Biotechnology Industry Organization

October 27, 2014

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2006-D-0031: Draft Informed Consent Information Sheet: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Availability

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Informed Consent Information Sheet: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors." BIO shares FDA's commitment to enhancing communication with, and thereby the protection of, human research subjects.

BIO represents more than 1,000 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.

GENERAL COMMENTS:

BIO believes that clearly and effectively communicating with potential research volunteers is essential to their protection, and as such, BIO greatly appreciates the Agency's work to publish the Draft Guidance. In general, BIO finds the Draft Guidance very well-written, informative, and comprehensive. There are several aspects of the Draft Guidance for which BIO offers additional considerations or requests clarification and/or revision.

A. Ensuring concise, least-burdensome, and comprehensible informed consent documents

BIO notes that it is imperative to provide meaningful information to potential study participants, however, the key challenge is to balance the need to communicate FDA requirements and guidance information, while keeping the consent form as concise as possible, so as to not overwhelm the subject. Excessive details in the informed consent document may, in fact, burden the informed consent process. BIO believes that the information included in the informed consent document should be prioritized in a risk-

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based manner in order to facilitate the most informed decision-making on the part of the potential subject. BIO recommends that FDA address this important issue as the guidance is finalized, and we have included specific suggestions to achieve this end in the accompanying table. Additionally, BIO believes that the Informed Consent Information Sheet should ensure that subjects understand the content of the informed consent document and suggests, therefore, that the guidance document should promote use of reliable comprehension testing methods for informed consent documents and procedures.

B. Harmonization with previous and related FDA Guidance Documents and efforts to simplify/improve informed consent documents

The 2006 FDA Draft Guidance on Informed Consent (page 9, last paragraph) addresses the use of multiple consent documents, observing that:

> *For some studies… using multiple documents may improve subject understanding by "staging" information in the consent process. This process may be useful for studies with separate and distinct, but linked, phases through which the subject may proceed. If this technique is used, the initial document should explain that subjects will be asked to participate in the additional phases. It should be clear whether the phases are steps in one study or separate but interrelated studies. For certain types of studies, the Agency encourages the process of renewing the consent of subjects.*

The recently released draft guidance omits this topic. BIO requests that FDA consider re-inserting this wording into the current guidance document or otherwise clarifying that this approach can be advantageous, since for certain study designs "staging" information provided to subjects may be useful.

Additionally, in the 1998 FDA Guidance on *Institutional Review Boards Frequently Asked Questions – Information Sheet*,[1] the answer to Question 45 states:

> *FDA does not require reconsenting of subjects that have completed their active participation in the study, or of subjects who are still actively participating when the change will not affect their participation, for example when the change will be implemented only for subsequently enrolled subjects.*

Assuming the FAQ document will be retired, BIO recommends that this section be incorporated into the current guidance document.

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[1] FDA Guidance on *Institutional Review Boards Frequently Asked Questions – Information Sheet* (1998), available electronically at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm

Finally, BIO encourages FDA to ensure, where possible, alignment between the Draft Guidance and related efforts to simplify and improve informed consent documents (*e.g.*, the National Cancer Institute's *Simplification of Informed Consent Documents*).[2]

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Informed Consent Information Sheet: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew W. Womack, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

[2] National Cancer Institute (2013) *Simplification of Informed Consent Documents*, available at http://www.cancer.gov/clinicaltrials/conducting/simplification-of-informed-consent-docs/page1/AllPages#1

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
II. SUMMARY OF THE CONSENT PROCESS		
Page 3:	BIO recommends rewording for clarity.	BIO recommends that FDA revise to read: "…clinical investigation. (See section III.C.5, Providing Significant New Findings to Subjects, for ~~a discussion of when findings developed during the clinical investigation must be communicated to subjects.~~ information on communicating new findings to subjects during the course of a study.)"
III. FDA INFORMED CONSENT REQUIREMENTS AND DISCUSSION		
A. GENERAL REQUIREMENTS FOR INFORMED CONSENT		
Page 4:	BIO believes that the protocol must contain safeguards to ensure that participation is voluntary.	BIO recommends that FDA revise to read: "For example, when an employing party seeks to enroll employees in a clinical investigation sponsored or conducted by the employing party, the protocol ~~should~~ must contain safeguards to ensure that participation is voluntary and that there is no undue influence by supervisors, peers, or others."
Page 5:	BIO believes that clarification of FDA's expectations for the appropriate reading level of the informed consent form would assist Sponsors in ensuring that the	BIO recommends that FDA clarify that, where possible, Sponsors should strive to write consent forms at an eighth grade or lower reading level, as per suggestion by the National Institutes of Health (NIH).[3]

[3] National Cancer Institute (NCI), HHS Office for Protection from Research Risks (now the Office of Human Research Protections, OHRP) and FDA (1998) *Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials*, available electronically at http://www.cancer.gov/clinicaltrials/conducting/simplification-of-informed-consent-docs/page2

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	consent form is "in language understandable to the potential subject or legally authorized representative."	
Page 6:	BIO believes that the phrase "although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research" may potentially be difficult to comprehend for some research subjects.	BIO recommends that FDA revise to read: "In the event that you suffer a research-related injury, your medical expenses will be your responsibility or that of your third-party payer, ~~although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research~~ although you do not lose any of your legal rights to seek payment by signing this form."
B. BASIC ELEMENTS OF INFORMED CONSENT		
Page 7:	BIO believes that the care a patient would receive if not part of the research may vary depending on the patient and is best addressed through a discussion between the patient and his/her physician. This is also addressed in *Sec. III.B.4* (*Alternative Procedures or Treatments* – "Prospective subjects must be informed of the care they would likely receive if they choose not to participate in the research."). BIO also recommends further explanation of double-blind and placebo-controlled studies.	BIO recommends that FDA revise to read: "FDA recommends that potential subjects ~~first be informed of the care a patient would likely receive if not part of the research and then~~ be provided with information about the research. ~~This sequence allows potential subjects to understand how the research differs from the care they might otherwise receive.~~ The description should identify tests, ~~or~~ procedures, or treatments that ~~would be part of usual care that will not be performed as well as those required by the protocol that would not be part of their care outside of the research, for example, drawing blood samples for a pharmacokinetic study. The information provided should also inform prospective subjects about the potential consequences of these differences in care.~~ are required by the protocol that would not be part of their care outside of research, for example drawing blood samples for a pharmacokinetic study. Note that all experimental

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		procedures must be identified as such. (21 CFR 50.25(a)(1).) ~~Procedures related solely to research (for example, protocol-driven versus individualized dosing, randomized assignment to treatment, blinding of subject and investigator, and receipt of placebo if the study is placebo-controlled) must be explained.~~ The informed consent process must explain procedures related solely to research, for example, protocol-driven dosing regimen for the study drug versus individualized dosing, randomized assignment to treatment and chance of being placed in any treatment group, and blinding of subject and investigator (and in double blind studies, if the patient's safety is at risk, the investigator can find out what drug the patient is receiving). For placebo-controlled studies, the informed consent should explain that placebo is a substance that looks like study drug (or comparator) but contains no active ingredient."
Page 8:	BIO believes that foreseeable discomforts associated with research-related procedures *only* should be required for the consent form. Additionally, BIO believes that describing risks or discomforts of standard medical procedures, exams, and tests in the informed consent document may make the consent form too lengthy or detailed, and could overwhelm the patient to read.	BIO recommends that FDA revise to read: "…previous research reports. ~~Reasonably foreseeable discomforts to the subject must also be described. (21 CFR 50.25(a)(2).) For example, the consent form should disclose the severity and duration of pain from a surgical procedure or the discomfort of prolonged immobilization for MRI.~~ All possible risks do not need to be described in detail in the informed consent form, especially if…" Additionally, BIO requests that FDA clarify that the subject may be informed of risks for standard of care procedures in

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		a chart as an addendum to the informed consent to enhance readability (See discussion of use of an addendum to describe study procedures in sec. B.1).
Pages 9-10:	While it is very important for the patient to know their options and risks/benefits associated with each alternative treatment, BIO believes that the specific risks and benefits of alternative treatments are better suited as part of the medical discussion between the primary health care professional and the patient. Nor should the informed consent form describe specific standard of care treatment regimens, including off-label uses or treatment regimens. Therefore, BIO recommends that alternative treatments be listed, but not described in detail, in the Informed Consent Form.	BIO recommends that FDA revise to read: "To enable an informed decision about taking part in a clinical investigation, consent forms must disclose appropriate alternatives to entering the clinical investigation, if any, that might be advantageous to the subject. (21 CFR 50.25(a)(4).) Prospective subjects must be informed of the care they would likely receive if they choose not to participate in the research. This includes alternatives such as other forms of therapy (e.g., surgical), ~~approved therapies for the patient's condition,~~ getting treatment without being in a research study, taking part in a different study, and when appropriate, supportive care with no disease-directed therapy. ~~This disclosure must include a description of the current medically recognized standard of care. Particularly in studies of serious illness. Standard of care may include uses or treatment regimens that are not included in a product's approved labeling (or in the case of a medical device cleared under the 510(k) process, in the product's statement of intended uses).~~ FDA believes that treatment options lacking evidence of therapeutic value do not need to be discussed. When disclosing appropriate alternative procedures or courses of treatment~~, FDA believes a description of any reasonably foreseeable risks or discomforts and potential benefits associated with these alternatives must be disclosed. Where such descriptions or disclosures can contain quantified comparative estimates of risks and~~

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		~~benefits (e.g., from the clinical literature), they should do so. The agency does not believe that imposing such a strict requirement for every case would be realistic or appropriate.19 Where such well-defined estimates are not possible, the agency believes that a description of the risks and benefits will be sufficient.~~ ~~It may be appropriate to~~, Investigators should refer the subject to a healthcare professional who can more fully discuss the alternatives…"
Page 10:	BIO believes the example text should be expanded to include representatives of the Sponsor.	BIO recommends that FDA revise to read: "The consent process must describe the extent to which confidentiality of records identifying subjects will be maintained (21 CFR 50.25(a)(5)) and should identify all entities, for example, the study sponsor and representatives of the sponsor, who may gain access to the records relating to the clinical investigation."
Pages 10-11:	BIO notes that while *Section III.B.5. Confidentiality* of the draft guidance states, "[t]he consent process must also note the possibility that FDA may inspect records (21 CFR 50.25(a)(5)), and ***should not state or imply that FDA needs permission from the subject for access to the records*** [emphasis added]," the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) *E6 Good Clinical*	To be in alignment with ICH-GCP 4.8.10(n) and data privacy/protection legislation, BIO recommends that FDA revise to read: "…[t]he consent process must also note the possibility that FDA may inspect records (21 CFR 50.25(a)(5)), and ~~should not state or imply that FDA needs permission from the subject for access to the records that~~ by signing a written informed consent, the subject or subject's legally acceptable representative is authorizing such access."

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	Practice: Consolidated Guidance[4] states in Section 4.8.10 "(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, ***by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access*** [emphasis added]."	
Pages 11-12:	BIO believes that the phrase "you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the hospital" may potentially be difficult to comprehend for some research subjects.	BIO recommends that FDA revise to read: "If no compensation is available, the consent process should include statements such as:[21] • Because of hospital policy, the hospital is not able to offer financial compensation should you be injured as a result of participating in this research. However, ~~you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the hospital~~ you do not lose any of your legal rights to seek payment by signing this form.

[4] FDA Guidance for Industry *E6 Good Clinical Practice: Consolidated Guidance* (1996), available at http://www.cc.nih.gov/ccc/clinicalresearch/guidance.pdf

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		• Because of hospital policy, the hospital makes no commitment to provide free medical care or payment for any unfavorable outcomes resulting from participation in this research. Medical services will be offered at the usual charge. However, ~~you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the hospital~~ you do not lose any of your legal rights to seek payment by signing this form. "
C. ADDITIONAL ELEMENTS OF INFORMED CONSENT		
Page 13:	BIO believes that the example statement should include potential risk to the pregnancy of the subject's partner.	BIO requests that FDA revise to read: "When appropriate, the consent process must contain a statement that the particular test article or procedure may involve risks to subjects (or to the embryo or fetus, if the subject is pregnant or if the subject or subject's partner may become pregnant) that are currently unforeseeable."
Page 13:	BIO notes that long-term safety studies will rarely be completed for most products in clinical trials, as collection of long-term safety data continues to NDA submission and even beyond. BIO believes that the original wording of 21 CFR 50.25 (b)(1) is sufficient to cover this issue.	BIO requests that FDA provide clarity on the adequacy of the regulation as currently worded.

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Page 15:	BIO believes that because the statement regarding payment to research subjects is unrelated to previous information in this section, the reference to "future payments" to a patient who withdraws early requires further explanation.	BIO recommends that FDA include a reference to the FDA Information Sheet, "Payment to Research Subjects" for further information.[5]
D. ELEMENT OF INFORMED CONSENT FOR APPLICABLE CLINICAL TRIALS		
Page 16:	BIO appreciates FDA's guidance for informing research participants about summary information that will be provided on *clinicaltrials.gov*. However, significant changes to international regulations will soon require broader dissemination of greater amounts of clinical trial data (*e.g.*, European Medicines Agency (EMA) Policy 0070). BIO recommends that FDA provide guidance to Sponsors related to international regulations governing clinical trial transparency.	BIO requests that FDA include recommendations in the guidance about the release of data publicly and to third parties as a part of international regulations governing clinical trial transparency.
E. DOCUMENTATION OF INFORMED CONSENT		
Page 17:	BIO applauds FDA's consideration of alternative methods using new technologies and would welcome the opportunity to further discuss with FDA new technologies that may serve as alternatives to the traditional paper informed consent form.	BIO recommends that FDA convene stakeholders (*i.e.*, health care providers, patients, and industry) to discuss opportunities to employ new technologies that may serve as alternatives to the traditional paper informed consent form.

[5] FDA Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors: *Payment to Research Subjects* (1998), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm

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IV. RESPONSIBILITIES FOR INFORMED CONSENT		
A. THE IRB		
Page 20:	BIO recommends rewording for clarity.	BIO recommends that FDA revise to read: "FDA requires that an IRB review ~~and approve, require modifications in (to secure approval), or disapprove~~ all research activities covered by the IRB regulations (21 CFR 56.109(a)) and indicate approval or disapproval of such activities, or specify any modifications required to secure approval of such activities."
B. THE CLINICAL INVESTIGATOR		
Page 25:	The draft guidance states that "…the investigator may use a prepared summary of the change to aid in an informative presentation to the enrolled subject," but, "…this summary does not constitute the revised informed consent document," thereby implying that a revised Informed Consent form (ICF) still needs to be signed. BIO believes that the use of a signed ICF addendum is an efficient way to communicate new information and changes to subjects, however, there would be no longer a benefit if the complete revised ICF is also required to be signed rather than, or in addition to, an ICF addendum.	BIO recommends that FDA consider revising this paragraph to clarify that an ICF addendum is an acceptable way to communicate new information and changes to subjects *in lieu* of a complete revised ICF.
D. THE FDA		

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Page 28:	BIO notes that the intent of expanded access programs (EAPs) is treatment; this differs from a clinical investigation where the primary purpose is research.	BIO requests that FDA provide further guidance related to the modifications, if any, required to the usual elements in a research investigation consent form to accommodate EAPs, wherein obtaining consent is feasible.
Pages 28-29:	BIO believes that additional guidance on the informed consent process for a clinical investigation that involves the co-development of an investigational new drug and a companion diagnostic would be helpful to Sponsors.	BIO requests that FDA provide additional guidance on the informed consent process for a clinical investigation that involves the co-development of an investigational new drug and a companion diagnostic.
V. ADDITIONAL CONSIDERATIONS		
A. REVIEW OF PATIENT RECORDS		
Page 29:	BIO notes that it may also be necessary to copy medical information of subjects to ensure the quality of the clinical investigation (*e.g.*, consultation with Sponsor's medical monitor) in accordance with institutional policies and applicable laws and regulations.	BIO recommends that FDA revise to read: "Sponsors and investigators may ~~seek~~ need to review and/or copy patient medical records for a variety of reasons related to a clinical investigation."
B. NON-ENGLISH SPEAKING SUBJECTS		
Page 31:	BIO recommends rewording for clarity.	BIO recommends that FDA revise to read: "A protocol amendment ~~in which the investigator proposes~~ to include use of translated informed consent ~~documents for a study already approved by the IRB with English language consent documents~~ , in addition to English language consent documents previously approved by the IRB, may be considered no more than a minor change to the research and may qualify for an expedited review procedure under FDA regulations at 21 CFR 56.110(b)."

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Page 31:	BIO believes that it is unclear from the description provided what, if any, follow-up is required when IRB-approved English long form is verbally translated for a subject who does not understand English.	BIO recommends that FDA outline what, if any, follow-up is required when IRB-approved English long form is verbally translated for enrolled non-English speaking subjects who neither the investigator nor the IRB reasonably expected to be enrolled.
Page 31:	Due to diversity in the US, BIO believes that it could be impractical to require Institutional Review Boards (IRBs) to have reviewers capable of reviewing and approving all non-English language versions of consent documents.	BIO encourages FDA to consider adding the option of submitting a certified medical translation certificate along with the non-English informed consent form to the IRB, rather than having the IRB review and approve all non-English versions of consent documents.
D. PHYSICALLY CHALLENGED SUBJECTS		
Page 34:	BIO recommends rewording for consistency and clarity.	BIO recommends that FDA revise to read: "FDA recommends that the subject's case history should indicate the reason for the lack of a signature and include a description of the specific means by which the prospective subject communicated agreement to take part in the clinical investigation and how questions were answered."
E. IMPAIRED CONSENT CAPACITY		
Page 35:	BIO recommends rewording for consistency and clarity.	BIO recommends that FDA revise to read: "Enrollment of subjects with partial impairment may require modifications to the consent form and process to enable those subjects to consent on their own behalf. In this situation, a progress note in the subject's case history should describe the additional steps taken by the site. When a subject's consent capacity is sufficiently impaired that the subject is unable to provide legally effective informed consent, the subject may not be enrolled unless

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		the subject's legally authorized representative consents on the subject's behalf. (21 CFR 50.3(l) and 50.20.)"
Page 35:	BIO believes that additional clarity or guiding principles for determining the "aspects of the clinical investigation that may impact on a child's willingness to participate" would be valuable to Sponsors.	BIO requests that FDA clarify the "aspects of the clinical investigation that may impact on a child's willingness to participate" or provide guiding principles for determining those aspects.
F. CHILDREN AS SUBJECTS		
Page 38:	BIO recommends rewording for clarity.	BIO recommends that FDA revise to read: "~~Children who are wards of the State or any other agency, institution, or entity can be included in a clinical investigation that is approved under 21 CFR 50.53 and 50.54 provided that two conditions are met.~~ FDA regulations require two conditions to be met before children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations involving greater than minimal risk and no prospect of direct benefit, but likely to yield generalizable knowledge about the subjects' disorder or condition (21 CFR 50.53), or clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (21 CFR 50.54). First, the clinical investigation ~~is~~ must be either: (1) related to their status as wards; or (2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. (21 CFR 50.56(a)(1) and (2).) ~~In other words, children who are wards may only be enrolled in clinical investigations involving greater than minimal risk and no~~

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		~~prospect of direct benefit, but likely to yield generalizable knowledge about the subjects' disorder or condition (21 CFR 50.53) or clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (21 CFR 50.54), if one of these two conditions is met.~~"
H. SUSPENSION/TERMINATION OF A STUDY		
Page 40:	BIO believes it is unclear what, if any, role the IRB has in determining what is communicated to subjects in the event of program termination.	BIO requests that FDA clarify the role of the IRB in reviewing what is communicated to subjects in the event of program termination.
I. DATA RETENTION UPON THE WITHDRAWAL OF SUBJECTS		
Page 41:	BIO believes that there may be situations where a sample is collected from a subject for a study-specific assay (*e.g.*, pharmacokinetic assay) in accordance with the informed consent form. The subject later withdraws from the clinical investigation before the assay is performed (*e.g.*, per the study plan, batch testing is conducted at a designated time).	BIO requests that FDA clarify that samples collected prior to the subject's withdrawal may be used, consistent with the original consent, to perform such study-specific testing even though the actual testing is performed after withdrawal of the subject. Test results would become part of the data collected on the subject up to the time of withdrawal from the clinical investigation and remain in the study database to ensure the scientific and ethical integrity of the research.
Page 41:	BIO notes that it is not always clearly documented when a subject withdraws informed consent from what the subject is withdrawing (*i.e.*, from treatment, from all interventions, or from any further data collection).	BIO requests that FDA clarify why a separate consent would have to be signed for a subject to agree to follow-up, if this was already foreseen in the initial consent. Additionally, BIO requests that FDA clarify whether a note by the investigator in the subject's records related to the withdrawal would be sufficient in these circumstances.