ENGELBERG CENTER for Health Care Reform at BROOKINGS

September 2010

DISCUSSION GUIDE

Expert Workshop: Methods for Signal Refinement in Active Medical Product Surveillance

Workshop Overview

The U.S. Food and Drug Administration (FDA) reviews multiple data sources to evaluate medical product safety, including the premarket development program, reports submitted to the Adverse Events Reporting System (AERS), relevant medical literature, and postmarket safety studies. Development of the Sentinel System will augment FDA's postmarket safety assessment process by enhancing its active surveillance capabilities.

Conducting active surveillance may be thought of in three sequential steps: signal generation, signal refinement, and signal evaluation.

Potential Steps in Active Surveillance

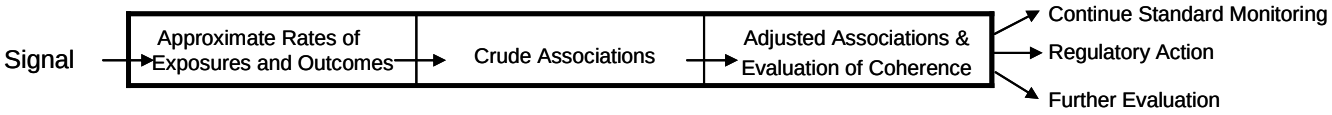
- **Signal generation** includes a collection of methods for identifying potential associations between medical products and health outcomes of interest (HOIs).
- **Signal refinement** is a process for evaluating the magnitude and clinical significance of a suspected association.
- **Signal evaluation** consists of the implementation of a formal epidemiological analysis to more definitively establish or refute causality between exposure to the medical product and the HOI.

This workshop will focus on signal refinement, a stage in the active surveillance process that begins with a potential association between a medical product and an adverse HOI that has emerged from available data. Two general signal refinement scenarios can be envisioned:

- Concern about a specific medical product-HOI pair emerges during the product's development program OR there is a desire at the time of marketing to monitor a product for an association with an HOI that tends to be medical product-related but is too rare to be observed reliably in a development program (e.g., acute liver failure, Guillain-Barre syndrome). In this case, FDA would want to monitor the potential association at a regular interval over time as the product is taken up by the market.
- Concern about a specific medical product-HOI pair emerges distant to the introduction of the medical product to the market (e.g., years later). In this case, a one-time evaluation may be conducted to assess the potential association using the entire extent of marketing history.

Signal refinement may include the steps outlined below:

Potential Steps in Signal Refinement



To enable timely responses to potential safety concerns, the signal refinement process must proceed as rapidly as possible. The first phase of the signal refinement process involves attempts to establish the rate of exposure in the population and defining the characteristics of the exposed population. It also includes identifying those who experienced the HOI among patients exposed and not exposed to the medical product of interest (or those exposed to a comparator product). Rates of the HOI in exposed and comparator groups are calculated to develop crude estimates of the association. These estimates are adjusted for confounders and effect modifiers to produce adjusted associations. Such adjustment is necessary because unlike randomized controlled trials, patients represented in observational data are not randomly assigned to a treatment. Distribution of concurrent conditions and medications is non-random and can lead to a biased estimate of the medical product-HOI association. Adjusted associations form the basis for additional actions outside the scope of signal refinement, which may include continued standard monitoring, taking a regulatory action, or conducting further evaluation, depending on the magnitude and clinical significance of the medical product-HOI association. Evaluation of the coherence of an association involves questioning whether there are consistent and reinforcing signals elsewhere in the data, whether the signal has biological plausibility, and whether there are testable implications in the data at hand.

Workshop Objectives and Structure

This workshop will define the most effective and efficient ways to refine a potential safety signal within the scope of the FDA's public health surveillance authority. Development of a generalized framework applicable to a wide range of medical products will help expedite the signal refinement process and increase confidence in the results. This generalized framework should capitalize on similarities between signal refinement scenarios, while remaining flexible to accommodate specific products and HOIs. In exploring such a generalized framework, this workshop will focus on achieving greater clarity on the data needs, analytic methods, and acceptable levels of uncertainty in signal refinement.

To facilitate discussion on these topics, the workshop will include three sessions. The first will consider the elements included in and the feasibility of a generalized framework for signal refinement. The latter two sessions will focus on data needs and methods for signal refinement. Two case studies will guide discussion in these sessions:

1. Association between an oral anti-diabetes drug and acute myocardial infarction
2. Association between an injectable antibiotic drug (administered in an inpatient setting) and acute liver injury

These case studies represent two scenarios that differ in ways relevant to the signal refinement approach: route of administration, administration setting, HOI, and potential data sources. Discussion of the two scenarios will help elucidate similarities and differences in approaches to signal refinement and implications for development of a generalized framework.

Discussion Guide

Session I: Building a Generalized Framework for Signal Refinement

A timely signal refinement process is important to enable further evaluation of and response to potential safety concerns. A generalized framework for signal refinement that accommodates a variety of medical products would help ensure a rapid and efficient signal refinement process. Key discussion questions may include:

- What are the goals of signal refinement, and how do we know when they have been met?
- What steps in the approach to signal refinement can be standardized across products?
- What are the issues and challenges that must be addressed to create the capacity for signal refinement in Sentinel?
- What is the role for existing data from registries or clinical trials in signal refinement?

Session II: Exploring Data Needs for Signal Refinement

Signal refinement will require a range of data, including information on exposures, HOIs, and confounders. Presenters will describe data needs for each medical product-HOI scenario within the context of specific surveillance systems (e.g., Vaccine Safety Datalink, Mini-Sentinel, and the Ontario provincial health care system). Illustration of the similarities and differences between these systems and accompanying data sources may provide insights that help identify generalized data needs for a range of medical products and areas that may require product-specific tailoring of the signal refinement framework. The following questions will be discussed for each medical product-HOI pair example:

- Defining exposures of interest and identifying data sources that appropriately capture these exposures are keys to the success of signal refinement.
  - What is the source of exposure data?
  - How frequently should it be updated?
  - Is there a need to maintain earlier versions of a database? If so, for how long?
  - How is exposure defined?
  - Is validation required?
- As a foundation for effective signal refinement, validated definitions of HOI must be employed and appropriate data sources must be identified.
  - What is the source of outcome data?
  - How frequently must it be updated?
  - If a definition of an HOI has been validated elsewhere as having a high positive predictive value, for the purposes of active surveillance, can the HOI definition be assumed to be valid?
  - If not, when would a new validation study be required?
  - Is determining positive predictive value enough, or does negative predictive value need to be determined as well?
- Signal refinement must draw upon data sources that measure potential confounders of the medical product-HOI association, so that signal refinement methods may adjust for these confounders.
  - What are the confounders of interest?
  - Which are measurable and how?

Session III: Exploring Methodological Needs for Signal Refinement

Once appropriate data sources for signal refinement are identified, a variety of methodological approaches may be employed to evaluate the relationships between medical products and HOIs. Discussion will focus on the methods most appropriate for each scenario, ideally leading to a broader understanding of how various methodological approaches fit into a generalized framework for signal refinement.

- Which methods are most appropriate for signal refinement? Is there a sequence of analytic steps?
- How much can the signal refinement process be systematized to maximize efficient use of resources and still provide actionable information?
- To what extent do methods need be validated before they can be adopted for signal refinement? What kind of validation is required (e.g., method previously published in a peer-reviewed journal)?
- What are the most useful for reducing bias due to misclassification of exposures or HOIs?
- How should observable and unobservable confounders be addressed in the analysis plan?
- For the purposes of an active surveillance evaluation, where should the line be drawn with regard to confounder adjustment?
- Can the same data set be used for signal refinement and signal evaluation?