

# Safety Reporting: It Can Enter the 21st Century—If We Let It

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## Abstract

This is a commentary about the evolution of safety reporting, the new FDA Draft Guidance on Safety Reporting and possible paths forward.

## Keywords

safety assessment committee, safety reporting, clinical trial safety, data monitoring committee, IND Safety Reporting.

As a young cardiologist during the mid-1990s, I (J.S.) was excited to serve as a primary investigator. My site was selected to evaluate an innovative antihypertensive medication. It was one of many selected for a large global clinical trial, something today we would call a mega-trial. Funny how time plays with my memory—I no longer remember the name of the compound we studied, but I do recall being inundated by notifications of serious adverse events (SAEs). It seemed like several times per week I received an overnight mail from Federal Express notifying me of some event from somewhere in the world. Many, if not most, were cardiovascular events in a population that, by definition, was at heightened cardiovascular risk. Sure, there were reports in which the primary investigator felt that the study drug was ‘related’ to the event—but since this was a blinded, randomized trial, I could not figure out how these reports impacted my treatment or continuing enrollment of patients in the trial. Given the absence of actionable information provided, I could not figure out why the sponsor was expending the resources on notification.

Of course, we now know that, at the time, the US Food and Drug Administration (FDA) as well as other regulatory agencies required reporting of all SAEs. However, as the clinical trial enterprise has grown, so have the SAE reports and, apparently, the FDA became overwhelmed with safety reports. Consequently, in 2010, the rule for reporting requirements was updated. The FDA felt that “simply reporting all serious adverse events . . . may obscure safety information which is relevant to the investigational drug.” Therefore, the amended 21 CFR 312 differentiates the concept of an adverse event from that of an adverse drug reaction (ADR). The regulation defines a suspected ADR as an adverse event for which there is a *reasonable possibility* (emphasis added) that the drug caused the adverse event. These events fall into three categories: (1) a single occurrence of a known drug-related AE, (2) one or more occurrence of an uncommon event in the population, and (3) aggregate analysis of specific known events that occur at a

higher rate in the treatment group than in the underlying decision. Additionally, the regulation calls for the sponsor to determine whether the event has a “reasonable possibility” of relatedness.

This attempt to rationalize the safety reporting process, however, was not widely adopted. A survey in 2011 revealed that most sponsors had not changed their approach to expedited reporting of serious adverse events.<sup>1</sup> To encourage adoption of the amended safety reporting rule, in December 2012, the FDA released a Guidance titled “Safety Reporting Requirements for INDs and BA/BE studies.”<sup>2</sup> This Guidance focuses on the background of safety reporting, the rationale for change, and definitions in the amended safety reporting rule. Essentially, this was an expansion and explanation of the amended safety reporting rule. It provided specific instructions that, for example, would have obviated the reporting of many of the cardiovascular events in the antihypertensive trial mentioned earlier.

1. Sponsors should not submit IND safety reports for those serious adverse events that were prospectively identified as anticipated to occur in the study population unless the evidence suggests a causal relationship between the drug and the event (see § 312.32(c)(1)(i)(C))—*which is a matter of judgment*.
2. Determining when the aggregate safety data provide evidence to suggest a causal relationship between the drug and a serious and unexpected adverse event or show a clinically important increase in a previously

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recognized serious adverse reaction rate is a complex judgment that is, in most cases, not a simple application of a planned statistical analysis. The first mention of safety assessment committees is in relationship to deciding whether adverse event rates are “clinically important.”

Unfortunately, this Guidance, which was a well-written and well-reasoned explanation of the rationale and implied changes inherent in the amended safety reporting rule, did not affect reporting. A survey in 2014 revealed that most sponsors had not changed their approach to expedited reporting of serious adverse events. They cited the following reasons: (1) lack of global harmonization with reporting requirements, (2) determining causality with the investigational drug (especially in blinded studies), and (3) the burden associated with performing an “analysis of similar events.”<sup>3</sup> Similarly, the FDA’s office of Oncology and Hematology Products (OHOP) reported receiving an average of 17,868 expedited safety reports per year. An audit of randomly selected 2015 safety reports was undertaken to objectively determine the number of “informative” safety reports. Only 24% met criteria for serious, unexpected, and suspected adverse reaction, and of these, the FDA found that a large percentage were “expected” events for the population.<sup>4</sup> Another way to look at these findings is that OHOP, at a minimum, receives over 1100 uninformative, unrequired, safety reports per month.

Currently, there is no evidence that the 2010 amended rule and the 2012 guidance did not engender change in safety reporting behavior from clinical trial sponsors. Although we are unaware of any published information on why this failed to happen, we are aware that the common areas of confusion have to do with assessment of safety with respect to aggregate reporting—how to protect blinded data and how to establish the safety “thresholds” for reporting. Additionally, there was concern that the FDA’s amended safety rule was not consistent with the safety reporting in the rest of the world.

Consequently, in December 2015, the FDA released a new draft guidance that focused on the safety assessment process that should underlie the reporting requirement. This guidance specifically acknowledges the concerns regarding aggregate reporting and suggests that “using a safety assessment committee and developing a safety surveillance plan will help sponsors resolve these concerns discussed below in FDA’s draft guidance in 2015.”<sup>5</sup>

### **FDA’S 2015 Draft Guidance on Safety Assessment for IND Reporting**

The FDA released a draft guidance in December 2015 titled “Safety Assessment for IND Safety Reporting—Guidance for Industry” that advocated a systematic approach to improve the Safety Reporting Requirement for serious adverse events for human and biological products developed under the IND. This

new draft guidance is a follow-on to the 2012 Guidance on the “Safety Reporting Requirements for INDs and BA/BE studies.”

The new draft guidance focuses on the Sponsor’s responsibility in managing a drug development program with multiple studies. The recommendations, among other things, include the creation of a Safety Assessment Committee (SAC) for a pharmaceutical drug development program. The guidance suggests that the SAC is charged with reviewing safety data at the program level of the investigational drug and other relevant safety information outside of the program to make a judgment about the likelihood that the investigational drug could cause any serious adverse event. Specifically, it recommends to focus on the following: (1) “an aggregate analysis of specific events observed in a clinical trial indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control groups,” and (2) “clinically important increase in the rate of a serious suspected adverse reaction.” Once implemented, the SAC streamlines the safety reporting requirement to the FDA so that only the unexpected suspected adverse events and reports of expected events that appear “over-threshold” are reported.

Whereas the “traditional” IND Safety reporting requirement focused sponsors on the detection and reporting aspects of all adverse events associated with the use of investigational products, the new rule aims to focus energies on reporting only meaningful adverse drug reactions. Additionally, whereas sponsors traditionally were expected to review blinded safety data, the new rule intends for the review of unblinded safety information both for establishment of “relatedness” and for the detection of increased incidence of expected events. (Currently, data monitoring committees [DMCs] may perform this duty, but their use is seen in no more than 25% of phase 2 and 3 industry-sponsored trials and specific DMC methodologies are unknown.<sup>6</sup>)

Through implementation of an SAC and the Safety Surveillance plan, the 2015 guidance recommends that sponsors develop a consistent and documented process across all compounds by which serious adverse events be evaluated on a periodic basis based on their incidence rates on the program level against the expected rates in the population of interest, the disease severity, potential effects due to the treatment class and all other available information. Furthermore, the sponsor is to determine if these are unexpected events plausibly due to treatment, and hence get reported to the agency appropriately. This will reduce reporting of uninformative individual cases and will focus only on reporting of drug-related “serious unexpected suspected adverse reactions” (SUSARs).

### *Public Reaction to the Draft Guidance Document*

In response to the FDA’s request for public comments, biotechnology companies, pharmaceutical manufacturers, and industry associations indicated strong support for rationalizing the safety reporting process. Feedback indicating potential improvements and/or clarifications to the guidance revealed

many worthwhile concerns, which we have categorized in Table 1.

## Discussion

Since the issuance of the draft guidance, the authors and colleagues have conducted informal interviews with key personnel at many sponsor organizations about the impact of the 2015 draft guidance. We queried their reaction, plans for implementation, and potential issues. These organizations run the gamut—from the largest multinational pharmaceutical companies to start-up biotech companies. Although the interviews were “off the record,” some common themes exist, many of which mirror those listed in Table 1. We’d like to offer our thoughts on addressing the concerns expressed and suggest a way forward with the implementation of a process that meets the scientific goals of the amended safety reporting rule in a cost-efficient fashion.

This section discusses considerations on implementing the SAC for Sponsors. This will also address the analytical framework that could be developed to help the SAC in defining the threshold for the incidence rates for the safety events of interest, above which the SAC could discuss the potentiality of reporting the issue to the agency.

## SAC Establishment and Duties

The Safety Assessment Committee’s primary role would be to improve the quality of Safety Reporting for trials. To do so effectively, the FDA, in its guidance, recommends a systematic approach to safety surveillance that could help the SAC in deciding the necessity of reporting potential safety issues to the FDA or other regulatory bodies. Safety surveillance should focus on evaluating the safety of an investigational product beyond the current ongoing study. Therefore, it should also review other related studies across indications within the sponsor company. In effect, the SAC will be expected to review, evaluate, and manage accumulating data on serious adverse SAEs (and potentially other adverse events of interest) from the entire clinical trial database, and to compare the serious event rates across treatment groups. This will help identify previously recognized SAEs and their rates of occurrence, to detect the unexpected serious adverse reactions for the current asset under investigation, or expected SAEs with higher frequencies than expected. This approach would also include the SAEs that could be foreseen in the population under study, consideration of the disease state and severity, the treatment class that is based on information in literature on these factors, and any available epidemiology and postmarketing safety information.

## Role of the SAC

The Safety Assessment Committee will consist of a group of individual medical and scientific experts that are tasked with administering certain responsibilities as described in the safety

surveillance plan. *We believe that the operational details of how this is implemented should be charter-defined*, similarly to the processes used to establish and operate a DMC. The charter should, for example, specify reporting timelines (eg, Is the reporting timeline from investigator report or SAC decision? What if SAC requests adjudication of an event, does that delay timelines?). The SAC will be tasked with reviewing the safety information at the program level and recommend to the sponsor whether safety information should be reported to the FDA as part of the IND Safety Report requirement. Through periodic review of unblinded aggregate data, the SAC will evaluate the evolving safety profile of the investigational drug. The SAC will assess the cumulative evidence of adverse events from all the trials in the drug development program. Additional safety information from epidemiology, preclinical, and other relevant areas will inform their decision, allowing them to assess the safety information considering the cumulative evidence across treatment, disease, and epidemiology. They would then decide if the unexpected adverse reaction was potentially caused by the treatment of interest, or if the aggregate rate of expected events crossed the reporting threshold per definitions in the safety surveillance plan.

As SACs regularly examine unblinded data, maintaining the blind to study personnel is a serious concern. A large sponsor, as they likely have sufficient unrelated personnel to preserve the blind, may have a person with whom the SAC communicates in making the final reporting decision. In contrast, smaller organizations may need to entirely outsource this activity in order to preserve the blind. If research is outsourced to a contract research organization (CRO) or multiple CROs, the sponsor needs to make sure that both the internal sponsor team and the CRO team are insulated from any unblinded data. This can be accomplished either by having an independent SAC provider or, if the CRO offers to provide the SAC, sponsor certification of “firewall” protection of the blind.

## SAC vs DMC

Although a Data Monitoring Committee (DMC) may share the same trial-specific unblinded information with the SAC, these 2 independent committees have different roles. In general, the DMC’s focus is on monitoring the trial or program level by assessing the ongoing safety and efficacy for the active treatment against the placebo or standard of care comparator. Their recommendations center on the conduct of the trial; they do not have a reporting responsibility. Additionally, in contrast to the specific, guidance-defined, characteristics (eg, vulnerable population, known toxicity) that suggest establishment of a DMC, the SAC is recommended for all development programs.

One should decide carefully if the trial fulfills the criteria for requiring a DMC. If so, it may be advantageous to extend the scope of the DMC to include SAC roles. In fact, this may end up being the common practice, especially for rare diseases or conditions with low prevalence. However, it is important to keep in mind that the role of the DMC is different from that

**Table I.** Public Reaction to Safety Assessment for IND Safety Reporting—Guidance for Industry Draft Guidance, December 2015.

Analytical Issues	SAC Structural Issues	Operational Issues
<ul style="list-style-type: none"> <li>• Predicting rates of SAE occurrence and data-pooling practices, including the similarities among studies to be pooled, may be challenged scientifically;</li> <li>• Statistical complexities in the pooled analysis remain w.r.t. interpretation and challenges for meta-analysis</li> <li>• The rates may vary between subgroups/patient populations</li> <li>• Applying aggregate analysis and review to research for products with multiple INDs could be problematic</li> <li>• There is a need for stringent rules to safeguard the negative consequence of using data from various ongoing studies in a program</li> <li>• To use all available data, internal and external, for SAC to evaluate the safety issues, may need warehousing of external data so that these external data could be combined with internal data to assess SAE rates</li> <li>• The guidance focuses on event rate, but if the event rates are not available for some types of treatment, one could consider target disease state rates or study population anticipated SAEs for cause</li> <li>• Trial size needs to be considered for pooled analysis. Most of the SAEs come from large outcome trials, and they can influence decisions for small trials</li> <li>• Complexities and challenges for aggregated analysis (different dose, formulation, therapeutic area, patient population, etc) need to be stated. Guidance should specify conditions where aggregate analysis should be performed</li> </ul>	<ul style="list-style-type: none"> <li>• If the sponsor's associates are also part of SAC, then the "independence" could be compromised, especially in smaller institutions</li> <li>• Could SAC be formed within a CRO supporting many trials for the sponsor, the independence could be hard to establish</li> <li>• Frequency of the SAC meeting may need further clarification, and guidance on when an ad hoc meeting is needed</li> <li>• For small and midsize companies or in rare diseases, could a "consultant safety expert" be recommended instead of SAC?</li> <li>• Lack of number of experts on an SAC, without conflict of interest of some sort (because of their potential involvement with sponsor or competitor studies as key opinion leaders), especially for rare diseases</li> <li>• Overlap of scope and responsibilities between DMC and SAC; given DMC's role, could the safety surveillance and SAC come under DMC's purview</li> <li>• How binding is the SAC's recommendation? If SAC's recommendation about SUSAR is not agreeable to the sponsor based on their evidence internally, what would the reconciliation process be?</li> <li>• Potential of unintended bias, invalidation of statistical analysis plan, conflict of interest, and compromise of trial integrity through unblinding</li> <li>• Acceptance of the notion of unblinding the patient when he/she withdraws from the study could also affect the integrity of the study</li> <li>• Unblinding smaller studies could be compromised by sharing treatment assignments for 1 or 2 patients.</li> <li>• Clarity is needed for the scope of SAC based on types of trials and development program</li> <li>• Clarification of the 15-day time limit to inform FDA is needed—the day the sponsor knew about the SAE, or the day SAC deliberated on the event and sent their recommendation to the sponsor</li> <li>• For early new molecular entity (NME), when the use of SAC for a trial could be delayed until initiation of other trials, to make room for aggregate analysis, sponsors should have a process for reporting to IND safety report without aggregate analysis</li> </ul>	<ul style="list-style-type: none"> <li>• Significant operational challenges, especially with resources, increase timelines for setting up SACs and funding, and for small and midsize companies.</li> <li>• Warehousing of external data and the setup where the internal trial data and the external data need to be pooled into a database for aggregate analysis could be cumbersome to do.</li> <li>• Concerns about redundancies of safety reviews, with internal safety management team as described by the the CIOMS working group report (2005<sup>7</sup>)</li> <li>• Robust internal processes are established in Big Pharma for safety monitoring, and external DMC to review safety. How does that change with the addition of SAC?</li> <li>• Lack of harmonization with other regulatory agencies on reporting SAEs</li> <li>• Concern about the practicality of unblinding on a periodic basis</li> </ul>

of the SAC. Although both committees do look at aggregate data, there are important differences in the operations of SACs and DMCs that should be considered if a single DMC/SAC is created. From an operational level, the SAC may be required to have frequent evaluation of events, as opposed to the quarterly schedule favored by many DMCS. Additionally, rapid evaluation and decisions must be made by SAC members as opposed to a more deliberative approach often used in DMCs. Finally, SAC members will likely need additional training to understand the reporting requirements and their implications.

### Configuration of the SAC

Like many other scientific committees, the SAC would be formed from experts in multiple disciplines. It should include at least one physician with a strong familiarity and experience in the therapeutic area of investigational target, other clinicians with general or specific (eg, cardiology, hepatology, neurology, oncology) safety experience if relevant, and other ad hoc members as necessary (eg, from the disciplines of epidemiology, clinical pharmacology, toxicology, chemistry, biostatistics). As recommended by the FDA guidance, any sponsor personnel evaluating the postmarket safety of a marketed drug should also be included in the committee for a marketed drug under investigation. Active study personnel blinded in a development program should not be included in the SAC to avoid unintentional bias in the ongoing trial(s).

Possible models for SACs include the following: (1) SAC could be formed within a sponsor's organization, (2) SACs with both sponsor representations and substantial external experts, or (3) a fully independent external group with access to information on many investigational drugs across multiple sponsors. As sponsors may be the best source of expertise for the drug in early development, sponsor membership may be the best pathway for early-stage SACs. If this is the case, sponsor members may be replaced by external experts as development progresses. Similarly, as the safety profile of the compound emerges, the character of the SAC may change. It would be important to have some members who participate for the duration of the SAC to maintain historical knowledge of the compound. However, the construct should be flexible to allow different therapeutic or safety expertise as needs arise throughout the development program. Independent groups that organize and manage committees such as DMCs for sponsors might be a natural place to house the responsibilities of SACs in consultation with the sponsors. These groups, skilled at forming groups that provide independent expert opinion, could form an SAC with safety experts as needed for specific safety issues to evaluate and vote individually and collectively for a particular SUSAR to be reported to the agency. Upon SAC decision, the recommendation can be passed on to the sponsor, who has the ultimate responsibility to comply by the FDA Safety Reporting requirement.

### Operations of the SAC

Implementing an SAC should be efficiently accomplished. As far as meeting format, the draft guidance is silent. In fact, the cost of actual 'meetings' might be entirely avoided as current technology allows for an entirely virtual SAC, analogous to what we have seen in Clinical Endpoint Committees/Endpoint Adjudication Committees. In these situations, committee members are notified immediately when there is a new case, they sign onto a secure Internet site, review the information, and cast their vote. When the members cannot reach decision according to a charter-mandated voting majority, there is a brief teleconference to achieve consensus. In supporting SACs, efficiencies can be gained by establishing data standards (eg, CDISC) from early development. This would substantially reduce costs of repeated and integrated aggregate safety reporting.

A major concern is the lack of harmonization, especially with European safety reporting regulations, and we agree this need to be explicit. That said, we are aware of sponsors who have negotiated a protocol-defined SAC process for safety surveillance in global trials with European sites. Although this is anecdotal evidence, it does demonstrate that the European Medicines Agency is willing to incorporate an SAC process in at least some circumstances.

Although some have expressed the feeling that an SAC would be an additional financial burden, this may not be the case. In fact, it is possible that the savings from reporting may exceed the cost of an SAC. (For example, if the Jarow<sup>4</sup> paper estimates are realized, reporting may decrease as much as 85%.) In addition, the increased quality of SAC analysis may well deliver additional value.

### Analytics Issues

To facilitate the collection and perform the aggregate analysis of the safety across various evidence and data from a variety of information sources within and between trials, within the treatment classes, the patient population, and the disease states, a comprehensive analytical strategy will be necessary.

### Establishing Expected Events and Incidence Rates

First and foremost, much of the scientific information about the potential safety issues and related events and their rates of occurrences in the appropriate population could be estimated from literature reviews and available safety databases. A systematic literature review should be initiated to consider available information on the disease, the treatment class the current investigational drug belongs to, and the disease population of interest. The systematic review across reported trials and epidemiology and registry studies should identify the following potential safety issues:

- Known consequences of the disease condition under investigation
- Anticipated events common in the study population that are unlikely to be related to the underlying disease or the intended treatment
- In addition to the systematic review, available registries and databases registering information on drug safety by the regulatory agencies and other for-profit organizations could be explored. A list of anticipated adverse events and their occurrence rates could also be obtained and/or maintained by the sponsor as part of their drug development plans.

All the information could be collated to develop a list of all possible known adverse events, serious adverse events due to the population in the study, the disease severity of the patients, and the treatment classes. In addition to the list, their expected rates based on literature and other sources could also be estimated against each of these events in the list.

Once the list of potential adverse events (common and rare) and their expected incidence rates (as estimated from literature or appropriate databases) are established, an analytical strategy could be developed in supporting the SAC with the quantitative assessment of the expected incidence ratio for these events of interest. Such an analytical strategy based on determining a “threshold” could be developed, with a rule that when the incidence rate for an adverse event exceeds the threshold, an SAC review could be automatically triggered. It is important to note that the incidence rates from studies of different durations vary; hence, exposure to drugs need to be accounted for. One way to address this is to consider incidence rates per thousand hours of exposure. This is quite standard in the drug safety domain and should be used instead of pure incidence rates unless the drug exposures and study durations within a drug development program of interest are similar.

### Methodologies for Evaluation of Adverse Event Thresholds

Simple statistical methods, that is, “probability of observing the adverse event” or a “risk of a particular adverse event to occur,” as described by Duke and colleagues<sup>8</sup> could be utilized to determine the expected number of cases in each of the control/placebo and treatment regimens, and determine if there is any evidence of seeing a higher incidence in the treatment group that could trigger a SAC review to determine the need for reporting to a regulatory agency. A decision rule of such procedures could be developed so that the SAC review could be triggered when the probability of such incidence or the risk of such an adverse event exceeds a predefined threshold.

For some adverse events, the “probability of observing the adverse event” could be calculated using the binomial probability of observing the observed number of events or more to occur. Depending on the risk tolerance, decided a priori, of

observing these events, the SAC could judge its relevance and recommend appropriate actions to the sponsor.

The risk-based method uses the incidence rates (IR) from the whole trial and calculates the 95% 2-sided confidence interval (CI) around the baseline IR. The incidence rate could be calculated based on the exact Poisson distribution of events, but in rare events, a binomial distribution could be utilized as an approximation. If the observed IR in the treatment group exceeds the upper 95% confidence limit of the baseline IR, there is sufficient evidence of the treatment group IR to likely be different from the control or baseline. The upper CI would then be considered the threshold above which the SAC will review from the medical perspective and decide on the reporting of the SUSARs.

For background incidence rates available from historical or epidemiological data, an additional analytical methodology could be to employ a Tolerance Interval approach<sup>9-12,14</sup> of the incidence rates (per thousand hours of exposure) of adverse event rates so that the upper tolerance limit could be considered as the upper bound of the expected incidence rates below which these events will be considered “expected within the tolerable limit.” If the incidence rates in the aggregated analysis at a program level are found to be higher than the upper tolerance bound for the particular (serious) adverse event, this should be noted and shared with the SAC evaluating the safety of the patients. In this situation, the upper tolerance limit will be the “threshold” that triggers the events to be sent to the SAC for further evaluation for its reporting to the regulatory agencies. These could be further explored from a methodological aspect in the future. Bayesian analysis<sup>13,14</sup> could also be used to estimate the posterior probability of the incidence rate, assuming an appropriate prior distribution of the incidence rate based on a Poisson (or Binomial) distribution of the event of interest. With this posterior probability of the rate, the expected number of events of interest could be estimated for a particular trial, or in aggregate for a program. If the observed rate in the current program is higher than the expected rate, as estimated by the posterior distribution, there will be sufficient reason for the SAC to weigh in and explore the plausibility of the treatment being the cause of the increased prevalence in the treatment group.

In addition, disproportionality analysis<sup>15</sup> may be used to analyze the FDA’s Adverse Events Reporting system (FAERS<sup>16</sup> database), in assessing the background rate for the ADRs, if such scope is defined in the SAC charter. Similar databases available using real-world postmarketing safety databases could also be used to ascertain these background rates for the populations and/or the disease areas and the treatment classes. EudraVigilance<sup>17</sup> from EMA, IMEDS<sup>18</sup> database modeled after FDA’s Sentinel initiative, and other databases could be a great resource for exploring background safety information that could be incorporated into the aggregate analysis for the SAC.

### Next Steps and Potential Implementation Strategies

Additional methodological research could be undertaken based on the approaches discussed above to help the SAC with a scientifically objective way to incorporate the available research and evidence through the literature, registries, and past studies, so that the SAC can medically assess the significance of the finding and the possible cause of the safety events. New methodological approaches could also be undertaken depending on the need of the SAC, the specific situation, and the appropriate questions related to the adverse events that the SAC would like to assess.

In a well-defined disease area with many treatment options available, it is possible to generate an extensive list of expected AEs and SAEs along with these threshold a priori appended to the list. This could help the SAC to review these listed adverse event rates during their regular meetings and provide guidance, based on their medical expertise, to the sponsor about any potential SUSARs. This master list will also be used by the SAC to rule out reporting an SAE if the AE of interest had been observed in aggregate for the program within the expected ranges of their incidence rate.

The AEs and SAEs not in the previously mentioned list will be considered “unexpected” by definition, and hence there is a significant chance of these being reported if the causality to treatment is suspected or considered plausible. It will be the SAC’s role to evaluate the occurrence of such unexpected SAEs in the program and explore the plausible causalities of such cases and their consistent occurrences across the studies, based on medical judgment.

In summary, analytical tools could be used to help an SAC trigger further scientific evaluation of AEs and SAEs for reporting to the regulatory agency. It is the SAC—with the medical knowhow of the members and their thorough discussions of scientific rationale—that will be able to identify whether or not the investigational drug will be suspected as a plausible cause of a particular unexpected serious adverse event that warrants reporting to the agency. In addition to the medical and clinical aspects of evaluating safety at the program level, there will be a great opportunity for biostatisticians to develop and implement such an analytical framework for analyzing aggregated safety data, incorporating evidence from ongoing and completed clinical trials from the sponsors, trials in the same disease area and/or treatment classes including competitor drugs, and epidemiology studies.

### Conclusions

The December 2015 Safety Assessment for IND Safety Reporting—Guidance for Industry makes a significant step forward by describing a process whereby the goals of the amended 21 CFR 312 safety reporting rule may well be realized. That said, there remains a considerable amount of work to be done prior to its widespread implementation. (Eg, the American Statistical Association’s Biopharmaceutical Section are currently

working on a consensus approach in evaluating the scope, suggested procedures, and guidance for implementing the draft FDA guidelines of 2015.) Given the feedback received by the authors as well as the public statements from other concerned stakeholders, we believe that the next draft of this guidance might benefit from addressing the following concerns:

1. Harmonization with global standards
2. Increased specificity with respect to analytical aspects of safety analysis of aggregate data
3. Clarification of which types of trials may not require SACs

We suggest that, in general, any rewrite of the guidance should allow for more flexibility in evaluating the safety given the preexisting internal safety monitoring processes, the quality of “baseline” data, and the availability of expertise. For instance, will it be reasonable to have a safety surveillance plan where an SAC is optional if the sponsor determines IND safety reports require significant analytics best handled by a team of experts? Should the DMC and SAC have clearly differentiated roles, scope, and responsibilities, or should they be combined with one revised role, scope, and responsibilities? Are there certain types of analysis done routinely in blinded fashion, and only under certain conditions, unblinded?

We agree with other stakeholders that the FDA should host a public meeting to discuss these issues further before implementing a revised recommendation on SACs. Since SACs are essentially a “noncompetitive” arena, we would suggest initiation of a 1-year pilot implementation with a formalized feedback process. The information gained from the pilot phase could inform finalization of the guidance. Finally, once the guidance is completed, it would be prudent to directly link it with the 2012 guidance “Safety Reporting Requirements for INDs and BA/BE Studies” and have one overall document for stakeholders.

Practically speaking, of course, no matter how thorough, no guidance can address every possible situation. Therefore, to ultimately meet the goal of rationalizing safety reporting, the clinical development and safety community have the responsibility to experiment and communicate best practices.

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