutics.

Several of these extensively peer-reviewed white papers from the CSRC are currently in progress and will be published as an ongoing series in the *American Heart Journal*. This first such white paper in this issue of the Journal provides an example of the typical issues that the CSRC is attempting to address. Specifically, international regulatory guidances (International Conference on Harmonization [ICH] E14 and ICH S7B) are requiring extensive electrocardiographic QT analysis for all new drugs and some biologics. These QT analyses required by the ICH guidance are very complex and may not be able to be performed in the intended manner in certain populations such as oncology patients. This can have direct consequences (eg, patients being inappropriately excluded or discontinued from clinical trials of promising new agents based upon compounds effects on cardiac repolarization). Unfortunately, these ICH documents fall short in describing alternatives to these standard detailed QT analyses required for marketing authorization. This white paper, which is a collaborative effort between academics, several members of the pharmaceutical

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industry, the FDA, and Health Canada, provides a basic framework for reasonable approaches that can be taken to evaluate the QT interval without resulting in a significant limitation to patient participation in clinical trials, a delay to market approval, or compromises to cardiac safety.

It is notable that many of the challenging issues in cardiac safety evaluation are not well appreciated by cardiologists. Such evaluations most often include "off target" effects of noncardiac therapies such as the oncologic agents in this first white paper. The CSRC hopes that this series of articles will effectively engage stakeholders and cardiologists to foster safer medical products and provide approaches for increased efficiency in the development of medical products. In this manner, the CSRC can continue to work closely across a broad range of organizations to better promote cardiac safety in medical product development. To find out more about the CSRC, please visit the Web site at www.cardiac-safety.org.

References

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