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FDA Docket No. 02N-0528

Three Concept Papers entitled Premarketing Risk Assessment, Risk Management Programs, and Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

Dear Sir/Madam:

As a leader in the discovery, development, manufacture and marketing of prescription medicines, Johnson and Johnson pharmaceutical business and research organizations are committed to improving health and well being through innovative products and services. We share the Agency's goal of bringing safer and more effective drugs to the market as rapidly as possible. We embrace the importance of risk management, and are pleased to have the opportunity to comment on the FDA's Concept Papers of March 7, 2003, entitled, "Premarketing Risk Assessment, Risk Management Programs, and Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment." I am sending these comments on behalf of the Johnson and Johnson pharmaceutical business and research organizations.

We agree with the FDA that the ultimate goal of any risk management plan (RMP) is to ensure that efforts and costs involved in a RMP are expended on effective processes that achieve a positive benefit/risk balance for patients. With proper use, drugs can provide enormous benefit to patients and can reduce overall healthcare costs.

We have several broad comments to make about the overall risk management concept. This general feedback is found below. More specific comments as they pertain to each concept paper can be found in the subsequent *attachments*.

- It seems that several of the proposals within the concept papers have the potential to change the standard for approval of new drugs or new indications. It is our opinion that these concept papers are not the avenues by which to try to effect any changes in existing regulatory standards.

- Any assessment and decision about a RMP should be based on the benefits as well as the demonstrated risk profile of the drug product. We believe that risk management programs and attendant interventions should balance access by patients to needed drugs with the level of concern about risk.

- Specific concrete concern(s) about risk for a drug should drive any risk reduction activities and not theoretical risks. Decisions made concerning individual drug benefits and risks, and any resulting RMPs, must be based on adequate scientific evidence.

- Some of the strategies proposed have little evidence to support the assertion that utilizing them would result in safer drugs reaching the market compared to current standards. We believe that RMPs should utilize proven strategies.

- We are concerned that the FDA may attempt to require identification of all risks prior to approval. Such an approach may result in significant delays in drug development, and may ultimately be impossible.

- Collaboration between the FDA and industry on the development and approval of RMPs and pharmacovigilance plans is critical. However, there are a number of additional stakeholders who must collaborate, including academic institutions, healthcare providers, pharmacists, professional societies and patient groups.

In closing, we appreciate the opportunity to comment on this important new proposal and look forward to working with FDA to ensure the safe and effective use of all prescription drug products.

Sincerely,

Janice K. Bush, M.D.
Vice President, Safety Strategy and Liaison
Drug Safety and Surveillance

Attachments (3)

Pre-Marketing Risk Assessment Concept Paper

General:

Overall, this concept paper describes many possible safety assessments, which might be done during drug development. We request that the FDA provide as much specific guidance as possible concerning when certain studies may be requested.

The FDA has stated publicly that they will base decisions on data. We support that approach, but our concern is that increased amounts of data will be required prior to approval, which will result in delays in drug development and delays in getting needed medicines out to patients.

Specific Comments:

Lines 85 - 96:

The guidance on appropriate sizes of databases addresses the chronic use of products that are novel in mechanism or class but is silent on the well-characterized products. It should be made clear that these patient numbers may not apply to well-characterized products.

Lines 98 - 126:

The draft concept paper suggests the need for a larger database than recommended by ICH Guidelines. The language in this section includes conditional and ambiguous language that could be broadly applied in a highly subjective or arbitrary manner. We think that increasing the size of the database above the ICH requirement without specifically defining the concern or objective is not likely to significantly add to an assurance of patient safety.

Lines 128 – 136:

The concept paper refers to a situation where "a very safe alternative to the investigational product is already available". Please define "very safe alternative"; also please explain the criteria for such a determination. Also, please address the situation where the new drug has greater efficacy than the "safe" alternative. Also, how will the determination of the size of the larger database required be made, especially if there is not a specific safety issue being addressed? In addition, one proposal (line 136) that seems to have the potential for changing the standard of approval for new drugs will be a requirement for a larger database when there is the potential for rapid exposure to a large population. This seems to be a subjective criterion, and one which has not been a prior standard. How and when would this be defined? And how would such an assessment be communicated to and discussed with the sponsor?

Lines 143 - 157:

Long-term placebo-controlled safety studies could be problematic from a patient and operational standpoint (recruitment and drop-outs).

Lines 196 - 197:

While J & J supports the idea of using a diverse population in the clinical trials database, it is not clear that the suggestion in the concept paper is different from what is already practiced based on the current guidances. If this is a new suggestion, will it apply to small subgroups? It is not clear what is meant by "genetic diversity" and how will this be determined? How will it be determined which of the many diverse factors possible will be evaluated in an NDA database?

Lines 228 - 236:

While comparative clinical trials may provide interesting and useful information, it is not clear that they would allow accurate assessment of relative risk, and certainly not with regard to rare events. If such studies were undertaken, how would the information be used and communicated to physicians?

Lines 238 - 244:

For any products other than very similar/same class products, a comparable safety profile is difficult to establish. If there are differences in mechanism of action, formulations, efficacy parameters and other outcome measures, how will comparative safety data be utilized? And how will equally serious but different adverse events (e.g., neurological vs. cardiac side effects) be compared? It would be only appropriate to compare if one took the whole benefit risk balance into consideration.

Lines 253 - 309:

The recommendations in this section are broad and could result in a huge increase in study requirements for individual drugs. We suggest that requests for such studies be based on specific risks and clear areas of public health concern. In addition, it should be clear that such data would be critical to be able to make better decisions about patient safety.

There are always resources to consider when drug development programs are planned. The costs of any new requirements must be weighed carefully against potential benefits. If the recommendations increase the number or complexity of studies required, this could significantly increase the cost of drug development.

Lines 337-338:

J&J is concerned that the concept papers state that <u>all</u> drug development programs should include assessments for QTc prolongation, liver toxicity, drug-drug interactions, and polymorphic metabolism. It is not explained when preclinical studies or data could be appropriate. We recommend that there be a discussion about these potential issues, but that there not be an absolute requirement for such assessments.

Risk Management Programs Concept Paper

General Comments:

The FDA states in the concept paper that for most products, that risk management planning will be handled by the information contained in the PI. J&J agrees that an appropriate PI along with good post marketing surveillance should be, in essence, the Risk Management Program for the majority of drugs. We think that this is a key message of the concept paper and needs to be emphasized in the final guidance, since this major premise gets lost in the detailed discussions of tools and measurements.

Details should be provided about how the FDA plans to ensure that products in the same class with similar safety profiles meet RMP expectations in a uniform matter.

J&J believes that specific benefits and risks should drive the RMP and the tools used. Tools needed for individual products should depend on their specific benefits and risks, which will drive the goals and objectives of a RMP.

In the public workshop, it was suggested that the FDA include a complete review of all current and past RMPs so as to demonstrate the value of these overall programs as well as the individual tools used to achieve the objectives. J&J agrees that this should be done. This would also help in developing criteria for deciding when to implement an RMP, which is currently not clearly described. We believe this is important in order to provide an evidence-based rationale for this new initiative.

While J&J supports appropriate risk management activities, care must be taken not to overburden the healthcare system by using too many resource-intensive tools in RMPs. There are many stakeholders who may not be able to handle the increased burden of RMPs, especially if they are initiated on a routine basis. Too complex and administratively burdensome procedures may keep effective and appropriate medicines from reaching patients in need for whom the potential risks would be acceptable from a public health point of view and also accepted by the target patient population as reasonable in relation to their particular medical need.

There are several international/global initiatives ongoing in the risk management area (ICH E2E, CIOMS VI, EMEA strategy, Japanese EPPV). Standard nomenclature, definitions and consistent strategies should be agreed upon as much as possible.

Specific Comments:

Lines 49-50:

The document "proposes that the sponsor of every product submitted for approval consider how to minimize the risks from the product's use." It is not clear whether an acceptable RMP will now be prerequisite to a new drug approval. Please clarify, especially in light of our next comment.

Lines 120-122:

The "FDA anticipates that the decision to develop, submit, and implement an RMP will be on a case-by-case basis". J&J requests that the FDA develop specific criteria that delineate when it would be appropriate to institute a RMP.

Lines 244-260:

The rationale for categorizing RMPs into levels is not clear from the concept paper. J&J does not believe that this is a useful proposal: in fact, there are no objective criteria presented for selection of levels, nor is it clear what value using levels will add to patient protection. RMPs should be determined on a case-by-case basis and tailored to the drug and population to achieve a balance of reasonable risks given the magnitude of the expected benefits. Including the characterization of levels will be confusing to patients, since levels as presented are based on tool selection and do not include any regard to benefits the patient may receive. We suggest that using levels is not needed, since if it is made clear when a RMP is

needed beyond the PI/PMS, then the rest of the program should be determined on a case-by-case basis using specific risks to drive the selection of tools.

Lines 277- 278:

The concept paper states that the FDA is considering recommending that risk management tools be pretested prior to the implementation of the RMP. J&J requests that FDA clarify what degree of pretesting will be carried out and the process involved. J&J believes that it is important that expectations for pre-testing RMP elements for products that are already marketed be distinguished from those that have RMPs in place at the time of initial launch.

Lines 368-372:

The concept paper indicates that continuing reports of adverse events may signal a persistent problem and a decrease in reporting does not constitute assurance that a safety problem has been resolved. Such views seem to be biased against a potential use of the data for a RMP. It will be very important that goals are established with a shared view of what is realistically achievable and under what time frame. Any decision to require further interventions or reduce interventions requires a comprehensive assessment of all available information rather than focus on an isolated metric or a view of that metric only from the negative perspective.

Lines 428- 434:

The draft concept paper presents the concern that an extensive RMP for one product in a therapeutic class may unintentionally encourage the use of equally risky products that do not have an effective RMP. J&J agrees with this concern and suggests that more consideration should be given to the unintended consequences of the RMP. Patient safety will not have been served if patients are afraid to take a needed drug nor will patients' needs have been served if doctors do not want to prescribe a beneficial drug based on an onerous or inappropriately restrictive RMP.

Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

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.

Specific Comments:

Lines 30-38:

The concept paper introduces the FDA's description of a safety signal. Given the statements in lines 55-60, J&J suggests that the guideline define 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.

Lines 376-381:

When a "signal" is identified, the expectations of the FDA seem to include all of the following: synthesis of data, assessment of risk/benefit profile, additional investigations and risk management strategies. This approach does not seem to allow for a logical, sequential assessment of data and does not allow for judgment, which might determine that not all steps are necessary based on the actual assessment.

Lines 454:

FDA seems to be using the term "signal" instead of the more appropriate term "risk". An assessment of the signal is necessary before one should consider further action.

Lines 464-466

J&J supports development of best practices for improving the quality of spontaneous reports and for developing the methodologies for application of data mining techniques. It is our belief that data mining may be useful for "alerts" but not for confirming signals.

Lines 471-472:

If "registry" means registering every patient taking the drug, J&J suggests that it should be used as a last resort due to difficulty, burden to healthcare providers, privacy issues of patients, and expense. Please clarify under what circumstances a registry would be useful as a surveillance tool and when it would cease being useful. Also we would suggest evaluation of the effectiveness of simpler interventions such as patient alert cards and targeted patient education in addition to intensified health care provider targeted information.