FDA'S SENTINEL INITIATIVE MODERNIZING PHARMACOVIGILANCE

by Marinka Tellier

Pharmacovigilance (PV) is the continued assessment of the benefit-risk profile of new therapeutics that are approved for marketing by FDA and available for use in the real world. A therapeutic product's profile may differ from that observed in the clinical trials that supported the marketing approval, hence the regulatory requirement for postmarket surveillance.

The difference in profile can stem from several factors including exposure of a larger number of subjects that could reveal new adverse effects that occur at low frequency. In addition, exposure of the product to subjects with more variable medical backgrounds than specified under the inclusion/exclusion criteria of the pivotal clinical studies could result in a different benefit profile.

To date, PV has relied on active reporting to FDA by physicians and patients of adverse events including lack of effect (e.g. through FAERS) and required reporting by the product sponsor in the form of individual case reports, findings from medical literature and periodic postmarketing reporting (e.g. PSUR/PADER). A relatively newer tool that has supplemented FDA's PV surveillance has been the Sentinel System.

The Sentinel System was launched in 2008 following the 2007 FDA Amendment Act (FDAAA) which called for the creation of the postmarket Active Risk Identification and Analysis (ARIA) system to improve postmarketing surveillance. The Act required that FDA work with public, academic and private entities to develop a system to obtain information from existing electronic health care data from multiple sources to assess the safety of approved medical products.

This led to the creation of an electronic system by the Harvard Pilgrim Health Care Institute designated as the Sentinel Initiative. The system was initially piloted under the mini-sentinel study in 2009, with the full Sentinel System launching in 2016. The system focuses on drugs, vaccines and other biologics, and collects information from large amounts of electronic health

care data (e.g. electronic health records, insurance claims data and patient registries) from a diverse group of data partners and academic partners. Importantly, it is the most comprehensive multisite, distributed database available to monitor the safety of marketed medical products in a manner that protects patient privacy and allows for real-time tracking (e.g. number of patients using a specific drug and side effects against medical history and use of other medications).

FIVE-YEAR STRATEGIC PLAN

The FDA is seeking to strengthen the use of the Sentinel System and issued its five-year strategic (2019-2023) plan to expand its use in January 2019.

The outlined strategy focuses on five areas. One is the continued enhancement of the system's infrastructure, technology and operations to support the capture and analysis of data. The second objective focuses on improving use of new advances in data science and signal detection. One example for this objective is the TreeScan project, which is intended to proactively scan for potential safety issues. TreeScan will simultaneously evaluate large numbers of potential adverse events or disease outcomes to determine if any occur with higher probability among patients exposed to a therapeutic product. Through this enhanced signal detection capability, the Sentinel System can evaluate a product against the full spectrum of observed adverse outcomes as opposed to a pre-specified single adverse outcome. Eventually, when signal detection capabilities are fully developed, the system could examine all

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exposure variables across therapeutic products against all potential health outcomes simultaneously, and transform PV surveillance from a reactive to a continuous, real-time process.

The third strategic objective focuses on access and use of real-world data (RWD) and real-world evidence (RWE) generation. The Sentinel System will be used to establish standards for high-quality RWD and to evaluate RWE applications as part of FDA's catalyst program to advance the use of RWD in drug development and provide regulatory guidance in this area. In addition, the Sentinel System seeks to expand and validate new health outcome improvements (HOIs) relevant for the effectiveness of therapeutics to support adoption of RWD-sourced HOIs.

The remaining two strategic objectives focus on 1) expanding the stakeholders in the system to ensure its future as a national resource and its role in dissemination of knowledge and 2) using it to guide regulatory science, e.g. contribute evidence to support product label changes (see the Sentinel website for specific examples on how ARIA has been used).

FUTURE BENEFITS

The Sentinel System is here to stay and seeking to play a more prominent role in PV by FDA and may be able to replace the manufacturer-driven PV activities in the future. Its potential to support use of RWD against validated HOIs in drug development and its ability to perform real-time monitoring of both safety and efficacy marks an important change in PV efficiency and effectiveness. It could contribute to shortened drug development time where in an ideal world it eventually may be capable of reducing the need for multiple Phase III trials to support marketing applications. Lastly, it can contribute to personalized medicine by being able to quickly evaluate efficacy in different patient groups, identifying those that benefit versus those that fail to benefit from new therapies.

For up-to-date information on the Sentinel Initiative and the full strategic report, see: **www.sentinelinitiative.org** ▶

and the FDA Sentinel Initiative section of the FDA website. ▶

If you have questions, contact us at **USpharma@nsf.org**.

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Cite as: NSF International. May 2019. FDA's Sentinel Initiative Modernizing Pharmacovigilance. NSF: York, UK.

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