Alan L. Bess, M.D.
Vice President
Clinical Safety & Epidemiology

Novartis Pharmaceuticals Corp.
One Health Plaza
East Hanover NJ 07936

Tel 862-778-5555
Fax 973-781-8477

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Dockets Management Branch
Food & Drug Administration
5630 Fishers Lane HFA-305
Rockville, MD 20857

Submission to Docket No. 96-0041
International Conference on Harmonisation: Draft Guidance on Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

Dear Sir or Madam:

In response to the revision of Docket No. 96-9004 (published in the Federal Register, 31 December 2002, 67(251); 79939-40), Novartis Pharmaceuticals Corporation hereby submits formal comments on the proposed guidance.

Thank you for the opportunity to provide input.

Sincerely,

Alan L. Bess, M.D.
Vice President
Clinical Safety & Epidemiology
Novartis Pharmaceuticals Corporation

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Comments on Addendum to ICH E2C

Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

Cover page. States "Released for consultation at **step 2** of the ICH process on 12 September 2002". The European Agency for the Evaluation of Medicinal Products (EMEA) released a **step 3** document with the same contents on 19 September 2002. The discrepancy is not clear.

1. Introduction, 2nd paragraph, last sentence: "In addition to covering usual safety issues, the PSUR also includes ...etc" may require further clarification as "urgent safety issues and major detection/evaluation" belong by definition in a PSUR, whereas "changes in efficacy which have been or will be addressed in other documents" normally do not belong in a PSUR (unless they qualify for inclusion in Chapter 8.: Lack of efficacy).

1.4 General Principles: Preceding subchapters appear to be missing (chapter 1.2, 1.3).

1.4.4.1 Synchronisation of National Birthdates with the IBD, last paragraph: In 1.4.4 it is indicated that PSURs should be based on the IBD. As a consequence, if the long interval between approvals in different countries puts a drug in a 5 year cycle in one region and a 6 month cycle in other regions, it should be possible to negotiate with Has to accept the 5-year cycle, rather than a 6 month cycle. Indeed, the fact that a drug is already on the market in at least one country for a period of more than 5 year, gives another country, where the product is newly registered, additional assurance with regard to the safety of the product.

1.4.4.2 Summary bridging reports:
First sentence reads: "A summary bridging report ... integrates two or more PSURs to cover a specified period over which a single report is required ...etc". However, if an Addendum Report (see 1.4.4.3) is required, it seems logical to also include this in the summary bridging document, as it may also be part of the bridging period. Therefore, we propose to re-phrase the sentence as follows: "A summary bridging report ... integrates two or more PSURs and, if applicable and considered appropriate, an Addendum Document, to cover a specified period ... etc". This is also in line with the CIOMS V document, Chapter 4, section. Summary Bridging Report, where it is indicated that "this (addendum) report would also be (...) referenced in the bridging report."

Statements such as "It should not contain any new data", and "The data should not be repeated", appear to be in contradiction with each other and may need further clarification.

Novartis has received a request from Health Authorities to include in a bridging period an overall summary tabulation covering the complete bridging period. This is also addressed in the last paragraph of this section "If summary tables covering the period of the appended

PSURs are considered appropriate...etc". However, in our opinion, an overall summary tabulation is repetition of data (individual PSURs contain summary tabulations and for safety issues identified, cumulative data are presented in chapter 9 of individual PSURs) and reduces the readability of this **summary** document. Therefore, we would like to propose that an overall summary tabulation should normally not be part of the summary bridging document, as is currently also indicated for line listings.

1.4.4 3 Addendum reports, second paragraph last sentence reads: "It might also be appropriate to provide an addendum to the summary bridging report". As indicated above, another possibility would be to prepare the addendum report and include/address this, just as the PSURs, in the summary bridging report because an addendum report is part of the bridging period (see above). We propose this as an alternative approach

1.4.5 Reference safety information, paragraph 5: This paragraph may need further clarification e.g. with regard to the situation for companies assessing listedness at the time of case data entry When the CCSI has changed during the review period--resulting in certain events changing from unlisted to listed--reports of these events may appear in the 'unlisted' or the 'listed listing', depending on the time of case receipt. The guidance does not clarify if this is acceptable It seems to be justifiable, as it would represent the most conservative approach (some reports that are listed according to the updated CCSI, are presented as unlisted) It goes without saying that this must be explained by the company in section 6 of the PSUR

2 1 Executive summary: If the concept of an executive summary for each PSUR is accepted, one may consider whether there is still a need for a bridging summary report. A compilation of the executive summaries may then replace the bridging document

2.6 Presentation of individual case histories: This section may need further clarification. The addendum indicates that "this section (presentation of individual case histories) should contain a description and analysis of **selected** cases containing new or relevant safety information and grouped by medically relevant headings/System Organ Classes (SOCs)." However, we have been requested by Health Authorities "to provide in PSURs an evaluation for every system-organ class and to discuss serious unlisted suspected adverse reaction, irrespective of the presence of other factors", suggesting that **all** system-organ classes should be addressed and that **all** serious unlisted reactions should be discussed in chapter 6. The current text in the Addendum to ICH E2C recommending to describe only selected cases appears to contradict the current view of some Health Authority. Particularly in PSURs with a high volume of reports (e.g. 5-year reports) a description of all serious unlisted cases appears very impractical As serious unlisted reports have already been reported to most or all regulators (depending on the local labeling) on an expedited basis, there appears to be no justification for another description of all serious unlisted cases in the PSUR. A description of selected cases, identified as relevant safety findings, should be sufficient.