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.

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Introduction

The FDA regulates the investigational use of drugs to ensure the safety and rights of human subjects in all phases of investigation and to make certain that safe and effective drugs are available. Clinical trials in which an investigational drug, whether marketed or not, is administered or dispensed to one or more human subjects are typically conducted under an investigational new drug (IND) application. It is the responsibility of IND sponsors and participating investigators in clinical research to report and monitor all adverse events occurring in clinical trials conducted under an IND. An updated safety profile is described in the annual report and the investigational brochure distributed to investigators and the FDA.

Expedited IND safety reports generated by the sponsor are required by regulation to alert participating investigators and the FDA of potential serious risks in a more timely fashion (no more than 15 days) than the annual report or the investigator’s brochure. In addition, expedited IND safety reports often include information on how this new risk will be managed (e.g., via change in protocol and/or consent or further monitoring). For a single adverse event to meet the criteria for submission in an expedited safety report, the event must be a serious, unexpected, and suspected adverse reaction. These terms, along with reporting procedures, are defined in the code of federal regulations (1). Historically, the majority of expedited IND safety reports have been uninformative. On September 29, 2010, the FDA published a final rule amending the IND safety reporting requirements due to sponsors’ frequently uninformative safety reports with no reasonable possibility that the drug caused the adverse event. The major changes were related to the causality concept and included (i) clarification of the definition of reasonable possibility for the determination of causality; (ii) assessment of causality by the sponsor, not the investigator, determining reportability; and (iii) introduction of IND safety reports based on the aggregate analysis of adverse events that may be anticipated due to the disease being treated or the population being studied. The goal of the final rule and subsequent guidance was to reduce the number of uninformative safety reports that could obscure the detection of valid safety signals, straining the limited resources of the FDA, investigators, and institutional review boards (IRB; refs. 2, 3).

Herein, we present the results of an audit to determine the impact of the final rule on the number and quality of expedited IND safety reports submitted to the FDA’s Office of Hematology and Oncology Products.

Materials and Methods

The number and type (initial and follow-up) of expedited IND safety report submissions by commercial sponsors, excluding research INDs from academic institutions, to FDA’s Office of Hematology and Oncology Products from January 1, 2006, to December 31, 2014, were analyzed through a search of FDA’s electronic Document Archiving, Reporting and Regulatory Tracking System. The number of initial expedited IND safety reports per commercial IND per year was calculated for the period of study that straddles the year of the publication of the final rule (i.e.,...
2010). In addition, a matched pairs analysis was performed using both initial and follow-up safety reports submitted by 198 commercial sponsors that had active INDs before and after 2010. The year 2010 was defined as the year of intervention, and data from this year were excluded from the matched pairs analysis.

The authors performed a formal audit on twenty consecutive initial expedited IND safety reports submitted in 2015 to eight randomly selected commercial INDs. The individual safety reports were reviewed to determine whether the events were serious, unexpected, suspected adverse reactions (i.e., causally related to the study treatment based on the assessment of sponsors). Audit results were cross-validated, and discrepancies were resolved through group discussions by the authors. Safety reports that met all three criteria for expedited reporting were further assessed to determine whether the adverse events were anticipated on the basis of underlying disease, concomitant therapies, or patient population and should have been analyzed in aggregate to determine whether they met the IND safety reporting criteria.

**Results**

There were 1,793 active commercial INDs with 483 sponsors during the time period of examination. The total number of safety reports was 159,174, of which 70,233 were initial 7-day and 15-day reports. There was no change in the number of safety reports per IND per year following the modifications to IND safety reporting regulations in 2010 (Fig. 1). The mean number of reports per IND per sponsor increased from 38.9 before 2010 to 48.4 after 2010 in the matched pairs analysis. The number of active INDs and expedited safety reports increased each year over the time period (Table 1).

In the audit of the selected commercial INDs in 2015, only 38 (24%) of the 160 expedited IND safety reports reviewed met all three criteria of containing serious, unexpected, suspected adverse reactions. All but one of the reports contained serious adverse events. More than half (54%) were expedited reports of expected adverse events, listed in product labeling or the investigator’s brochure. The sponsor did not conclude that the reported adverse event was suspected in 50% of the cases examined. Of the 38 expedited safety reports that met all three criteria, 16 (42%) were anticipated based on FDA review (e.g., febrile neutropenia in a patient receiving cytotoxic chemotherapy as backbone therapy). Therefore, of the 160 audited expedited IND safety reports, only 22 (14%) were informative.

**Discussion**

From January 1, 2006, to December 31, 2014, the FDA’s Office of Hematology and Oncology Products received a total of 159,174 expedited safety reports from commercial sponsors, corresponding to an average of 17,686 reports per year. On September 29, 2010, the FDA issued final regulations governing expedited safety reporting to codify expectations of the agency for timely review, evaluation, and submission of relevant and informative safety information. The final rule went into effect on March 28, 2011. The revisions to the IND safety reporting rule were intended to increase the utility of IND safety reports and expedite the FDA’s review of critical safety information by reducing the
number of reports that do not contribute in a meaningful way to the developing safety profile of the drug.

The results of our study suggest that not only was there no reduction in the number of expedited safety reports submitted to the FDA’s Office of Hematology and Oncology Products by commercial sponsors following the final rule, but also a slight increase was detected. Furthermore, in a random audit of expedited safety reports, only 14% (22/160) met the criteria of serious, unexpected, suspected adverse reactions, with the remainder not providing any useful information for understanding the safety profile of the investigational drug. The purpose of expedited IND safety reporting is to call attention to important safety signals of an investigational agent so that appropriate monitoring and patient management decisions are promptly instituted to ensure protection of human subjects participating in clinical trials. Reporting of uninformative adverse events is inappropriate and can consume the limited resources of investigators, IRBs, and the FDA. Moreover, large numbers of uninformative expedited safety reports, as observed in our study, can obscure important and valid safety signals.

Single reports of adverse events, even if they are serious and unexpected based on the known toxicity profile of the investigational drug, can be uninformative if they are anticipated based on demographics, underlying disease, or concomitant therapies of the subject. For example, although it is possible that an investigational drug may be causing febrile neutropenia, report of a single instance in a study in which the investigational drug is added on to cytotoxic chemotherapy is uninformative. Aggregate reporting is the only way to determine that common or anticipated adverse events are potentially causally related to the investigational drug (3, 4).

This study demonstrates that the FDA’s revisions to IND safety reporting regulations and guidance did not have the intended effect on the safety reporting practices of commercial sponsors of oncology drug products. Over 5 years after publication of the final rule, the majority (86%) of expedited safety reports are uninformative. Barriers to the adoption of new procedures for optimal management of IND safety reporting by commercial sponsors have been examined by the Clinical Trials Transformation Initiative (5). Perceived barriers of sponsors include lack of international harmonization for reporting rules, liability risks, and lack of clarity of threshold rules for aggregate reporting. The results of our study suggest little progress in overcoming these perceived barriers, and the number of expedited safety reports submitted to investigators, IRBs, and the FDA seems to be on the rise. The FDA is currently evaluating options for modernizing expedited IND safety reporting submissions via electronic transmission of adverse events and relevant data, including patient narratives, which can streamline reporting and monitoring activities. However, improving expedited IND safety reporting practices calls for sponsors to identify and address the reasons for submission of uninformative reports, independent of the mode and methods used for submission.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: J.P. Jarow, S. Casak, S. Khozin
Development of methodology: J.P. Jarow, S. Casak, L.A. Ehrlich, S. Khozin
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.P. Jarow, S. Casak, M. Chuk, L.A. Ehrlich, S. Khozin
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.P. Jarow, S. Casak, L.A. Ehrlich, S. Khozin
Writing, review, and/or revision of the manuscript: J.P. Jarow, S. Casak, M. Chuk, L.A. Ehrlich, S. Khozin
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.P. Jarow, L.A. Ehrlich, S. Khozin
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References

Table 1. Expedited IND safety reports submitted to FDA’s Office of Hematology and Oncology Products by commercial sponsors from January 1, 2006, to December 31, 2014.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of active INDs</th>
<th>7-Day initial</th>
<th>15-Day initial</th>
<th>Follow-up</th>
<th>Total number of safety reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>469</td>
<td>724</td>
<td>5,944</td>
<td>4,585</td>
<td>9,253</td>
</tr>
<tr>
<td>2007</td>
<td>519</td>
<td>816</td>
<td>4,450</td>
<td>5,137</td>
<td>10,403</td>
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<tr>
<td>2008</td>
<td>555</td>
<td>794</td>
<td>5,281</td>
<td>6,555</td>
<td>12,436</td>
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<tr>
<td>2009</td>
<td>569</td>
<td>941</td>
<td>6,100</td>
<td>8,172</td>
<td>15,273</td>
</tr>
<tr>
<td>2010</td>
<td>580</td>
<td>1,756</td>
<td>6,327</td>
<td>9,626</td>
<td>17,709</td>
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<tr>
<td>2011</td>
<td>621</td>
<td>1,453</td>
<td>6,120</td>
<td>9,708</td>
<td>17,281</td>
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<tr>
<td>2012</td>
<td>669</td>
<td>970</td>
<td>6,935</td>
<td>11,083</td>
<td>18,988</td>
</tr>
<tr>
<td>2013</td>
<td>721</td>
<td>958</td>
<td>9,446</td>
<td>15,819</td>
<td>26,203</td>
</tr>
<tr>
<td>2014</td>
<td>854</td>
<td>1,837</td>
<td>11,401</td>
<td>18,256</td>
<td>31,494</td>
</tr>
<tr>
<td>Total</td>
<td>5,537</td>
<td>10,229</td>
<td>60,004</td>
<td>88,941</td>
<td>159,174</td>
</tr>
</tbody>
</table>

Abbreviation: IND, Investigational New Drug.
Clinical Cancer Research

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