



# New FDA Guidance: Impact on Clinical Safety Data

**As the FDA continues to tighten legislation around suspected adverse events, it becomes more important than ever to stay fully up-to-date with all the obligations and requirements in order to know how best to deal with them**

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The FDA is not satisfied with the quality of data arising from clinical trials. They continue to complain about the quality of expedited drug safety reports, in particular. In a recent audit by FDA officials of 160 randomly selected, expedited safety reports submitted to the FDA's Office of Hematology and Oncology Products in 2015, only 22 (14%) were informative (1). They concluded that most investigational new drug (IND) cases are uninformative, or even fail to meet the Agency's criteria – and the number of them has not been reduced, in spite of a 2010 final rule and additional guidances issued by the FDA to clarify how adverse events are handled and reported.

The officials believe the “lack of international harmonisation for reporting rules, liability risks, and lack of clarity of threshold rules for aggregate reporting” act as hindrances, and have asked sponsors to tackle issues associated with over-reporting. They have not mentioned whether the views of their Good Clinical Practice (GCP) colleagues have been aligned, and whether the inspectorate (both pharmacovigilance and GCP) have been re-educated to change their inspection practice.

This makes the new guidance released by the FDA in December 2015 even more important (2). It reiterates many of the same principles from the previous guidance safety reporting requirements for INDs and bioavailability and bioequivalence (BA/BE) studies (3,4). As desired by the FDA, the guidelines help to differentiate between events which are, or are not, informative as single cases – and the appropriateness of reporting those events. In addition, it tackles perennially tricky topics, such as unblinded reporting to the FDA and investigators, the requirement for – and importance of – periodic review of accumulating data and the processes and components involved (which could be called signal detection), leading to reporting findings from aggregate analyses.

## Suspected Adverse Events

A new concept of the anticipated suspected adverse events (SAEs) – and how to prospectively identify them – has been introduced, and the FDA is the only ICH regulatory agency to mention such a notion. The FDA defines anticipated SAEs

as “events which do not warrant IND safety reporting as individual cases because it is not possible, based on a single case, to conclude that there is a reasonable possibility that the investigational drug caused the event. As a result, these events do not meet the definition of a suspected adverse reaction.”

Thus, anticipated SAEs occur with some frequency independent of investigational drug exposure, in the general patient population under study, in patients with the disease under study, or both. This means that at the time of protocol development, the sponsor should identify in the safety surveillance plan (and/or the protocol – although under GCP, we suggest both) the anticipated SAEs that it does not plan to report individually in an IND safety report, together with a plan for monitoring the events.

Examples of factors to consider when identifying anticipated SAEs include:

- Characteristics of the study population
- Natural progression of the disease
- Background event rates
- Background drug regimens
- Comorbid conditions
- Past experience with similar populations

This is not an exhaustive list, although identified, anticipated SAEs should be limited to those events for which individual occurrences are not interpretable, and for which an overall analysis is needed.

The FDA suggests that the principal aggregate analyses are pooled ones of SAEs from completed and ongoing trials consisting of datasets from among the following:

- Pre-specified, anticipated SAEs
- Previously recognised suspected adverse reactions
- Unexpected SAEs

The FDA recommends unblinded comparisons of event rates to a control and pooling across multiple studies under an IND

and across other INDs (who have the same sponsor) where this is appropriate (although not specified, presumably when there are comparable formulations and posology). Examination of individual studies is of high interest, and is now encouraged to determine consistency of findings across studies.

## Aggregate Analysis

An analysis of aggregate reports may require investigating if there are indications that the events were occurring more frequently in the drug treatment group than in a control group. So, as with individual cases, the concept of increased frequency as a criterion to expedite applies to aggregate data. The factors to consider in assessing whether there is a signal or not include:

- Size of the difference in frequency between test and control groups
- Consistent increase in multiple trials
- Preclinical evidence to support the finding
- Evidence of a dose response
- Plausible mechanism of action
- Known class effect
- Occurrence of other related adverse events

The FDA guidance discusses the role of the safety assessment committee (SAC) in supporting the sponsor with assessing aggregate analyses, the unblinding, determining policy reporting thresholds for IND safety reporting by expanding on identification of anticipated events, and monitoring implementation of a safety surveillance plan. Such a plan, along with an SAC, are concepts currently variably adopted by sponsors, although it looks like the FDA will now expect these as the norm.

## Further Implications

We strongly support the FDA's guidance, which is consistent with CIOMS VI – prompting sponsors to formulate a systematic process to identify, evaluate and minimise potential safety risks to subjects and patients during clinical trials. However, what impact will this have? After all, in September 2010, the FDA issued final regulations addressing the safety reporting requirements for IND applications, which was expected to improve the quality of safety reports submitted to the FDA (4). The actual reasons why sponsors have not embraced such good practice have not been examined. We have not seen any drivers for changing practice, such as incentives or praise during the approval process, or from inspectors.

Indeed, have the GCP inspectorate been briefed and advised on how their inspection practices should change? Because even if an SAE is anticipated, it can still appear as a risk to patients and will have to be managed accordingly. Conversely, how enforceable are these recommendations? Is there evidence that FDA approval has been delayed because of poor quality safety data? Where are other regulators, for example in the ICH regions, in supporting such good ideas? Of note, these latest recommendations do not

appear anywhere in suggested revisions to GCP in the Integrated Addendum to ICH E6 (R1). A concept such as 'anticipated SAE' should, ideally, be defined in the GCP glossary.

## Conclusion

Finally, the sponsor's pharmacovigilance unit can only do so much with the data they receive. They are completely dependent on the upstream clinical processes; thus, protocols, supporting documents and training materials will all need to be amended to reflect the new guidance with motivators in place to encourage clinical teams and sites to cooperate. Therefore, regulatory guidances – while well intended – require system-wide buy-in and implementation to assure any significant degree of success. There is only so much that can be achieved from the FDA issuing a guidance document. Organisations representing clinical trial sponsors should reach out and debate how the systems should change in the best interests of patients.

## References

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