Precompetitive Use of Algorithms to Predict Adverse Events

Sean Khozin, MD, MPH
Acting Associate Director, Oncology Center of Excellence
Director, Information Exchange and Data Transformation (INFORMED)
Food and Drug Administration
@FDAA oncology
@SeanKhozin

The information in this presentation does not necessarily represent the view of the FDA
Disclosures: None
Precompetitive Use of Algorithms to Predict Adverse Events

A great idea!
But...

Houston we have a problem!

We need more data!
Safety signal detection at the FDA (and beyond)

Preclinical
\textit{in vitro} \rightarrow \textit{in vivo}

Clinical
phase 1 \rightarrow 2 \rightarrow 3

Postmarket
spontaneous "passive" reporting

IND
- 7 & 15 day
- Annual reports

NDA/BLA
- Trial level

\textbf{Data assets}

None

CDISC

FAERS

\textbf{Deductive}
(reports, tables, and narratives)

\textbf{Analytic}
How many “Post Its” does it take: FDA Oncology Premarket reports (commercial sponsors) 1/1/2006 to 6/29/2015

<table>
<thead>
<tr>
<th>Division</th>
<th># INDs</th>
<th>15-day</th>
<th>7-day</th>
<th>f/u</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHP</td>
<td>473</td>
<td>18,243</td>
<td>3,326</td>
<td>27,547</td>
<td>49,116</td>
</tr>
<tr>
<td>DOP1</td>
<td>651</td>
<td>22,327</td>
<td>4,300</td>
<td>32,539</td>
<td>59,166</td>
</tr>
<tr>
<td>DOP2</td>
<td>669</td>
<td>25,723</td>
<td>4,266</td>
<td>39,327</td>
<td>69,316</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,793</strong></td>
<td><strong>66,293</strong></td>
<td><strong>11,892</strong></td>
<td><strong>99,413</strong></td>
<td><strong>177,598</strong></td>
</tr>
</tbody>
</table>

473 Sponsors
Number of safety reports per year

Categories
- 15 DAY
- 7 DAY
- FOLLOWUP

Increasing
Average number of safety reports/IND
Safety reports/IND over IND’s lifespan

Mean = 33 reports/INDs/year

Peak: year 6
The Majority of Expedited Investigational New Drug Safety Reports Are Uninformative

Jonathan P. Jarow, Sandra Casak, Meredith Chuk, Lori A. Ehrlich, and Sean Khozin

Abstract

Sponsors of human drug and biologic products subject to an investigational new drug (IND) application are required to distribute expedited safety reports of serious and unexpected suspected adverse reactions to participating investigators and the FDA to assure the protection of human subjects participating in clinical trials. On September 29, 2010, the FDA issued a final rule amending its regulations governing expedited IND safety reporting requirements that revised the definitions used for reporting and clarified when to submit relevant and useful information to reduce the number of uninformative reports distributed by sponsors. From January 1, 2006, to December 31, 2014, the FDA’s Office of Hematology and Oncology Products received an average of 17,686 expedited safety reports per year. An analysis of FDA submissions by commercial sponsors covering this time period suggested a slight increase in the number of expedited safety reports per IND per year after publication of the final rule. An audit of 160 randomly selected expedited safety reports submitted to the FDA’s Office of Hematology and Oncology Products in 2015 revealed that only 22 (14%) were informative. The submission of uninformative expedited safety reports by commercial sponsors of INDs continues to be a significant problem that can compromise detection of valid safety signals.

Clin Cancer Res; 22(9); 1–3. ©2016 AACR.
10% (Median; range 2-55)

16% (average)

Based on 44 responses to the following question:

On average, what percent of your time in the last 3 months has been spent reviewing expedited premarket 15- and 7-day safety reports?
Information Exchange and Data Transformation (INFORMED)

A holistic approach to regulatory science

Launch of FDA’s New Digital Health Incubator

... to support the integration of data analytics into regulatory decision making, we’re taking another new step with the creation of an internal data science incubator called the Information Exchange and Data Transformation; or INFORMED

Remarks by Scott Gottlieb, M.D.
Commissioner of Food and Drugs
Academy Health’s 2018 Health Datapalooza
Washington, DC
April 26, 2018

https://www.fda.gov/NewsEvents/Speeches/ucm605697.htm
Information Exchange and Data Transformation (INFORMED)

Input

- CDISC
- Electronic health records
- Digital premarket safety
- Biometrics
- Apps

Collaborative partnerships

Output
Creating new data assets

IND 7 & 15 day

Biobusiness Briefs

Regulatory watch: Evaluating the potential for digital submission of expedited premarket safety reports to the FDA

Sean Khozin, Meredith Chuk, Tamy Kim, Suranjan De, Sanjay Sahoo, Geoffrey Kim & Richard Pazdur

Creating new data assets

IND 7 & 15 day

Biobusiness Briefs

Regulatory watch: Evaluating the potential for digital submission of expedited premarket safety reports to the FDA

Sean Khozin, Meredith Chuk, Tamy Kim, Suranjan De, Sanjay Sahoo, Geoffrey Kim & Richard Pazdur

Central global safety data bank
Recommendation 4.a. A neutral third party should develop a central electronic portal for reporting AEs.

A neutral third party, such as a nonprofit organization formed by an industry consortium or a public-private partnership, should create a globally available, central electronic portal that enables users to report and access AE data relevant to all trials in which they participate. This would provide investigators with context to inform clinical judgments regarding attribution of AEs, as well as facilitate regulators, sponsors, and IRBs identification of important safety signals.
Thank you
Back up slides
No “economies” of scale
Matched pairs analysis

• Method
  – Reports divided into two groups:
    • Before 2010; after 2010
  – Excluded
    • Year 2010 (intervention) and 2015 (partial)
    • Sponsors with no INDs either before or after 2010

• 198 Sponsors identified
Reports per IND before and after 2010 ruling: Matched pairs analysis

Sponsors with increase in average number of reports per IND

Mean difference = 9.6 (95% CI 19.9, -0.72)

Mean #reports/IND:
--Before 2010 = 38.9
--After 2010 = 48.4

Sponsors with decrease in average number of reports per IND

Mean: (Reports per IND after 2010 – Reports per IND before 2010)/2