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February 8, 2008

The World Medical Association  
13, ch. du Levant  
CIB - Bâtiment A  
01210 Ferney-Voltaire  
France

Re: Review of the Declaration of Helsinki

Dear Sir or Madam:

BIO appreciates the opportunity to comment on the World Medical Association's (WMA's) Declaration of Helsinki. The Biotechnology Industry Organization (BIO) represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations in 32 nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products.

### **1.1 General Comments**

The integrity and safe conduct of clinical trials is of the utmost importance to BIO members developing biomedical products. BIO believes strongly in protecting the rights and welfare of human subjects involved in biomedical research. We recognize that well-accepted international standards for clinical research, including those published under the International Conference on Harmonization (ICH) and associated with Good Clinical Practice (GCP), draw on the important principles articulated in the Declaration of Helsinki.

Clinical trials involving the administration of a new drug to a human being should be conducted in accord with the ICH GCP guidelines, which are available at [www.ich.org](http://www.ich.org). These ICH guidelines provide an internationally accepted ethical and scientific quality standard for designing, conducting, recording and reporting trials. Compliance with this standard provides public assurance that the rights, safety, and well being of trial subjects are protected consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. The guidelines cover issues such as the selection and training of trial investigators, gaining informed consent from trial participants, trial monitoring and quality assurance.

In the United States (U.S.), the Food and Drug Administration (FDA) also provides GCP Guidances, and the GCP regulations for studies conducted in the U.S. can be found in the U.S. Code of Federal Regulations (21 CFR 50, 21 CFR 54, 21 CFR 56, 21 CFR 312). These

guidances and regulations detail the responsibilities of sponsors, investigators, and institutional review boards (IRBs) and also outline monitoring practices to ensure regulatory and study design compliance and subject safety.

BIO opposes the current draft of the Declaration of Helsinki for the following reasons:

1) The nature of the Declaration changes from high level principles and becomes increasingly prescriptive, thereby duplicating the functions of legislation and regulation.

2) In some instances, the text that has been changed or added does not align with ICH GCP guidelines, the EU Clinical Trial Directive, United States law and FDA regulations, local laws/regulations, and other more comprehensive ethical guidance documents such as those published by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO). This lack of alignment creates confusion and a lack of regulatory clarity. We note that many of these other documents have been developed specifically to provide guidance or oversight for large multinational clinical research programs involving many diverse stakeholders. Because the Declaration was and is written by treating physicians for treating physicians, its scope cannot easily be expanded to cover these types of programs appropriately, in a way that reflects current law/regulation and contains the detail necessary to be useful.

BIO considers the Declaration of Helsinki a significant document that exists to safeguard the safety and well being of trial participants and strongly advocates that the Declaration remain a high level document that provides important guiding principles for the ethical conduct of clinical research.

## 1.2 Specific Comments

### A. INTRODUCTION

<b>BIO Proposed Change</b>	<b>BIO Comment and Rationale</b>
Title Revision: We suggest retaining the original subtitle of the Declaration of Helsinki, with the exception of the change from “medical” to “biomedical”, <i>i.e.</i> , “Ethical Principles for Biomedical Research Involving Human <b>Subjects</b> .”	The proposed change is inconsistent with language used in ICH GCP guidelines and FDA regulations. The phrase “human subjects” should be retained throughout the Declaration because it is widely used and well-understood.
Paragraph 1. We suggest retaining the word “identifiable” in this sentence: Biomedical research involving human beings includes research on <b>identifiable</b> human material and <b>identifiable</b> data.	The scope of the Declaration should not be expanded to include biomedical research on unidentifiable human material and data. This type of research raises very different issues from the research which is the focus of the rest of the Declaration (and of Good Clinical Practice guidelines) and therefore expanding the Declaration in this way has the potential to create considerable confusion as to which paragraphs of the Declaration apply to which types of research.

<p>Paragraph 4. We suggest the following alternate wording in this sentence, “Populations that have previously been underrepresented in biomedical research, such as children and pregnant women, should be provided equitable access to participation in research <b>when appropriate.</b> <del>provided equitable access to participation in research.</del>”</p>	<p>The WMA’s proposed wording is vague, and may lead to unintended negative consequences, <i>i.e.</i>, individuals participating in research when it is not appropriate for them to do so.</p>
<p>Paragraph 8. We suggest the alternate wording, “Biomedical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. These include the <del>educationally,</del> economically or medically disadvantaged, those who cannot give or refuse consent for themselves, those who may be subject to giving consent under duress, and those for whom the research is combined with medical care.”</p>	<p>It is unclear what “educationally... disadvantaged” means. The other text in this paragraph relating to consent is clear and appropriate, and may cover whatever was intended by the reference to education.</p>
<p>Paragraph 10. We suggest the alternate wording, “It is the duty of <u>biomedical researchers</u> to protect the life, health, <u>dignity, right to self-determination,</u> and privacy, <del>and confidentiality of information</del> of research participants.”</p>	<p>The previous language was redundant, because “the right to self determination” and “confidentiality of information” are covered by other words in this sentence.</p>
<p>Paragraph 12A. We suggest that this paragraph be deleted:</p> <p><del>The welfare of animals used for research must be respected.</del></p>	<p>While we fully support and endorse this statement, it is misplaced in a document on the ethical principles for medical research involving human subjects.</p>
<p>Paragraph 13. We suggest the alternate wording, “The design and performance of each research procedure involving human beings should be clearly formulated in a research protocol. <b><u>For clinical research and when appropriate for other research,</u></b> this protocol should be submitted for consideration, comment, guidance, and approval to an ethical review committee, which must be independent of the researcher, the sponsor and any other kind of undue influence.”</p>	<p>We have made this insertion because in some countries ethics committees do not review observational epidemiological studies. (Please note that WMA’s comments on paragraph 15 in the consultation draft indicate that the term clinical research is used in the Declaration to distinguish this research from other types of research (non-clinical epidemiological, observational, etc.) that do not require supervision by health professionals).</p> <p>In addition we have some questions regarding WMA’s proposed deletion of the phrase “specially appointed” from this</p>

	<p>paragraph. In its consultation draft, WMA notes that the proposed change from “specially-appointed ethical review committee” to “an ethical review committee” is based on the idea that such committees should exist whether research is conducted or not, and should not have to be specially-appointed. However, we are unclear whether this change would have an impact on the ability to submit to a central Institutional Ethics Committee (IEC), and what impact this change might have on research in countries that do not have IECs or do not require IECs for particular types of studies (for example post-marketing surveillance studies in Japan). We urge WMA to clarify the impact of this change and seek further comment before finalizing it.</p>
<p>Paragraph 16. We suggest the following alternate wording in these sentences, “The design of all <b><u>clinical research studies of prophylactic, diagnostic, therapeutic and palliative procedures</u></b> should be publicly available. In particular, <del>before recruitment of the first participant, each clinical trial</del> <b><u>all controlled clinical investigations other than Phase I trials</u></b> should be <del>included</del> listed in <b><u>a registry</u></b> <del>a database register</del> that is freely accessible by members of the public.”</p>	<p>We have inserted the phrases “clinical research” and “of prophylactic, diagnostic, therapeutic and palliative procedures” because in some countries ethics committees do not review observational epidemiological studies. (Please note that WMA’s comments on the revised paragraph 15, in WMA’s consultation draft, indicate that the term “clinical research” is used to distinguish this research from non-clinical epidemiological, observational etc.)</p> <p>Also, we note that under Section 113 of the US FDA Modernization Act (FDAMA), all controlled clinical investigations other than Phase I trials should be registered and provided in a summary format within 21 days after the first patient is enrolled. Therefore in order for BIO members to comply with Paragraph 16 as revised, they would have to meet two different requirements in the United States. Further, we are concerned that this language includes Phase I trials. Registration of Phase I trials could signal to competitors what research the sponsor is targeting, thereby severely diminishing incentives for research.</p>

<p>Paragraph 22 – We suggest replacing this sentence,  <del>“Potential research participants should be informed that secondary/chance findings or information on genetic disease dispositions may impact their personal or professional lives.”</del></p> <p>with this alternate language,  <u>“Potential research participants should be informed that information collected that indicates the need for immediate clinical intervention or is of acknowledged clinical significance at the time of the study may impact the provision of healthcare.”</u></p> <p>We also suggest a return to the original wording, “After ensuring that the potential participant has understood the information, the researcher should then <b>obtain</b> seek the potential participant’s freely-given informed consent, preferably in writing.”</p>	<p>Any health care information discovered during a trial may impact a participant’s personal and professional life. The protections outlined in the Declaration not only apply wherever a trial takes place, but also regardless of whether the trial is studying genes or a genetic disease. Thus, it is not appropriate to single out genetic information as that which needs special attention. Doing so gives the false impression that genetic information is inherently more “dangerous” than other personal health information, which, in turn, could unnecessarily dissuade patients from enrolling in certain trials.</p> <p>We ask that WMA reconsider its suggested change from “obtain” to “seek.” This change would mean that the paragraph no longer implies that consent should be obtained, only that it should be sought.</p>
<p>Paragraph 22A. We suggest the alternate wording, “In observational epidemiological research, conducted by examining large databases, there may be situations where <u>the research goes beyond the scope of the original</u> informed consent <b>and re-consent</b> is impossible, difficult, or unethical to obtain or poses a threat to the validity of research. Such research should be done only after consideration and approval of an ethical review committee <u>or the removal of identifying information and destruction of the link between the participants and their data.</u>”</p>	<p>Currently, the ability to conduct research that goes beyond the scope of the original informed consent differs according to local privacy laws and the protections in place for the data set.</p> <p>We note that a requirement to obtain ethics committee approval for all research using de-identified data would unnecessarily inhibit biomedical research and could delay the generation of information that is important for patient care.</p>
<p>Paragraph 26. We suggest the alternate wording, “Clinical research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population and the research <b>intervention</b> cannot be delayed.”</p>	<p>We suggest this change to clarify that this paragraph does not imply that the initiation of the research project must be delayed.</p>
<p>Paragraph 26A. We suggest the following</p>	<p>The proposed inclusion of “and” goes</p>

<p>alternative wording in this sentence, “In addition, if the samples are then reused for a different purpose from that for which consent was originally obtained, appropriate consent <del>and/or</del> approval of the ethical review committee should be obtained for such reuse.”</p>	<p>beyond current practice and may unnecessarily block research that helps patients.</p>
<p>Paragraph 26B. We recommend that this new paragraph be deleted:</p> <p><del>Re-exposure of ‘professional participant’ patients to clinical trials should be actively discouraged. Guidance as to the number of exposures of patients per time, or in clinical trials, should be developed by regulatory authorities, in consultation with ethics committees.</del></p>	<p>We suggest the deletion of this new paragraph because it is unclear what the phrase “professional participant” means. Patients that meet the inclusion and exclusion criteria for a study should have an opportunity to participate in research. Because of the ambiguity of the phrase “professional participant,” this section would be very hard to implement and enforce. In addition we note that in certain Phase I studies and cross-over studies, re-exposure is a necessary or anticipated event. It would be very problematic if this new paragraph inadvertently made such studies impossible to conduct.</p>
<p>Paragraph 27. Please clarify to which types of trials this paragraph refers. We suggest the following alternate wording, “Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Researchers are accountable for the accuracy of the results. They and have a duty to make publicly available the results of research <b><u>that can improve patient care</u></b> <del>on human participants</del>. In so doing ... [retain the rest of the revised paragraph as is]”</p>	<p>We are concerned that unless WMA specifies to which trials this language applies, this paragraph can be interpreted to mean that results from <i>all</i> trials should be made public. That would include Phase I trials as well as trials for products that were not approved. This is not consistent with US law. In addition, it is not clear what purpose it would serve to publish the results of Phase I trials, because such trials typically have limited statistical power and serve primarily to generate hypotheses for possible future trials. BIO supports public disclosure of the analysis of the results of confirmatory trials for marketed drugs within one year of the completion of the analysis.</p>
<p>Paragraph 28. Please clarify the following language, “and if he or she is convinced that participation in the research study will not adversely affect the care of the patient.”</p>	<p>WMA’s proposed language could have unintended negative effects and may need to be clarified. Physicians can never be completely convinced that a patient’s participation in research will not adversely affect the patient’s care. Most interventions carry risks, and not all research participants will fare as well as</p>

	<p>they would have done if they hadn't participated in the research. Therefore, the benefit/risk ratio must be evaluated by individual research participants through the informed consent process. In addition, the overall benefit/risk ratio must be carefully evaluated by investigators for each proposed research program.</p>
<p>Paragraph 30 - We suggest the alternate wording, "At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to <del>share any benefits that result from it</del> <b><u>be provided with care as described in the study protocol,</u></b> for example, access to <del>prophylactic, diagnostic, therapeutic or palliative treatments identified by the study."</del></p>	<p>We are concerned that this section as written is inconsistent with paragraph 14 as revised in the consultation draft. The revised paragraph 14 states that the research protocol should "identify arrangements for post-trial access by study participants ...". We support that policy and believe participants are entitled to benefits identified in the research protocol and reviewed during the informed consent process.</p>

## Conclusion

BIO appreciates this opportunity to comment on WMA's Declaration of Helsinki. We look forward to seeing the next draft, and would be pleased to work with WMA to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe  
Vice President, Science and Regulatory Affairs  
Biotechnology Industry Organization