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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: **Novartis Comments on FDA Draft Guidance for Industry: Development and Use of Risk Minimization Action Plans**

Docket No. 2004D-0188

Dear Sir/Madame:

Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG (NYSE: NVS), a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group companies employ more than 78,000 people and operate in over 140 countries around the world.

Novartis Pharmaceuticals Corporation researches, develops, manufactures and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

Novartis and the FDA share a mutual interest in making safer and more effective products available to patients as rapidly as possible, as well as ensuring their appropriate use and minimizing the occurrence of preventable adverse events. As one of the world's largest pharmaceutical companies, Novartis commits extensive resources to developing drugs and bringing them to market. It is essential that FDA ensure that its policies and expectations regarding risk management are clear and transparent to all stakeholders, and that the standards are consistently applied. We appreciate the opportunity to provide comments on the draft guidance documents.

General Comments:

Novartis positively acknowledges that FDA has made significant effort in this draft Guidance to incorporate the public input it received on the corresponding concept paper. We are pleased to see that the FDA explicitly states in the proposed guidance that for most products, routine risk minimization measures are sufficient, and that only a few products are expected to have risks warranting a RiskMAP. We agree that for most products appropriate product labeling along with good post-marketing surveillance is sufficient. RiskMAPs should be used judiciously to minimize risks without interfering with delivery of benefits to patients.

We believe the draft Guidance appropriately emphasizes evidence based decision-making and the need for ongoing dialogue with the Agency throughout the development of a product.

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However, we are concerned that situations when FDA may recommend that a sponsor consider a RiskMAP based on the “Agency’s own interpretation of risk information” may not be applied consistently across products and Review divisions. It is essential that FDA monitor consistency across the Agency, to ensure that products in the same/similar class with similar safety profiles meet risk minimization expectations in a uniform manner. FDA should also ensure that safety issues are evaluated as consistently as possible across Divisions, as well as the decisions to require additional studies or a RiskMAP and the selection of appropriate tools.

As knowledge and experience is gained with risk management tools and, it is important that this knowledge be shared with industry to the extent possible. As part of the proposed RiskMAP website, Novartis would be interested in statistics on the numbers of RiskMAPs, as well as an analysis by the Agency of implemented plans and the tools used, including overall feasibility assessments, advantages, disadvantages, and limitations associated with various tools. We understand the necessity of preserving confidential sponsor information, but believe that such an analysis could be done and still retain appropriate confidentiality since a number of programs have been publicly discussed.

Although the draft guidance document stresses that RiskMAPs will only be required for serious issues and should be quite rare, it is not clear whether a voluntary activity would be considered an element of a RiskMAP. This knowledge is important because it can be anticipated that any drug with a RiskMAP will be perceived as “riskier” than those without one. Since many of the items listed as tools for targeted education and outreach have other uses besides risk minimization, such as a patient package insert, we would appreciate clarification regarding when their use would and would not constitute the deployment of a RiskMAP.

Furthermore, while we believe the Agency has described in specific terms the risk management information that should be submitted in those instances when a RiskMAP is needed, it has not adequately addressed the expectations of relevant content and format that should be included in marketing applications for the majority of drugs that do not warrant a RiskMAP,

Novartis also believes that FDA has not adequately discussed the circumstances and mechanisms by which it would be appropriate for a sponsor to scale back or discontinue elements of a RiskMAP (e.g., goal achieved, prescribing habits established, etc.). We do not believe that a sponsor must expect that once established, a RiskMAP will always have to be a component of the product’s conditions of marketing.

Finally, we believe that a global approach to pharmacovigilance and risk management is essential, and that as a partner to ICH, we strongly urge FDA to harmonize with international consensus initiatives on this topic, specifically ICH E2E.

Specific Comments

Section: II.B. Overview of the Risk Management Draft Guidance Documents

Line(s)	Comment
58-59	We suggest that the sentence be revised to read: “(2) developing and implementing tools to minimize its risks while preserving or enhancing benefits to all or a subset of the target population.”
76-77	With regard to the statement that the recommendations in this guidance focus on situations when a product may pose an unusual type or level of risk, we suggest that FDA clarify that the guidance applies only to those established risks, and not to hypothetical risks. For example, the recommendations should not be applicable for a product with limited safety information at the time of approval (i.e., it is unknown whether this product may pose an unusual level of risk). We also suggest that this

	sentence be revised to read: "... when a product may pose an unusual type or level of risk to all or a subset of the target population."
88-89	Reference is made to international harmonization efforts, specifically the draft ICH E2E guidance on Pharmacovigilance Planning, which was recently published for public comment. We encourage FDA to harmonize their proposals with the ICH document and suggest that the draft guidance for RiskMAPs and the draft Guidance for Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment reflect how these FDA guidance documents will correlate with the ICH E2E guidance.

Section: III. The Role of Risk Minimization and RiskMAPs in Risk Management

Line(s)	Comment
	Since section C introduces the concept of a Risk Management Action Plan (RiskMAP), we suggest that this information precede the information presented in section B.
108	We suggest that the first sentence in this paragraph be changed to: "...risk assessment, risk minimization, and/or benefit enhancement."
112-113	We suggest that this sentence be changed to: "...while preserving or enhancing its benefits to all or a subset of the target population."

Section: III.A. Relationship Between a Product's Benefits and Risks

Line(s)	Comment
128-138	We believe that the discussion of the benefit-risk tradeoff is heavily weighted toward the "population" at risk and insufficiently targeted to the individual. Many sub-groups and individuals may be willing to accept (trade off) more risk for either more or less benefit depending on personal preferences, disease, stage of disease and aggressiveness of the progression of the disease. Moreover, risk assessments and plans can be employed that permit use by individuals for a treatment where risk is higher than that for the total at risk population, thereby enabling informed treatment choices by patients and their physicians. We suggest that a statement to this effect be added to the guidance document.
132-133	With regard to the statement that risks and benefits are usually measured in different units, it should be mentioned that a number of methods that put benefits and risks of a drug product in the same context are under development (see additional comments related to lines 212-217).

Section: III.B. Determining an Appropriate Risk Minimization Approach

Line(s)	Comment
143-150	<p>The draft guidance directs major efforts towards continuous risk ascertainment, minimization and evaluation of a small number of therapeutic safety issues, since as noted in lines 150-151, for most products, routine risk management will be sufficient and a RiskMAP need not be considered. We appreciate the efforts to provide clear guidance on RiskMAPs, however, this provides little guidance for FDA approved professional labeling, the method that FDA "considers the cornerstone of risk management efforts for prescription drugs", and which will be the risk minimization tool for most therapeutic agents.</p> <p>In addition, Novartis requests that FDA make an explicit statement that labeling changes are set forth pursuant to regulation and that the Guidance in no way alters, changes, or supplements those regulations. Our concern is that in a litigation situation, language such as "risk concerns" is ambiguous and opens the door to charges by plaintiffs that a sponsor should have made labeling changes based on</p>

	"risk concerns". It is important to acknowledge that all "risks" are "concerns," but they do not necessarily form the basis for labeling changes.
151	If the order of sections B and C are not switched, the first use of the term RiskMAP should be defined.
158	Suggest this statement be relocated to follow the text on line 165 (see comment above regarding switching the order of sections B and C).

Section: III.C. Definition of Risk Minimization Action Plans (RiskMAP)

Line(s)	Comment
163	This sentence should be changed to read: "...while preserving or enhancing its benefit."
171-173	We suggest that FDA change the last sentence of the paragraph to read: "Although it might not be possible to ensure that absolutely no one on X drug receives Y drug, FDA believes that a <i>goal</i> , as the term implies, is a vision statement of the ideal outcome of the RiskMAP."
179-181	Novartis is concerned that the proposed objectives may blur the line between the role of pharmaceutical companies and the role of health care providers. While we support the role of pharmaceutical companies in attempting to minimize risk to patients as much as possible through communication and possibly other efforts, Novartis does not believe it is the companies' responsibility to "police" health care providers.

Section: III.D. Determining When a RiskMAP Should be Considered

Line(s)	Comment
193 (footnote 6)	This note mentions that a generic product "... may have the same or similar benefit-risk balance as the innovator...". With the possible exception of brand name confusion, by definition generic products should have an identical benefit-risk balance as the innovator. We request that FDA either clarify other situations where a generic would not be identical to the innovator product, or modify this statement accordingly.
212-217	The document suggests that "nature and rate of known risks versus benefits" be considered when trying to determine if development of a RiskMAP is desirable. The need to compare benefits to risks is obvious, although we agree with the FDA that such an assessment is a very complicated process. To minimize bias in how the risks are weighted in light of benefits and to help bring scientific rigor and consistent thinking into the FDA review process, we recommend that FDA consider models to assist in making such assessments in the future. At present, benefit/risk assessment is based predominantly on individual judgment, in part due to the fact that most models are not sophisticated enough to be useful or have not been validated. However, as new models evolve, we recommend that these be evaluated. We also suggest that a statement be added to line 212 that "known risks" are not to be inferred as a statement by the sponsor of its knowledge of a causal association.
224	We suggest adding a bullet point specifying that a generic product should have the same RiskMap as the innovator product. We question why a generic product would not automatically have the same requirement for a RiskMAP as innovator product, since they would have the same benefit/risk profile.
225-228	This section appears to be an obvious reference to the case represented by the Oxycontin experience. However, it seems arbitrary and out of place that a specific category such as Schedule II controlled substances has been singled out as an

	example of when a RiskMAP should <i>always</i> be considered. We propose this section be deleted or simplified as an additional bullet: “there is significant risk-associated abuse and product diversion.”
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Section: IV. Tools for Achieving RiskMAP Goals and Objectives

Line(s)	Comment
230	When discussing various tools for risk management it is important to keep in mind that there may be an opportunity to learn and share various experiences. We endorse Agency’s plans to make tools available and transparent, within the bounds of preserving sponsor confidentiality.

Section: IV.B. Categories of RiskMAP Tools

Line(s)	Comment
258-343	Novartis is pleased to see that FDA has replaced the concept of risk management plan levels with categorization of tools. We also agree with the concept that a selection of specific tools should not be used in an assessment of comparative safety to another drug product.
279	The health care practitioner letters referred to in this section as a targeted education and outreach tool could be construed as another name for “Dear Healthcare Practitioner” letters, which are governed by regulation. We request that the Guidance document contain explicit language about how this tool will be integrated with labeling and the limits to what a sponsor can communicate to a health care provider. We are concerned that charges of “misbranding” could result from communication that FDA deems outside its regulatory scheme.
286	We suggest addition of another bullet at the top of the page: “disease management programs, such as patient-provider interaction systems”
310-313	From a liability perspective, it is problematic for manufacturers to certify practitioners. We suggest that successfully completing Continuing Education may meet this objective. We also request clarification regarding the distinction between a certification program for practitioners (as a reminder system) and training programs for health care practitioners (as targeted education and outreach). Similarly, we request clarification regarding the distinction between special educational programs that reinforce appropriate product use (as a reminder system) and training programs for health care practitioners and patients or continuing education for health care practitioners (as targeted education and outreach).
320-321	The last bullet, “specialized systems or records that attest to safety measures having been satisfied (e.g., prescription stickers, physician attestation of capabilities)” appears to belong in the third category, Performance-linked Access Systems.
323-343	Performance linked access systems should not be burdensome for prescribers or sponsors. If not carefully planned they may have an opposite effect.
332-343	We suggest that the guidance also reflect the use of distribution or use restrictions under 21 CFR 314 Subpart H (Accelerated Approval of New Drugs for Serious or Life-threatening Illnesses).

Section: IV.C Description of RiskMAP Tools

Line(s)	Comment
345-354	Novartis endorses a FDA web site that summarizes contemporary experience with risk tools consistent with federal laws and regulations governing disclosure of

	information to the public. However, as mentioned previously in under General Comments, we believe that the web site should also contain statistics on RiskMAPs and FDA's analyses of previous plans and the tools used, including overall feasibility assessments, as well as the known advantages, disadvantages, and limitations associated with a given tool.
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Section: IV.D. Selecting and Developing the Best Tools

Line(s)	Comment
391	We suggest that this statement be revised to read: "compatible with current technology that is widely available".
406-407	The proposed guidance states that the design of the RiskMAP should seek to avoid unintended consequences of tool implementation that obstruct risk minimization and product benefit; however, it does not provide sufficient detail on how FDA will ensure that this does not occur. For example, the draft guidance does not address how FDA will address an inappropriately onerous RiskMAP which drives doctors and patients to use a riskier drug that does not have a RiskMAP.
409-421	We recommend that FDA add text to reflect that like FDA, pharmaceutical manufacturers cannot control the actions of prescribers, and should not interfere with medical or surgical practice. However, tools applied as part of RiskMAPs are intended to facilitate safe use of the product in accord with its labeling. We also recommend that FDA consider modifying this statement to indicate that health care practitioners are "...one of the most important managers of product risk", since for some products and events, patients may be the primary target for risk communication.

Section: V.A. Rationale for RiskMAP Evaluation

Line(s)	Comment
453 (footnote 9)	The author of the Clin Pharmacol Ther paper is BL Strom (not Nordstrom).
469-471	There is an apparent contradiction between the statement in lines 469-471 ("Statistical hypothesis testing would not typically be expected, given the limitations of the data likely to be available") and a later statement in lines 817-819 ("measurement errors, sensitivity, specificity, as well as power and confidence intervals where appropriate"). This later statement implies that the data will have more rigor than is generally expected. We request that FDA clarify this seeming contradiction.

Section: V.B. Considerations in Designing a RiskMAP Evaluation Plan

Line(s)	Comment
476-477	RiskMAP evaluation plans are "...designed to assess whether the RiskMAP's goals have been achieved through its objectives and tools." However, most goals will not be 100% achievable because of human fallibility and the FDA's acknowledged lack of jurisdiction over physician's prescribing or medical practice. This limitation should be acknowledged in the guidance document.
482-508	RiskMAPs should seek continuous improvement until an acceptable risk-benefit balance is maintained. Specific quantitative reporting goals are particularly problematic as are <i>a priori</i> thresholds for action. Refinements of a RiskMAP require an assessment of the quantity and quality of reports, nature and severity of events that occur after the interventions have had time to make an impact. The decision to add, modify or remove tools requires a comprehensive assessment of all available information rather than focus on an isolated metric.

486-488	If the final guidance retains the requirement for specific quantitative goals, it is imperative that the agency provides guidance on the criteria to be used for goal setting. It may not be realistic to specify a number or rate of a complication at time of initiation of RiskMAP. For example, if a drug is the first in the class and/or the background rate of the adverse event of interest has not been studied, especially within the RiskMAP environment, it would be difficult to define the threshold.
488	We suggest that this sentence be changed to: "...than a specified number or rate of that complication, or improving the outcome of the adverse event."
488-508	<p>The draft guidance document states that if health outcomes cannot be practically or accurately measured, closely related measures can be used. We question how often health outcomes can be practically or accurately measured and at what cost. In addition, it should be acknowledged that it might take a significant time for enough data to become available to prove that rates of an event have gone down and by how much. Novartis would appreciate additional discussion in the Guidance document on the decision-making process for selecting to monitor an actual patient outcome versus a closely related measure.</p> <p>On line 493, we suggest that "pregnancy tests for pregnancy status" be deleted as an example of a surrogate health outcome measure, as pregnancy tests are often used to rule out pregnancy, not only to confirm it.</p> <p>On line 505, FDA refers to "complete ascertainment of pregnancies" as an example of a validity measure. We suggest the word "complete" be deleted since 100% ascertainment is an unrealizable real-world objective.</p>
516-518	Spontaneous AE data are described as "potentially" biased outcome measures. We suggest that this be corrected to say that spontaneous report data are "inherently biased outcome measures..."
522-530	This section appears to suggest that claims databases do not include patients of lower socioeconomic status. However, Medicaid claims databases have data on medical care to some categories of economically disadvantaged and disabled persons. In addition, because of the infrastructure of the European health care system, many European pharmacoepidemiologic databases include a sample of all patient groups, irrespective of socioeconomic status.
568-571	The proposed guidance discusses the potential for an evaluation of a RiskMAP to allow the opportunity to discontinue a tool if the individual tool is performing poorly. While poorly performing tools should be discontinued, we would also like to see the acknowledgment that it might be appropriate to discontinue a tool if it proved to be successful and therefore was no longer needed, or if there were another redundant tool which superseded the need for the tool.
590	We request clarification regarding the tools for which sponsors would be expected to perform pre-testing in a clinical trial setting. Including testing of tools in clinical trials would add a layer of complexity to both the performance and analysis of the trials and could possibly lead to an increase in sample size to assure adequate population of analytical cells.

Section: V.C. FDA Assessment of RiskMAP Evaluation Results

Line(s)	Comment
611-613	We believe that FDA should share the results of its assessment of the RiskMAP effectiveness with the sponsor and discuss any differences of interpretation (reference line 652).

Section: VI. Communicating with FDA Regarding RiskMAP Development and Design Issues

Line(s)	Comment
645-646	To initiate a dialog with FDA regarding the Agency's experience with previously implemented RiskMAPs, it would seem logical for a sponsor to also be able to contact the Office of Drug Safety, as they would have experience with a broader range of products and RiskMAPs than a single review division. We suggest revising the end of this sentence to read: "...contact the product's review division for product-specific risk management issues or the Office of Drug Safety for information on FDA's general experience with risk management tools".
666-670	Please clarify whether a pre-approval RiskMAP should be submitted to both the IND and the pending NDA/BLA, or to only one of these files. In addition, FDA recommends that RiskMAPs proposed post-marketing should be submitted as a supplement to the NDA or BLA. The Guidance should specify how or if user fees will apply to submission of these applications.

Section: VII.A. Contents of a RiskMAP Submission to FDA

Line(s)	Comment
679	In this section, we agree with the Agency's emphasis on what should be submitted to FDA in those instances when a RiskMAP is needed. However, as noted in our general comments above, we feel that the Agency should also address its expectations pertinent to the content/format issues related to risk management information to be included in marketing applications for the majority of drugs that do not warrant a RiskMAP.
728-730	It is unclear what success or failure experiences should be discussed here (e.g., for the specific product under discussion or for all RiskMap experience).
747-751	We request clarification regarding the type of evidence that should be provided. There are very few examples in the public literature of successes for any tools, and most, if not all, information has already been included in the guidance document. If the tools are recommended in the guidance, what other evidence needs to be provided?
770-773	This bullet should add language to clarify that RiskMAP modification can be in either direction; new tools can be added, but tools can also be removed, or the RiskMAP terminated altogether.
779	We recommend that the Agency reconsider expecting milestones and written progress reports for all RiskMAPs. Instead, constructive dialog and information exchange between FDA and the sponsor should be based on the circumstances of the particular product.
783-784	If the requirement for written progress reports is retained in the final guidance document, requiring these as part of the actual Periodic Safety Report or traditional Periodic Report adds an additional burden to a process already under significant time constraints. We propose that the sentence be changed to read: "FDA recommends progress reports be included in the Periodic Safety Reports (PSURs) or traditional Periodic Reports, or submitted at the same time as the sponsor submits these reports."

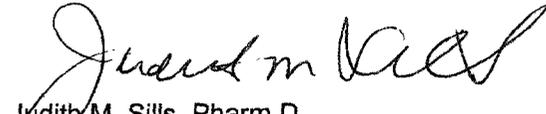
Section: VII.B. Contents of a RiskMAP Progress Report

Line(s)	Comment
817-818	We request that FDA clarify what measurement errors, sensitivity, etc. are being referred to in this paragraph.
838-839	The proposed guidance states that a sponsor might choose to propose modifications to the RiskMAP "if the RiskMAP goals were not achieved". As indicated in our comments regarding lines 770-773, we believe that modifications to

	RiskMAPs can and should occur in both directions. We would like to see some discussion about when it might be possible to modify a RiskMAP if the goals WERE achieved. In other words, will a RiskMAP be a never-ending activity or will there be the potential for modification based on success?
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If you have any questions regarding this document, please contact Dr. Judith Sills at (862) 778-2472.

Sincerely,



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Head, Global Safety Intelligence