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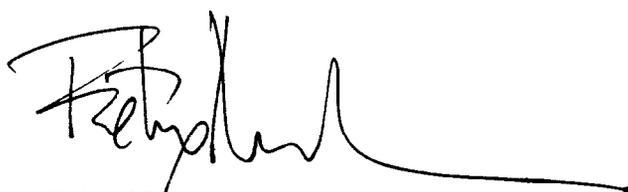
May 30, 2004

To Whom It May Concern:

Please find enclosed a document with comments on the draft "Risk Management Guidelines for industry". It contains both general comments and specific comments on the "premarketing risk assessment" (Docket number 2004D-0187).

Should you have any questions, please do not hesitate to contact me.

Sincerely,



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COMMENTS ON RISK MANAGEMENT GUIDELINES

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The following are comments on the “guidance for industry” documents entitled “Premarketing risk assessment”¹, “development and use of risk minimization plans”², and “good pharmacovigilance practices and pharmacoepidemiologic assessment”³. FDA distributed these guidelines for comments on May 5th 2004.

Risk Management Resources (RMR) commends FDA for undertaking such a demanding task and supports its efforts to provide guidelines on a field in development.

General Comments

RMR agrees with some of the changes made by FDA with respect to the previous version, such as removing the categories of products that needed risk management plans (RMP). We also support the terminology change from RMP to Risk Minimization Action Plan (Risk MAP, or RMAP). We appreciate the idea behind the use of the term “minimization,” conveying the principle of the impossibility of risk avoidance. On the other hand, risk minimization implies that reduction in risk might outweigh other factors that should be considered in the balance between risk reduction and its costs and benefits. Risk minimization is an appropriate goal conditional on a given level of cost and benefit, but otherwise it might be more appropriate to speak of risk reduction rather than risk minimization. For example, one can minimize risks from automobile injury only by avoiding all use of automobiles. Seat belts, air bags, and speed limits reduce risk, but clearly do not minimize risks. Thus, minimization of risks may not be as desirable as risk reduction, if minimization entails too great a cost or the foregoing of substantial benefit.

We believe that the guidelines also have room for improvement in some other ways, and we respectfully request the FDA to consider our suggestions. When FDA launched the Risk Management initiative in 1999, it did so because “...*The recent market withdrawals of terfenadine, astemizole, mebendazole, bromfenac, and cisapride resulted, in part, from the health care system’s inability to manage the known and preventable risks associated with these products.*”⁴ The six other drug withdrawals from 1999 to 2002 remind us of the “health care system inability” to achieve a perfect risk management system. Although we agree with FDA that only a few products may require RMAP, we take issue with the statement made that most products will not need a pharmacovigilance plan (PVP).

Pharmacovigilance Specification/Plan.

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One of the guidelines³ contains a section entitled: “Beyond routine pharmacovigilance: Developing a pharmacovigilance plan” (page 17, line 699). Both the title and the text under the section specify that the development of a PVP should only be entertained if “routine pharmacovigilance” is not sufficient. As described in this guideline, a PVP will be developed by the sponsor in order to detect new safety signals and/or evaluate already identified safety signals. The PVP will only be developed when unusual safety signals have been identified, either before or after approval.

We believe there is a contradiction between these guidelines and the draft ICH E2E⁵, which has recently been published in FDA’s website and “...when finalized, will represent current FDA thinking on this topic”. On section 1.3 (Scope) the latter document states: “For products for which no special concerns have arisen, routine pharmacovigilance activities might be considered adequate for the Pharmacovigilance Plan”. ICH E2E requires sponsors to summarize the identified risks of any drug, the potential for important unidentified risks, the populations potentially at risk and “situations” that have not been adequately studied in what is known as the PV specification”. The PVP (section 3 of ICH E2E) is then based on the PV specification and describes the risk minimization steps to be taken based on the findings described in the specification. This directive implies that a PVP will be built for any new product, although it may be that the actions considered in the PVP will be limited to routine pharmacovigilance.

RMR believes that public health will be better served if the FDA guidelines contained language similar to that contained in the ICH E2E guidelines. Our rationale is as follows:

1. Given the pressures to place products in the market, drug development traditionally focuses on efficacy data. Safety studies are only performed in order to fulfill the minimum requirements to ensure registration. As FDA states “benefit and risk information emerges continuously throughout the product’s lifecycle”² (page 4, line 128). Thus it makes sense to develop a document (the PVP) that will place together the knowledge accrued during the development, the gaps in this knowledge and a plan to actively seek additional information once the product is approved. No other regulatory document (e.g. the integrated safety summary and equivalents) fulfills this objective. The need to develop a pharmacovigilance specification plan or equivalent will ensure that the sponsor gives the matter adequate, independent thought.
2. This view that only a few products will need a PVP seems to be contradictory to the views expressed by FDA itself in the guidelines for premarketing risk assessment¹. On page 9; section C; line 320 the Agency acknowledges that even “well conducted clinical pharmacology programs

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do not guarantee a full understanding of all possible risks related to product interactions” and “...risk assessment programs should address a number of potential interactions...”. Since this concern is applicable to most products (the potential for unforeseen interactions always exists), the best way to detect these interactions is to look for them deliberately, based on a PVP.

3. It is an unfortunate reality that some manufacturers have seen pharmacovigilance activities more as a regulatory obligation than as a public-health responsibility. It may be unrealistic to assume that sponsors are voluntarily going to develop pharmacovigilance or risk management plans for new products.

Routine Pharmacovigilance

In the three guidelines open for comments there is a statement that industry already performs “routine” risk minimization activities and that these will be sufficient for most products. RMR believes that the word “routine” will be understood differently by different groups. In the case of sponsors, experience dictates that “routine” will often mean the minimal activities that are thought to be required to fulfill the obligations imposed by the Code of Federal Regulations. This is another instance where adhering to ICH E2E would be a better option, as these guidelines⁵ clarify what is considered “routine”:

- The presence of systems and processes that will ensure that information reported to the sponsor are collected and collated in an accessible manner.
- The preparation of expedited and periodic (PSUR) reports.
- A continuous monitoring of the safety profile of approved products, including signal detection, issue evaluation, update of labeling, and liaison with regulatory authorities.

Suggested Action(s)

RMR suggests that the FDA guidelines be modified as follows:

1. All new products in development have a PVP developed, as per ICH E2E. The action plan included in the PVP may be the routine pharmacovigilance activities described above. In some, rare, instances a PVP may be needed for products already in the market.
2. The guidelines should describe clearly what “routine” pharmacovigilance activities are. At a minimum, this description should include the following points:

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- The presence of systems and processes that will ensure that information reported to the sponsor is collected and collated in an accessible manner.
- The preparation of expedited and periodic (PSUR) reports.
- A continuous monitoring of the safety profile of approved products, including signal detection, issue evaluation, update of labeling, and liaison with regulatory authorities.

RMR suggests adding a fourth point to the “routine” activities, which would entail the conduct of “drug utilization” studies to determine the correlation between the use of the product after launch and the utilization patterns expected during development.

Comments on “Development and Use of Risk Minimization Plans”

1. Page 2. Section B. We agree with FDA’s concept that risk management includes both risk assessment and risk minimization. We believe that risk management should also include risk communication...
2. Page 4; section A; lines 121 onwards. We support FDA’s definition of safety and encourage the Agency to maintain it.
3. Page 4; section B; line 149. Although RMR believes the importance of the label should be highlighted, we suggest that calling it the “cornerstone” of risk management activities may be an overstatement. It was precisely the lack of adherence to label changes that led to several recent drug withdrawals. The label is not read by most healthcare professionals and sponsors’ policies on inclusion of adverse events in the labels are inconsistent. We support keeping the section that acknowledges the efforts to make labeling more effective, but suggest omitting the statement describing the label as a cornerstone.
4. Page 5; section C; lines 162 to 191. We support the concept of having two levels of objectives, a first level that represents the idealized goal, and a second level that represents a more realistic goal that can be expected to be achieved within an imperfect healthcare system. Nevertheless, the choice of terminology used to express these concepts is unclear, because “goal” and “objective” are synonymous terms (both defined as “the end towards which effort is directed”⁶). A second problem lies with the definition of the “realistic” goal. The example starting in line 175 does not represent “pragmatic, specific, and measurable objectives that can result in processes or behaviors leading to the achievement of the goals”, but

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- those processes or behaviors. The description of these processes seems to correspond more to that of *tools* used to achieve the goals.
5. Page 5; section D. The section on determining when a RMAP should be considered seems to leave the central decision about whether one is needed to the sponsor. As the development of RMAP may be seen as a burden by sponsors, it may be unrealistic for FDA to expect them to develop RMAPs on their own volition. This situation will be further aggravated if there is no recognized need for the development of a PVP (see above) and no further guidance. Even if the burden of the decision as to whether a RMAP is needed is left up to industry, RMR suggests that the FDA offer guidance, encouraging the preparation of a RMAP when:
 - a. The evidence from the pharmacovigilance specification document suggests a risk that is medically serious and susceptible to mitigation. These circumstances will include idiosyncratic reactions that may be mitigated or prevented by rapid intervention.
 - b. The RMAP will not offset the benefit offered by the product
 6. Page 14; section 4; pages 573 onwards. We suggest adding a statement on the use of simulation techniques in evaluating the RMAP before implementation. As testing a tool before implementation may be impossible or unethical, simulated cohorts may be assembled and the effects of different intervention estimated. This approach has the advantage that it will provide a benchmark for the evaluation of the RMAP itself, as the results of the intervention may be estimated.
 7. Page 20; Methodology section; line 816. We support the recommendation that analytical plans address the issues mentioned in the document. Nevertheless, the phrase “since RiskMAP evaluations will often rely upon observational data” implies that the observational nature of the study makes paying attention to these matters more relevant. Attention to the topics described in the document (with the exception of bias) is *equally* relevant whether a study is experimental or nonexperimental. We strongly support and encourage the Agency’s endorsement of the use of confidence intervals. The agency should also emphasize that confidence intervals should not be used as surrogate significance tests, merely to determine whether the null value falls within the interval. It is never appropriate to interpret a confidence interval in this way, but it is particularly egregious in safety evaluations, because it encourages the common misinterpretation that a “nonsignificant” result implies the absence of an effect.
 8. Page 20; line 838. The sentence “in some cases the sponsor may choose to propose modifications to the RiskMAP if the RiskMAP goals were not achieved” seems too “soft”. FDA already states (page 2 of the same guidelines; line 61) that “[risk management] should be continuous... with

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the results of the risk assessment informing the sponsor' decisions regarding risk minimization". It would be difficult to imagine a situation where the sponsor "may *not* choose" to modify the goals of a RiskMAP if its goals were not achieved. We suggest to amend the sentence to: "In general the sponsor will be expected to propose modifications to the RiskMAP if the RiskMAP goals were not achieved"

Comments on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

1. Page 4; line 121. RMR objects to FDA's description of pharmacovigilance "principally involving the identification and evaluation of safety signals in reports suggesting an excess, compared to what is expected, of adverse events associated with a product's use". Pharmacovigilance activities may result in the confirmation of the safety profile observed during development or in the characterization of a better safety profile than a comparator. These activities are as important as the detection of previously unknown signals. In addition it constraints pharmacovigilance activities to the post-marketing arena, which is in contradiction with FDA's own definition (lines 115 onwards). Should FDA decide to use a definition, RMR suggests using the following: *A discipline involving detection, evaluation and prevention of undesirable effects of medicines*⁷.
2. Page 4; line 125. We agree with the statement that even a single case report may constitute a signal. In fact a single case may constitute a "confirmed" signal. For example a single case report of gangrene following the erroneous intra-arterial injection of an intravenous drug may be sufficient to amend the label.
3. Page 7; line 243. The exclusion of individual cases due to the presence of known causes is not a valid procedure⁹.
4. Page 8; line 319. The description of data mining as being the product of comparing an observed and an expected "rate" may lead the reader to interpret them as true rates. In addition the example given seems to apply only for the proportional analysis ratio (PRR). RMR suggests avoiding references to this particular analysis for a two reasons. First, the PRR has certain weaknesses and disadvantages compared with the reporting odds ratio¹⁰. Second, it is simply one method of "data mining" and should not be highlighted over any other. If FDA decides to keep the reference to this particular methodology we propose to avoid referring to "rates" and suggest the following definition: "The proportional reporting ratio is the proportion of spontaneous reports for a given drug that are linked to a specific adverse outcome divided by the corresponding proportion for all or several other drugs"¹⁰.

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5. Page 10; line 412. Using either person-time or number of patients in the denominator has advantages and disadvantages and the appropriateness of each method may vary from case to case. We suggest FDA should not endorse a particular methodology and should simply request that the sponsor provide the rationale for the use of a particular estimate as denominator and describe in detail how it was estimated.
6. Page 12; line 476. FDA refers to epidemiologic studies initiated “prior to marketing” as performed “in rare occasions”. This statement may lead the reader to infer that FDA endorses performing these studies only rarely. RMR believes that both natural history of disease and estimation of “background rate” of adverse events are essential for properly assessing the safety of a product. We suggest that the FDA endorse such studies.
7. Page 13; line 509. FDA states that “Because of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results.” In fact, experiments are also subject to an array of biases that can lead to conflicting results among trials. We agree with FDA in suggesting that more than one study should be conducted, but we suggest omitting the above mentioned sentence.
8. Page 13; line 516. The citation of a particular reference (number 13 and 14 in the guidelines) describing methodologies for pharmacoepidemiological safety studies may suggest to the reader that FDA endorses this particular textbook. We believe that these citations are unnecessary and suggest avoiding them. On the other hand we support citing the guidelines from the International Society for Pharmacoepidemiology.

Comments on: “Guidance for industry. Premarketing risk assessment”

1. Page 7; “Considerations for developing a premarketing safety database”; line 236. RMR strongly endorses the recommendations made by FDA in this section. We think it can be made even stronger by adding a sentence emphasizing the need to conduct studies specifically designed to evaluate one or more safety endpoints. During traditional drug development, studies are designed with an emphasis on evaluating efficacy. Safety endpoints are frequently collected as a secondary objective. There are clear limits to how much drug development can predict the final safety profile of a product. Nevertheless, we think that pre-marketing studies should be designed with specific safety endpoints, in order to characterize the products’ safety profile as thoroughly as possible before marketing.
2. Page 7; line 253. We think the sentence: “Although these data can be informative, it may be preferable in some circumstances to develop

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controlled, long-term safety data”, may be changed to: “When the need for collection of long-term safety data arises, sponsors should ensure it comes from appropriately designed epidemiologic studies whenever feasible”.

We thank FDA for opening these guidelines to comment, and we hope that the Agency finds our comments useful.

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References

- ¹ Draft guidance for industry. Premarketing risk assessment. FDA; May 2004. <http://www.fda.gov/cder/guidance/5765dft.pdf>
- ² Draft guidance for industry. Development and use of risk minimization action plans. FDA; May 2004. <http://www.fda.gov/cder/guidance/5766dft.pdf>
- ³ Draft guidance for industry. Good pharmacovigilance and Pharmacoepidemiologic assessment. FDA; May 2004. <http://www.fda.gov/cder/guidance/5767dft.pdf>
- ⁴ Honig P, Phillips J, Woodcock J. How many deaths are due to medical errors? JAMA 2000;284:2187-2188.
- ⁵ ICH E2E: Pharmacovigilance Planning (PvP) Draft version 4.1 dated on 11th November 2003. <http://www.fda.gov/cder/guidance/6002dft.pdf>
- ⁶ Webster's Ninth New Collegiate Dictionary. Merriam-Webster, Springfield, MA. 1991
- ⁷ Begaud B. Dictionary of pharmacoepidemiology; Wiley, 2000: 109.
- ⁹ Rothman KJ, Ray W. Should cases with a 'known' cause of their disease be excluded from a study? Pharmacoepidemiology & Drug Safety 2002; 11: 11-14.
- ¹⁰ Rothman KJ, Lanes SE, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiology & Drug Safety 2004 (in press).