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November 03, 2008

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2008-D-0386: International Conference on Harmonisation; Draft Guidance on E2F Development Safety Update Report; Availability.

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments supporting the International Conference on Harmonisation's (ICH) *Draft Guidance on E2F Development Safety Update Report (DSUR).* BIO welcomes the DSUR guidance which will help to harmonize global safety reporting requirements for ongoing clinical trials and provide valuable, consolidated safety information for regulatory bodies, investigators, patients, and industry. However, BIO encourages the FDA and ICH to minimize duplication among the DSUR and other reporting requirements and to implement the DSUR in the context of broader changes to the U.S. Investigational New Drug (IND) adverse event (AE) reporting regulations.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO SUPPORTS THE APPROPRIATE IMPLEMENTATION OF THE DSUR:

BIO supports this much needed guidance which will help to harmonize the U.S. IND Annual Report and the EU CT Directives Annual Safety Report into one annual report for all participating health regulatory authorities. The guidance establishes a sensible template which will serve as a valuable instrument for reporting pertinent safety information from ongoing clinical trials in a consolidated format that promotes consistency and efficiency. If implemented appropriately, the compatibility of the structure and content of the DSUR with the Periodic Safety Update Report (PSUR) will help health regulatory authorities, investigators, ethics committees and industry access important safety information in a timely and efficient manner.

If the DSUR is universally accepted for aggregate clinical trial safety reporting, this important global standard will promote transparency and efficiency regarding evolving safety data. Additionally, the information included in the DSUR may help to facilitate developing risk mitigation strategies early on during the premarketing period. We encourage FDA to continue to work towards final agreement among global regulators that the DSUR should be used as a common standard, in order to eliminate redundancy and duplication of efforts.

THE GUIDANCE SHOULD AVOID DUPLICATION WITH OTHER SAFETY REPORTING REQUIREMENTS:

However, the scope of the DSUR is overly broad as currently drafted and the guidance proposes to include information that is usually included in the PSUR, as the guideline itself acknowledges. Submitting duplicative information does not contribute to patient safety and well-being and places an unnecessary burden on the sponsor.

In order to avoid or minimize significant overlap and duplication of report content between the DSUR and PSUR, BIO recommends that the DSUR be limited to data from investigational sources. It is not clear why non-interventional/post marketed trial information is being included in DSUR, when it is already submitted as part of the PSUR. Additionally, it is unclear why post market data would be included if the main focus of the DSUR is data from interventional clinical trials. The overlap of information could cause some safety signals to be overestimated.

If the DSUR is not to be totally limited to data from investigational sources only, then there will continue to be considerable content overlap between the two documents. In that case, we request that further guidance be included on the relationship between a DSUR and PSUR and whether cross reference between the documents is a possibility.

THE DSUR SHOULD SERVE AS THE PRIMARY MEANS FOR REPORTING SUSARS TO INVESTIGATORS:

Implementation of the DSUR guidance is an important step towards harmonizing reporting requirements internationally, but BIO believes that the DSUR should be viewed as one element of a larger effort to streamline domestic IND safety reporting regulations. BIO strongly supports ongoing efforts to improve adverse event data collection in clinical trials, reduce the soaring volume of

individual case safety reports (ICSRs) that sponsors and clinical investigators file with institutional review boards (IRBs) and independent ethics committees (IECs), and harmonize adverse event reporting requirements. It could be unduly burdensome to industry if the DSUR is implemented on top of other inconsistent or conflicting domestic regulations governing sponsor adverse event reporting obligations during clinical trials, without reducing other current requirements.

Since the DSUR is intended to represent a more efficient and meaningful method to inform investigators, regulatory authorities and ethics committees of emerging safety information during clinical trials, BIO would like to see the U.S. IND requirement to routinely, expeditiously submit suspected unexpected serious adverse reactions (SUSARs) to all investigators harmonized with EU non-IND requirements. The current IND safety report requirement, which is outdated, is overwhelming investigators and institutional review boards with individual case safety reports that are difficult to interpret. Inconsistent or confusing requirements can lead sponsors to adopt the most conservative reporting practice and send SUSARs from nearly *any* source to *all* investigators without the important denominator context, such as SUSARs from different studies, spontaneous SUSARs, literature SUSARs, etc.

It is our understanding that EU sponsors of non-IND, interventional studies are only required to submit applicable SUSARs to the concerned competent authorities and to the Ethics Committee concerned, and not routinely to all investigators. When a global trial is conducted under a U.S. IND, however, the IND safety report requirement trumps other requirements and makes it necessary to send all applicable SUSARs to all global investigators.

BIO believes that the DSUR should serve as the primary mechanism to inform investigators of relevant, cumulative safety information with some sponsor interpretation.

If a significant safety issue is identified, either upon receipt of an individual SUSAR or upon review of aggregate data, the sponsor should then issue an expedited communication to all investigators. A safety issue that impacts upon the course of the clinical study or development project, including suspension of the study program or safety-related amendments to study protocols should also be communicated to investigators expeditiously.

In short, DSUR should replace routine expedited reporting of all SUSARs to all investigators with a few exceptions.

SPECIFIC COMMENTS:

BIO is pleased to offer the following specific comments in support of the guidance.

SECTION	ISSUE	PROPOSED CHANGE
Section 1: Introduction		
1.1 Objectives of the Guideline	**Line 86**: Many definitions used are not footnoted (i.e. other therapeutic use) and understanding the terms could aid the reader's understanding.	A reference to the glossary should be included in the introduction either here or earlier.
1.2 Scope of the DSUR	**Line 102**: Further definition of an "ongoing clinical trial" may be warranted.	We recommend that an ongoing trial be defined as an interventional trial for which a clinical trial authorization (CTA) or equivalent has been granted, until the day that a Clinical Research Report (CRR) or, under certain circumstances, an (abbreviated) safety report has been completed.
	Line 110: Comparability trials to support manufacturing changes are done under an IND/CTA. Since the drug made by the new process has not been reviewed and "approved" by regulatory authorities the trials conducted for the new material must be done under an IND or analogous mechanism.	We suggest inclusion of comparability trials within the bullet at line 104.
	Line 109: The meaning and scope of "other therapeutic use of an investigational drug" is unclear and could lend itself to misinterpretation.	We suggest that the scope of this term be clarified.
	Line 113-114: The guidance suggests that comparator information may be included in the DSUR.	Comparator information should not be included as part of the DSUR and this reference should be stricken.

Section 2: Guidance		
2.1 When Should a DSUR Be Prepared?	**Lines 119-124:** It is unclear under this wording if DSURs would be submitted for slightly different formulations, salts, or strengths of the product or if only one DSUR would be submitted for all formulations, as is current practice with the PSUR. **Lines 121-124**: The way this paragraph is written it is implied that a DSUR is not required if a sponsor conducts only one clinical trial.	The DSUR guidance should explicitly state that there should be one submission for all product formulations in order to provide consistency with the PSUR requirement. (see also lines 187-190 and 196). The reference regarding a sponsor overseeing "more than one clinical trial" of a single investigational drug should be changed to "one or more clinical trials."
2.2 Periodicity and DSUR Data Lock	**Lines 134-139:** In the unlikely event that a first study in humans occurs in a country with a notification or authorisation process for clinical trials, this sentence could potentially result in a Development International Birth Date (DIBD) which would not coincide with first trial use. In addition this sentence could pose a dilemma in the situation where a new formulation was being developed for an old, already marketed product as it would not necessarily coincide with the original DIBD (by the originator), nor with the PSUR's IBD.	Add the following at the end of the paragraph: "Where a drug is also marketed, the DIBD can be harmonised with the PSUR IBD. In any case the intended DIBD should be included in the trial application or notification documentation and if differing from the date of first approval of a trial authorisation the argument for this difference should be provided (see also section 2.3)."
2.3 Change of DSUR Data Lock Point	**Lines 146-150**: The sponsor should change the DSUR data lock point to coincide with the International Birth Date (IBD) so that the DSUR and the PSUR can be synchronized. In synchronizing the data lock points for the DSUR and PSUR, the period covered by the next DSUR should be no longer than one year.	Please clarify that when the period covering the DSUR is less than a year due to possible DSUR and PSUR synchronization, it should be named as a bridging DSUR to identify it as a different document.
2.6 Responsibilities for Preparing and Submitting a DSUR	**Line 187**: Indicates that multiple DSURs can be prepared if it is unavoidable, but only provides limited examples of when this would be appropriate.	Please clarify in the guidance what criteria will be used to judge acceptability of multiple DSURs and how will sponsors know if their proposal is globally acceptable?

2.7 DSURs for Combination Products	**Lines 192-209**: As currently drafted, the decision whether to submit a DSUR for a combination product is left up to the sponsor. In the absence of specified guidance, how will sponsors know if their approach will be globally acceptable?	Please clarify criteria for submitting a DSUR for a combination product.
2.8 Reference Safety Information (RSI)	**Line 215**: For the purposes of risk-benefit analysis, it would be preferable that the Investigational Brochure (IB) be that used at the end of the period. For coding purposes, the IB should be that which was in effect at the time the case is coded. **Lines 221-224**: The goal of the guidance is to globally harmonize requirements, but local labels would only be used in a local trial. It is unclear how document assessment would work if one country uses the local label and another country uses the IB.	Amend the guidance to reflect that the IB in effect at end of period is used for risk-benefit analysis. For case coding, Reference Safety Information (RSI) should be the IB in effect at the time the case is coded. Either eliminate these lines or add detail specific scenario, such as if studies in the DSUR are all conducted in one country and the RSI for that study is a local label, then the local label can be the RSI for the DSUR.
2.9 Format and Presentation of DSUR	**Lines 225-302**: Based on the Format and Presentation, the content is to be provided as a free standing report and not formatted in Common Technical Document (CTD) format as per ICH M4 "Common Technical Document." Additionally, as of January 1, 2008, sponsors submitting electronically are required to send new Annual Report submissions in eCTD format. This guidance, as written, does not provide for the submission of a DSUR in place of an eCTD IND Annual Report. **Line 242**: Estimated exposure	Clarify in the guidance that the DSUR can be submitted electronically in eCTD format in place of an eCTD IND Annual Report. Should be subdivided into estimated new exposure and estimated overall exposure during the reporting period to better define the emerging safety data.
2.10 Guidance on	**Line 285**: Under what circumstances can blinded information be included and will this be acceptable to	Please clarify that inclusion of unblinded information in DSUR would not provide better understanding of

Content of DSUR	all ICH regions? Certain regions have required that safety information, even from ongoing studies, be provided in unblinded fashion. **Line 350**: As per the current IND Annual Report regulations (21 CFR 312.33(c)), the annual report should include a "description of the general investigational plan for the coming year to replace that submitted 1 year earlier."	emerging safety but could produce an unnecessary burden to the sponsor who is trying to restrict unblinded information from the wider internal dissemination during DSUR internal review. Specify the appropriate location for inclusion of this information to fulfill the reporting requirements of 21 CFR 312(c). For example, if this information would be included in "Plans for new safety trials" (Line 350) in Section 3 (Update on Actions Taken in the Reporting Period for Safety Reasons).
Sections 3-5		
3 Update on Actions Taken in the Reporting Period for Safety Reason	**Lines 326-371**: This section should include a description of significant actions related to safety that have been taken by the sponsor, regulators, Data and Safety Monitoring Boards or independent ethics committees that could have an impact on the conduct of a specific trial or the whole clinical development programme. Any relevant updates to previous actions should also be summarised in this section. Changes to the Investigator's Brochure should be discussed separately in the "Changes to Reference Safety Information", see section 4…	Clarification is needed on the definition and scope of "significant actions" and what would be considered "important specific advice for safety reasons from a regulatory authority…" Having more examples of this "specific advice" would be useful, as it would aid the Sponsor in providing an appropriate listing of regulatory authority advice – so as to avoid the need to catalogue every regulatory discussion that has ever occurred with a regulatory authority. Such examples of "significant actions" to be reported could include changes to core safety information; early cessation of trial, and other specific changes).
4 Changes to Reference Safety Information	**Lines 372-378**: This section should list any significant safety-related changes to the IB within the reporting period. This includes information relating to contraindications, warnings, precautions, serious adverse drug reactions, adverse reactions of special interest, interactions, and any important findings from non-clinical studies (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the DSUR.	Clarification is needed as to whether Guideline is referring to Development Core Safety Information (DCSI).

7 – Presentation of Safety Data from Clinical Trials		
7.1 Presentation of Safety Data from Clinical Trials	**Lines 446-448**: Excluding "non-serious terms" may inadvertently create problems by necessitating significantly different line listings than those that are used for the PSUR.	It may be beneficial and more practical to include all events that occurred in a serious case.
	Line 448: Additionally, it is unclear what constitutes an "incidental" finding.	The terms adverse events, serious event and non-serious event would capture all incidental findings.
	Line 450: The words "if important" and "appropriate" are used to describe inclusion of adverse reactions of special interest in line listings and summary tabulations.	The guidance would benefit from examples of situations warranting inclusion of such events.
	Lines 450-453: The guidance states that "If important and appropriate, the report should also include adverse reactions of special interest within the line listings and adverse events of special interest in summary tabulations. The basis for selection of such events/reactions should be explained."	There is a need to define and further clarify what is meant by ADRs "of special interest." For example, clarification is needed as to whether this should be aligned with company's identified and potential risks. At a minimum, ADRs of "special interest" should be globally agreed upon rather than parsed across various agencies. In addition, it might be helpful to clarify the required format for line listings and summary tabulations (eg, MedDRA preferred terms will be used?). Additionally, adverse reactions of special interest can stem from significant abnormal lab findings, so it may not restrict to just AE data.
8 – Significant Findings from Clinical Trials During the Reporting Period		
8.2 Ongoing Clinical Trials	**Lines 520-524**: The guidance states that "the DSUR should provide a concise summary of any preliminary safety findings from ongoing trials, including safety issues that are the same or similar to those previously identified, as well as evidence of new clinically	Clarification is needed on summary of "same or similar" safety issues.

	significant safety signals."	
8.3 Other Therapeutic Use of Investigational Drug	**Lines 525-528**: The guidance states that "the DSUR should include safety information from expanded access programmes, compassionate use programmes and treatment INDs, because they each follow a specific protocol."	The nature of safety info should be clarified (e.g. AEs, ADRs, summary). In addition, the Guidance should clarify that when an Investigational Drug is the subject of two or more INDs, the Sponsor should be permitted to cross-reference the applicable IND where the requisite safety information is provided rather than duplicate all of the same information.
Sections 9-11		
9 Relevant Findings from Non-Interventional Studies	**Lines 543-547**: As stated previously, in order to avoid or minimize significant overlap and duplication of report content between the DSUR and PSUR, BIO recommends that the DSUR be limited to data from investigational sources. It is not clear why non-interventional/post marketed trial information is being included in DSUR, when it is already submitted as part of the PSUR.	This section should be removed. If this is not deleted, this requirement could be restricted until the first marketing authorization. On the first marketing authorization this data should belong in the PSUR.
10 Relevant Findings from Other Sources	**Lines 548-552**: The guidance states that "the DSUR should also discuss relevant safety findings from any other available sources (e.g., results from pooled or meta-analyses of randomised clinical trials, lack of efficacy from trials in high morbidity/mortality disease states and trials with vaccines)." **Line 551**: The term "lack of efficacy" is mentioned both here and in 12.6.	Clarify what it means by "results from pooled or meta-analyses of RCTs" Is it on the same product or other products in the same class? If the former, the sponsor usually has the most complete data on its product. Is this suggesting that the company should do its own meta-analyses for comparison purposes? It is recommended that the term "lack of efficacy" be deleted from this section. Many products, especially oncology drugs, have variable effect and there may be reports of lack of efficacy from individual smaller studies. What criteria should be used to report "lack of efficacy", as these studies may include case reports?

Section 12: Other Information		
12.2 Long-Term Follow-Up	**Lines 566-572**: This section of the DSUR should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g., gene therapy, cell therapy products and tissue engineered products). This section could be the only information presented in the DSUR when the clinical trials are completed and long-term follow-up is the only ongoing activity generating data for the DSUR. This may contribute to unnecessary report volume if a sponsor reporting only long term follow-up information were to write the report to include only "no info" in all other subheadings.	Clarify what type of safety information should be included (e.g., SAEs, adverse events of special interest, or significant safety findings). It is also recommended that the guidance state that it is acceptable to provide the Long-Term Follow-Up information in a cover letter, if that is the only information presented.
12.3 Literature	**Lines 573-580**: After a drug or biologic has reached the market, the PSUR literature search is required, making this requirement duplicative.	This section should be eliminated for marketed products or a cross-referencing to the PSUR literature search should be allowed. If the literature search is required, clarification is needed on the scope and meaning of the statement that "this section should also include relevant new information on drugs of the same class." Literature searches should be conducted and findings, if any, should be reported in DSUR until first marketing authorization. After first marketing authorization, literature searches and findings should be included only in the PSUR. For example, a cancer product with one or two marketing authorizations could result in an extensive literature search and findings leading to a large burden in preparation of DSUR and interpretation of the data.
12.4 Other DSURs	**Lines 581-584**: The guidance states that "When available, a commercial sponsor should summarise significant findings from the DSUR provided by	Please clarify that in the case of two INDs for the same product, cross-referencing should be permitted.

	another sponsor conducting clinical trials with the investigational drug during the reporting period."	
12.5 Significant Manufacturing Changes	**Lines 585-589:** As per the current IND Annual Report regulations (21 CFR 312.33(b)(7)), the annual report should include a "summary of any significant manufacturing or microbiological changes made during the past year." The draft guidance, Section 12.5 (Significant Manufacturing Changes), specifically covers the significant manufacturing changes but is unclear on the microbiology changes requirement.	Specify the appropriate location for inclusion of the summary of any significant microbiological changes to fulfill the reporting requirements of 21 CFR 312.33(b)(7) (e.g., Section 12.5).
12.6 Lack of Efficacy	**Lines 590-594**: The term "lack of efficacy" is mentioned both here and in Section 10.	As mentioned above, many products, especially oncology drugs, have variable effect and there may be reports of lack of efficacy from individual smaller studies. What criteria should be used to report "lack of efficacy", as these studies may include case reports? It is recommended that this section be removed or clarified.
Section 15: Summary of Important Risks		
15 Summary of Important Risks	**Lines 663-670**: This section should provide a concise cumulative list of important identified and potential risks (e.g., those that might lead to warnings, precautions, or contraindications in labelling). The information in this section could provide the basis for the Safety Specification of a risk management plan (ICH E2E). The list should be continuously evaluated and updated from DSUR to DSUR and include risks that require further evaluation, as well as safety concerns that have been fully addressed or resolved. **Line 675**: An "Appendix of Important Regulatory Advice" is listed, but the purpose of this appendix is not discussed.	Should further clarify that a list format is sufficient. The purpose and required content of this appendix should be discussed in the text of the document.

Appendices		
Appendix A	**Item #3**: Item #3 in the glossary includes a reference to a treatment IND in the definition of "Other Therapeutic Use of an Investigational Drug".	It should be noted that this is a mechanism unique to the United States.
Appendix B	**Line 707:** "**Based upon the total number of patients recruited as of [date] and applied randomization schemes" **Line 716:** "Estimated cumulative subject exposure to [study drug] in all clinical studies by origin"	Footnote for Subject exposure says "number of patients recruited". It might also be useful to have number of patients who received IP in database at time of lock since that is the denominator for the summary count tables. Categories seem more racial than ethnic and "Asian" is preferred to term, "oriental"

CONCLUSION:

BIO appreciates this opportunity to comment in support of the International Conference on Harmonisation's *Draft Guidance on E2F Development Safety Update Report.* We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Director for Science and Regulatory Affairs
Biotechnology Industry Organization