31 Aug 2016

Submission of comments on 'Summary of Clinical Trial Results for Laypersons'

Comments from:

Name of organisation or individual
Amgen, 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)*

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)*
Lines 50-52		**Comments:** The template recommendations may result in a lay summary that is longer than optimal for understanding by audiences with low health literacy. Provide a statement that it is not mandatory to include content recommended in the template but not specifically required by regulation. **Proposed change (if any):** Add a sentence: "**Suggested content not specifically required by the regulation is recommended but not mandatory.**"	
Lines 88-94 (a)		**Comments:** It says that the summary should be aimed at IALS/OECD literacy "level 2-3". There is no such level, only "level 2" and "level 3". In practice, does this mean that authors should strive for level 2? Does it mean that the text if subjected to readability testing is understood by a majority of level 2 readers and a majority of level 3 readers? In addition, it would be helpful, if possible, to equate the target reading level to a chronological age (eg, 9 years of age, 12 years of age…). **Proposed change (if any):**	
Annex 1 Preface		**Comments:** It is counterproductive that a document whose entire purpose	

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		is to communicate to a lay audience, using simple language, be organized around headings pulled verbatim from text of a Regulation. The document should be structured, and headings written, in a way that is optimal for communication to the lay audience. This aspect should be at the sponsor's discretion. **Proposed change (if any):** "~~**It should be noted that the wording of the ten elements cannot be changed.**~~"	
Annex 1 Section 4.2		**Comments:** A breakdown of age and gender in EU vs non-EU countries is not very scientifically informative, not required by the regulation, and will make the document longer and less accessible to the reader. Recommend to provide only the breakdown for the overall trial population. Also, please clarify whether summary statistics for age, eg range, are sufficient? **Proposed change (if any):** "Provide ~~**basic breakdown of participants by**~~ age **range** and **gender breakdown**~~**in the EU (and non-EU if the studies includes countries outside of the EU).**~~"	
Annex 1 Section 6 (a)		**Comments:** The determination of adverse reactions for a medicinal product is normally not made on the basis of results of a single trial,	

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		particularly trials that are small and/or uncontrolled. Summaries of "adverse reactions" within a single trial will therefore have limited validity in many cases. Without defined objective criteria for sponsors to follow, lay summaries may be perceived as misleading or selective in their results reporting. **Proposed change (if any):** Recommend to outline one or more unambiguous options for reporting, eg, present AEs reported by the investigator as treatment related and with a frequency > 5%, and SAEs reported by the investigator as treatment related and with a frequency > 1%....or other criteria that can be objectively applied within the framework of a single trial.	
Annex 1 Section 6 (b)		**Comments:** There is inconsistency within this section about whether the list of adverse reactions is to be comprehensive (eg, "The most serious adverse reactions need to be listed first, followed by *all other* side effects") or selective (eg, "List *the most serious and/or most prevalent* adverse reactions for each study drug(s) tested"). A comprehensive list may be extremely long, which would be detrimental to understanding for a lay audience. It is also unclear whether events not related to the investigational product are to be reported in this section. (The section heading, "Adverse reactions," indicates a causal	

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		relationship to the drug, yet there is a statement that "*deaths*" and "*any adverse events* which have led to … the withdrawal of patients" are to be reported, which may include both related and unrelated events.) Please make the section internally consistent and consistent with the heading. **Proposed change (if any):** "The most serious adverse reactions need to be listed first, followed by ~~**all**~~ other side effects listed by frequency (starting with the most frequent) and not repeating the most serious side effects listed above. The number of serious adverse reactions and ~~**deaths**~~**fatal adverse reactions** should be clearly stated together with any adverse ~~**events**~~ **reactions** which have led to the early closure of the trial or the withdrawal of patients... ~~**Where deaths and adverse reactions may be attributable to the treatment rather than the condition, this needs to be made clear.**~~"	
Annex 1 Section 7 (a)		**Comments:** Sponsors should be permitted to report results for only the primary and key secondary endpoint(s) prespecified in the statistical analysis plan. Studies that measure "Patient relevant secondary endpoints" and "Key patient reported outcome measure" are not necessarily powered or designed to test the significance of a treatment effect on these endpoints, and instruments may not be validated. Results reported in	

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		this context may be difficult for a lay audience to interpret. (eg, if small effects were seen but their significance was not assessed, what conclusion can the public take away? We are making the document longer without communicating anything useful to patients). Asking the sponsor to select which results are interesting or relevant to patients may also raise a perception that presentation of results is biased, misleading, or promotional. **Proposed change (if any):** "This section should describe each of the study arms including the name of the drug (generic only) as well as the outcomes (both positive and negative), using text and graphics where appropriate, including: • Information on whether the study completed as planned, or was stopped and for what reason. • The primary endpoint(s) and results by study arm • **Prespecified key secondary endpoint(s) and results by study arm (if applicable).** **Where prespecified by the statistical analysis plan as a primary or key secondary endpoint, these results should include:** • Patient relevant secondary endpoints and results by study arm • Key patient reported outcome measures (PROMS) or other quality of life indicators of interest to patients (Any scales	

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		used for measurement should be explained). Dealing with multiple endpoints: ~~**If there are only a small number of end points (both primary and secondary), they should all be reported. Sponsors should include patient relevant secondary endpoints as some of the quality of life measures and PROMs are likely to be of interest to patients.**~~ • In some cases it might be possible to summarise closely-related endpoints jointly. • Sponsors may wish to point out that a complete list of outcomes based on all endpoints is available in the technical results summary for each clinical trial is available on the website."	
Annex 1 Section 7 (b)		**Comments:** Please add guidance as to how numerical differences vs statistically significant differences are to be reflected in lay language. For example, the statement, "This means that more patients in Group B had tumours that shrunk."—should this be reserved only for cases where statistical testing demonstrated a significant between-arm difference? We recommend that if numerical differences were seen but significance was not reached or was not assessed, this be explained to the reader. **Proposed change (if any):**	

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		"This section should describe each of the study arms including the name of the drug (generic only) as well as the outcomes (both positive and negative), using text and graphics where appropriate.~~**, including:**~~ **Where statistical testing was performed, indicate whether results were statistically significant, using lay language. Where statistical testing was not performed, state this in lay language.** **Example text:** **"Statistical testing showed this difference [*was unlikely to have been*] OR [*could have been*] due to chance alone"** **"Researchers did not test whether the difference between Group A and Group B could have been due to chance alone"** "	
Annex 1 Section 8 (a)		**Comments:** "[Include the state of result analyses (including dates of intermediate analysis date, interim/final analysis stage, global end of trial date – describe as appropriate)]."—Our assumption from the Regulation is that the lay summary to be submitted to the database at end of trial should reflect final (end of trial) results. If this is not always the case, this needs to be clarified earlier in the guidance. **Proposed change (if any):**	
Annex 1		**Comments:**	

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Section 8 (b)		For many trials, subgroup analyses will not have been done and may not be valid. In some therapeutic areas, rarely is a trial large enough to perform the statistical testing for the proposed subpopulations. Furthermore, for fair balance it would be important to provide results for both safety and efficacy endpoints, which will be a lengthy endeavor. Recommend to remove the suggestion to provide subgroup results in this section. **Proposed change (if any):** "~~**Describe if there were any significant differences between sub-groups; in particular by age, gender and ethnicity where the sample size is sufficient to show statistical differences. The Drug Trials Snapshots produced by the FDA provide a useful model for this, for example:**~~"	

Please add more rows if needed.