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Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Dear Sirs:

This letter is to express my opinions regarding the recently released three concept papers on risk, i.e., docket no. 02N-0528, beginning with the concept paper on premarketing risk assessment.

Premarketing Risk Assessment

On page 7, lines 218-226, the document proposes a large series of biomarkers which could be studied during premarketing clinical trials. I would urge you to consider as well, however, whether those biomarkers are indeed valid predictors of post-marketing safety issues. For example, it is clear that marked QT prolongation is associated with an increased risk of cardiac arrhythmia. However, at what level of QT prolongation is a risk clinically important? Further, is what matters the average QT prolongation, or the number of people with extreme prolongation, or QT prolongation in the presence of pharmacokinetic inhibitors? All of this needs to be evaluated and considered before the studies are required.

On page 11, lines 414-417, you state that the development of clinical toxicity and the need for surgical intervention should be analyzed using a "time-to-event" analysis. Whether or not this is appropriate would depend on the setting. Certainly, if there is unequal follow-up in different patients, the proposal is correct. However, if the follow-up is the same for each patient, other than those who have these uncommon outcomes, then time-to-event analysis would be unnecessary, and even potentially misleading; it is evaluating whether an event occurs sooner in exposed patients vs. unexposed patients, while the real clinical question is whether it occurs more often.

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On page 12, where one is discussing data pooling, it would be useful to add a discussion about the importance of zeros. In other words, in a premarketing clinical trial, having zero outcomes is potentially an important indicator of drug safety. Yet, in the typical meta-analysis, such a study would contribute no useful information statistically. Methods are needed to be able to address this, so that studies with zero outcomes are not dropped out of such analyses.

On page 13, lines 484-489, the paper states that an appropriately pooled analysis would include subgroup analyses for patients conducted with different baseline or disease characteristics. While I strongly agree with this, it would be important to be clear that those subgroups need to be identified a priori. Otherwise, you risk sponsors performing fishing expeditions, looking for subgroups at greater benefit, and finding them purely by random error.

On page 13, lines 495-499, you propose that data pooling would be inappropriate if there is a diminished statistical association or risk obtained from the pooled result as opposed to one of the individual contributing clinical trials. This statement is unclear to me. If this is the case, why would one ever do the pooling, or believe the pooling? It seems like you are stating a pooled result can never contribute more information than one of the single studies being pooled.

Also on page 13, in lines 503-508, you state that pooled and subgroup analyses have the potential to provide a more reliable estimate of risk for important subgroups. However, the result wouldn't be more reliable if the sample size was smaller, assuming you are comparing the subgroup analyses to the larger overall analyses. I suspect you mean that subgroup analyses are more reliable if one does them within the context of pooled data. The wording here is unclear, however. Also, it is important, as above, to clarify that such subgroup analyses should be undertaken based on a priori hypotheses, rather than on post hoc analyses. Alternatively, if done without a priori hypotheses, then they are exploratory only and could not be used for labeling.

Post-marketing Risk Assessment

Moving on to the paper on risk assessment of observational data, overall, once again, I think this is excellent. I would increase the emphasis on measuring the incidence of and risk factors for drug-induced disease, including identifying those patients at high risk of suffering from these reactions, through analysis of statistical interactions.

More specifically, on page 5, lines 141-151, I would strongly encourage sponsors to mount such studies prophylactically so that answers can be obtained quickly from such data as questions arise.

On the top of page 6, where you talk about protocols, I would emphasize that protocols should be created for all studies to be considered epidemiologic studies, whether ad hoc studies or database studies, and indeed this would be one way of differentiating true scientific efforts from market seeding studies.

On page 6, lines 182-184, I would agree with the statement that validation of diagnostic findings in claims database studies is essential. I would add a qualification that this does not apply to medical records databases, where one is studying the actual medical record itself.

On page 7, lines 202-209, you appear to be suggesting that a protocol is not necessary for the use of registries. This concerns me, as it could leave the registry open to poor science and to manipulation. Indeed, simply from an IRB point of view, there should always be a protocol available, if this is truly research. Further, the protocol needs to be specific, whether the registry is collecting sequential subjects or simply a convenience sample, with the former being far, far preferable.

Also on page 7, lines 202-209, I have substantial concerns with plans to create and use registries without control groups. I've seen such data misused too often. The results of the registry are often impossible to interpret, absent a control group, and I would urge that the addition of a control group be recommended when possible.

On page 8, lines 230-235, once again you suggest that a written protocol is elective, in this case for a survey. If this is to be science, a protocol is mandatory before such a survey is undertaken. To do otherwise, leaves substantial room for manipulation.

On page 9, lines 276-286, you are obviously being very cautious about the use of reporting rates from spontaneous reporting data. I agree with this. I would add a further caveat that, given these rates "can by no means be considered incidence rates either for absolute or comparative purposes", one should not attempt to apply a large series of correction factors in order to try to make them into apparent incidence rates. The data simply do not warrant such and it tends to make the data look more quantitative and interpretable than they are.

On page 12, lines 411-412, you state that the development of a pharmacovigilance plan is useful. I certainly agree. I would go much further, and require them from now on.

Risk Management

Moving on to the concept paper on risk management programs, once again, this is excellent. However, on page 3, line 56, and in many other places, I would make clear that such plans should be required of all drugs. In some cases, the plan would simply be appropriate labeling and spontaneous reporting to be certain there are no unexpected problems. However, risk management plans should become a routine part of every drug approval.

Analogously, on page 5, lines 123-124, the wording suggests that the package insert is not part of a risk management plan. However, conceptually, it is a central part of every risk management plan.

In contrast, on page 7, section D, I find the conceptualization exactly correct. Level 1 risk management plans are those which include the package insert only. This is exactly the logic which should be applied throughout the document, but the document is inconsistent.

Personally, I would make minimum acceptable more than the current level 1, i.e., level 1 plus active screening for previously undetected problems.

On page 8, line 275, you state that risk management interventions have been variably effective. Clearly, this is true. In addition to the references showing they do not work, however, one might want to include references showing they do work, to some degree. For example, there's a cisapride paper published in Pharmacoepidemiology and Drug Safety indicating that such interventions did work, but only against the drugs that were specifically named in the label, as opposed to all of the drugs that were contraindicated, by name or by class.

On page 8, section A, I strongly agree that such risk management programs need evaluation. I would go somewhat further, and indicate that such evaluations must be scientifically rigorous and valid, including a protocol for evaluation. One way of documenting that would be to subject them to peer review. While the FDA cannot require they be published, that could be strongly encouraged.

Overall, I think this is a superb set of documents. I much appreciate the opportunity to comment on them, and I look forward to watching them continue to evolve.

Yours truly,

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Cc: Paul Seligman, M.D., M.P.H.
Victor Raczkowski, M.D., M.S.c.

BLS/mmo