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European Commission
Health and Consumers Directorate-General

E-mail: sanco-pharmaceuticals@ec.europa.eu

Brussels, August 30, 2010

Re : Draft Guideline on the collection, verification and presentation of adverse reaction reports arising from clinical trials

Dear Madam, Sir,

Merck & Co., Inc is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today.

Merck has reviewed the above referenced document and is providing the following comments for your consideration. Merck welcomes guidance from the European Commission.

Merck supports the initiative to update the guidance towards clarification and simplification of the existing detailed guidance.
We do note however that the degree of cross reference introduced in this version makes it hard to follow, and would recommend that full explanations and/or definitions are provided wherever possible.

On a more specific note, we have two main concerns, more detail being in sections below:

1. That periodic reporting of SUSARs to Ethics Committees by the sponsor has been deleted, with all SUSARs now required to be expedited. This would seem to be a retrograde step as ECs themselves have been requesting sponsors to report foreign SUSARs periodically.
2. A new requirement for Investigators to assess 'expectedness' (currently performed by the sponsor) has been introduced. This will place a new and onerous workload on both Investigators and Sponsors and require extensive system changes for no apparent gain.

We appreciate the opportunity to comment on this document and hope that you will take our comments into consideration.

Should you need additional information or wish to hold further discussions with our company experts, do not hesitate to contact me.

Yours sincerely,

A. Joos

Angelika Joos
Encl.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

August 30, 2010

Submission of comments on **Draft Guideline on the collection, verification and presentation of adverse reaction reports arising from clinical trials** (sanco.ddg1.c.8(2010)384118)

Comments from:

Name of organisation or individual
Merck Sharp & Dohme (Europe), Inc.

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Merck supports the initiative to update the guidance towards clarification and simplification of the existing detailed guidance. We do note however that the degree of cross reference introduced in this version makes it hard to follow, and would recommend that full explanations and/or definitions are provided wherever possible. On a more specific note, we have two main concerns, more detail being in sections below: 1. That periodic reporting of SUSARs to Ethics Committees by the sponsor has been deleted, with all SUSARs now required to be expedited. This would seem to be a retrograde step as ECs themselves have been requesting sponsors to report foreign SUSARs periodically. 2. A new requirement for Investigators to assess 'expectedness' (currently performed by the sponsor) has been introduced. This will place a new and onerous workload on both Investigators and Sponsors and require extensive system changes for no apparent gain.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Page 5 Section 2.3.2		Adding protocol guidance to the IB is counter to the CIOMS III wherein the IB should really be the start of the DCSI. Proposed change (if any): Suggest aligning with CIOMSIII / DCSI proposals	
Page 5 Section 4.2.1 (28) and page 8 Section 4.5 (48)		Defines what is NOT a SUSAR, but does not give any guidance on how to report such non-SUSARs. Proposed change (if any): Suggest inclusion somewhere in Guidance (even if only reference to applicable section of V9A)	
Page 7 Section 4.3.3 (45)		It is accepted that a sponsor should take into consideration an investigators assessment of expectedness if provided, but requiring them to do this as a routine will mean extensive changes to company databases and systems, ~~that~~ Investigators will need extensive training, and ensuring compliance will be difficult. In addition, and perhaps even more important, the sponsor is far better placed to assess expectedness from the regulatory (vs. expectedness in that patient, that disease area etc.) perspective than Investigators. Proposed change (if any): Delete paragraph (45) as the expected benefit is not evident	
Page 7 Section 4.4 (46)		2nd sub-bullet: This section does not encapsulate the complexity of business development agreements, i.e. 'SUSARs to be reported from trials performed by ...sponsored by	~~sponsored by another sponsor who is either part of the same mother company or who holds a development agreement with~~

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		another sponsor who is either part of the same mother company or who holds a development agreement with the sponsor' Proposed change (if any): Suggest adding ***'or as stipulated in a safety data exchange agreement***'	~~the sponsor,~~ ***~~as stipulated in a safety data exchange agreement.~~***
Page 8 Section 4.5 (48)		2nd bullet: The current wording is somewhat confusing as it is not completely clear whether and/or when there is no need to report literature trials from another sponsor.	
Page 11 Section 4.7.2.2 (70):		Birth-dates assist with the critical activity of duplication detection. It is therefore advisable to maintain the need to send a correction when sponsor becomes aware of an error.	
Page 11 Section 4.7.3.2 (75)		Whilst understanding that until Eudravigilance is considered fully validated by the Member States there will need to be interim arrangements, the proposal to give choices of routes (per sponsor and per CA) will cause confusion. In addition, this raises the probability of duplication in that, if sent directly to EV by the sponsor, ICSRs could also be submitted by a CA which chose indirect reporting.	
Page 12 Section 4.7.3.2 (76)		Whilst appreciating that some sponsors may not have the resources or experience for direct reporting, we are concerned that, despite the fact that final accountability will always reside with the sponsor, business partners which assume SUSAR reporting from academic collaborators could become exposed from a compliance perspective. Proposed change (if any):	

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Page 14 Section 4.11.1 (95):		Modify this section such that delegation can occur if offered by the commercial partner, documented in an agreement between the sponsor and business partner and on the understanding that compliance with reporting requirements will remain with the sponsor. No mention of how end-point studies occurring outside the EEA only, but where there are studies ongoing in the EEA with same IMP should be handled re: waivers (as no EEA approval process in which to discuss with CA). Proposed change (if any): This needs to be clarified within the guidance	
Page 14 Section 4.11.1 (95)		The provision that "for trials in high morbidity or high mortality disease, where efficacy endpoints could also be SUSAR….." unblinding should not be systematic is very much welcomed. ~~as w~~We would like to share that in the current process these agreements cause many misunderstandings. We therefore propose that Under these and similar circumstances, it may be appropriate to reach agreement in the authorisation process which serious events that would be treated as disease-related and not subject to systematic unblinding and expedited reporting. ***The agreement should be part of the CA approval process and be obtained within the given timelines or through a substantial modification within 35 calendar days.***~~to further support this provision by adding the following procedural recommendation: "The agreement should be part of the CA approval process and be obtained within the given timelines or~~	~~Under these and similar circumstances, it may be appropriate to reach agreement in the authorisation process which serious events that would be treated as disease-related and not subject to systematic unblinding and expedited reporting.~~ ~~***The agreement should be part of the CA approval process and be obtained within the given timelines or through a substantial modification within 35 calendar days.***~~

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	**Outcome** *(To be completed by the Agency)*
		~~through a substantial modification within 35 calendar days.~~"	

Please add more rows if needed.