

Attachment III

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment Proposed Guidance

General Comments:

J&J agrees with the FDA that it is not possible to detect all safety concerns during clinical trials. Post approval safety data collection and risk assessment is vital to ensure that patients are able to take our drugs safely, and we are pleased to see that the FDA supports that for most products routine pharmacovigilance is sufficient for postmarketing risk assessment.

One of our main concerns with this proposed guidance is that the document suggests that data mining methods be used. No estimates of sensitivity or specificity of such methods are offered. For example, there are no estimates of the frequency with which such methods generate false positives or of the cost of pursuing them. Because all resources are limited, choices must be made among the various strategies available for risk reduction. Thus, such estimates (specificity, cost of false positives) are necessary for forming a rational decision about the use of data mining methods.

The concept paper on this topic was somewhat vague about the FDA's expectations regarding the difference between a "signal" that represents an investigative lead or alert and a "signal" that may require a Pharmacovigilance Plan or other specific action on the part of the sponsor. The proposed guidance still does not actually define what a "signal" is. There is an implied definition of an excess of AEs associated with a product, but then there is a whole list of "safety signals that warrant further investigation" (lines 361-384 in text) which are potentially more substantial than just a simple excess of events. However, the one place in the proposed guidance where the term signal is defined is in the Data Mining section where it is stated "a signal is operationally defined as any product-event combination with a score exceeding the specified threshold". To further add to the confusion, the FDA appears to envision a sequence of "signal to potential safety risk to safety risk". Since we will be asked to do quite a bit of investigation based on "signals" it seems appropriate to have a clear definition stated and to use it consistently throughout the final guidance.

Since both the ICH E2E document and the FDA guidances are in draft, we urge the FDA to ensure that terminology is harmonized among these documents; for example, currently the Pharmacovigilance Plan in the FDA draft guidances and the one in the ICH E2E document appear to have different attributes.

The guidance refers to "observational studies", "Pharmacoepidemiologic Safety Studies", "registries" and "surveys" with no clear definition of what these are and the difference among them. While we understand that the focus is on a higher broader view, it does not provide adequate guidance on individual case reports from all these sources, how often the company needs to search for valid cases and when is a case valid. What is the sponsor obligation in these activities? It would also be helpful if the "observational study", "registry", and "survey" definitions/usage were consistent with EU use of the term (volume 9).

Indeed, to some degree, this document is so "general" regarding theory and caveats of performing pharmacovigilance, that it might be better to present it as a "Points to Consider" document and not as "guidance".

Specific Comments:

Lines 145-149

While ideally, specially trained safety clinicians would best perform follow-up, this recommendation has significant resource implications for industry and has been addressed in the comments to the "Tome".

Lines 157-159

What is the definition of "aggressive follow-up"?

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Lines 252-271

Although we agree that a series of cases may be evaluated regarding potential associations between an AE and drug exposure, there is no methodology that is reliable and reproducible for individual causality assessments. Therefore, we recommend that case level causality assessment should not be a requirement.

The proposed guidance includes the WHO terms for causality, yet does not recommend any specific categories for causality assessment. Since we do agree that causality assessments may be used for aggregate data, a recommendation from the FDA would be helpful in standardizing assessments.

Lines 316-317:

The sentence "Data mining is not the only technique used to make causal attributions between products and adverse events" should be deleted. Data mining is NOT a technique which can be used to make causal attributions, so such a sentence would be very misleading if it were to stay in the final guidance.

Lines 333-338

The various data mining methods are not compared. The document asserts that they yield similar results when the number of reported events exceeds 20. However the point of using data mining methods is early detection of signals, so performance differences among the various data mining methods on small numbers of reports may be critical.

Lines 347-349:

We were pleased to see that the FDA regards "signals" generated by data mining as hypothesis-generating only.

Line 375:

FDA seems to be inserting the idea of "potential" medication errors into this guidance document as a consideration of a "safety signal that may warrant further investigation". This is not an accepted term, nor is this the appropriate place to attempt to effect changes in existing regulatory standards.

Lines 388-416

The document appears to prefer risk (events per person exposed) to rate (events per person time exposed) as the measure of event frequencies. For many drugs, e.g. anti-hypertensives, benefits are proportional to person time exposed to the medication, not to persons using the medication, and for such medications, adverse event rate (rather than risk) appears to provide the preferable comparison to benefit.

Lines 425-431

In addition, the likelihood of observing an event unrelated to the medication (a baseline event) is more closely related to the person time of exposure than to the number of persons exposed, and data on person time exposed are more widely available and likely to be more reliable than data on people exposed, so again, rate appears to be the FDA's preferable measure. Finally this proposed guidance specifically suggests the use of rates rather than risks (later on in lines 696-702 and 825-826). Greater clarity on rates vs. risks would be helpful.

Lines 491-493

We suggest that the sentence should read "relative risk to exposed patients" instead of "relative risk of exposed patients".

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Lines 511-513

The advice to conduct multiple studies on the same question appears to ignore the issue of resource limitations.

Lines 553-556

Although all three of these guidance documents indicate that the protection of patient privacy is critical, no evidence is offered that there are real problems in this arena. The advice on the importance of confirming diagnoses suggests different and more permissive policies for access to patient data, e.g. access to medical charts, from the policies suggested by the advice that protection of patient privacy is critical. Thus, it would be useful to clarify the policy issues raised by the apparent tension between these two laudable objectives (privacy and complete data).

Lines 636-642

It would be helpful if the FDA would expand on what is meant by “further study”. To what extent is this a strong recommendation rather than a suggestion?

Also, can the FDA comment on using equivocal data from preclinical studies as weight of evidence?

Lines 644-646

This sentence should be rewritten. As written now, it says: “When a safety signal is identified that may represent a potential safety risk, the FDA recommends...” Our issue is that with *may* and *potential* and *risk* all strung together, one is so far from an actual event that there seems to be no minimum for the recommendation. Anything could qualify!

Lines 700-735

When implementing a Pharmacovigilance Plan, either initiated by the sponsor or at the request of the FDA, is it expected that Evaluation Plans and timeframes be in place at the start? If not, when should the sponsor address the Evaluation Plan with the FDA? And when should the evaluations occur? Annually? Bi-annually? How are the Pharmacovigilance Plans/RiskMAPs to be coordinated across divisions, especially when a marketed product is under evaluation in a second division?

Lines 739- 742

It is stated that pharmacovigilance plans may be appropriate for products which have “safety signals” identified pre- or post-approval. Again, the use of the term signal is confusing here and perhaps you mean to use the term “ safety risk” instead of “safety signal”.

Lines 756-761

Please include a definition of “active surveillance”.