

ABBOTT LABORATORIES

Global Pharmaceutical Regulatory Affairs

Douglas L. Sporn
Divisional Vice President
Global Pharmaceutical Regulatory Affairs
Telephone: (847) 937-7986
Facsimile: (847) 938-3346

200 Abbott Park Road
D-RA78, AP30-1
Abbott Park, Illinois 60064-6157
E-mail: doug.sporn@abbott.com

July 2, 2004

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

Re: Docket No. 2004D-0187 Request for Comments on the Draft Guidance on Pre-Marketing Risk Assessment

Abbott Laboratories (Abbott) is pleased to have the opportunity to comment on the Draft Guidance on Pre-Marketing Risk Assessment, published in the Federal Register on May 5, 2004.

In general, Abbott supports the Pharmaceutical Research and Manufacturers of America (PhRMA) responses sent to the FDA on this draft guidance and provides the additional attached comments.

Abbott wishes to acknowledge the Agency's foresight in addressing this very important issue in a multi-step process, e.g., a Concept Paper, public workshop, and Draft Guidance. This has afforded stakeholders the opportunity to provide well-considered and thorough input. It has also provided stakeholders a prospective view of the Agency's evolving thinking so that they can begin to consider system adjustments that will meet the needs of a robust risk management approach. We urge the Agency to consider a similar transparent and multi-step commentary process for other initiatives of like stature.

Should you have any questions, please contact Jill Sackett at (847)-937-4085 or by FAX at (847) 938-3346.

Sincerely,

Douglas L. Sporn / jms
Douglas L. Sporn

2004D-0187

C6



**Abbott Comments on FDA Draft Guidance for Industry:
Pre-Marketing Risk Assessment
Docket No. 2004D-0187**

July 2, 2004

General Comments

Abbott Laboratories appreciates the opportunity to provide comments on this Draft Guidance. We are pleased to see the Agency's responsiveness to stakeholder concerns as reflected by some of the improvements made to this document in both content and clarification over the previously issued Concept Paper. In particular, we are reassured to see the Agency's improved emphasis that "routine" risk assessment and risk minimization are sufficient for most products. We are further encouraged to see risk discussed in a more balanced fashion with benefit, as both are inextricably linked.

We seek additional clarification on whether certain recommendations apply to all products or only to a subset of products that pose "an unusual type or level of risk." In addition, there remain several areas of concern that deserve specific mention as tabulated below.

The majority of this guidance relies on the collection of adverse events as the mechanism for risk assessment. The role of ancillary analyses should be acknowledged. Evaluation of controlled data points such as lab values, diagnostic imaging, and vital signs can reveal important trends and are valuable assets in the overall review of drug exposure.

Drug development is a necessarily lengthy process. Some NDAs that are submitted well after the effective date of this Guidance will contain data based upon studies that were underway prior to the genesis of the Guidance, the designs of which may not meet all new recommendations, e.g., late-stage dose finding, size of safety database, comparator use, etc. We seek clarification from the Agency that retrospective application of these new recommendations will not be applied to studies that were submitted to the Agency and underway before finalization of this Guidance.

Specific Comments

Line(s)	Comment
155, 226, 382-385	We object to the suggestion of a higher standard of approval for products that are developed in the presence of approved therapies. At line 155, the draft guidance states that the size of the safety database will depend on "the potential advantages of the product over existing therapy" (among other things). At line 226, it is further stated that a larger database may be appropriate when "a safe and effective alternative to the investigational product is already available." Line 382 indicates that when "there is a well-established related therapy," safety data with an active comparator would be desirable. This troubling theme throughout the document suggests that any

	<p>drug preceded by existing therapies would require larger subject numbers and a comparator arm. This suggests that the performance of the investigational drug will be compared, at least from a safety aspect, with at least one of its predecessors. It further implies a higher standard of approval for subsequent drugs.</p> <p>As pointed out in the draft “Guidance for Industry: Development and Use of Risk Minimization Action Plans” (lines 119-121), the statutory standard for FDA approval of a product is that the product is “safe and effective for its labeled indications under its labeled conditions of use.” There is no basis for interpreting the statutory standard for approval to require each subsequent product for a particular indication to be safer (or more effective) than available approved and marketed products. These statements suggest that the path to market is increasingly steep, not only for each follow-on product in the same class, but for each subsequent product for a given condition.</p> <p>The Agency’s recommendations for a larger safety database and comparator arm appear to apply to nearly all new drugs because, with the exception of a completely unmet need, some type of safe and effective alternative treatment usually exists.</p> <p>We suspect that these recommendations apply only to that subset of drugs that may pose “an unusual type or level of risk” (line 64-65). Even then, these recommendations would apply on a case-by-case basis, as evidenced by the Agency’s use of the word “may”. If this interpretation is correct, please clarify the referenced passages. If not, this recommendation is unreasonably broad and inconsistent in the context of the preceding text in section IV.</p>
175-184	<p>In this paragraph the Agency seems to be drawing a distinction between the terms “long-term treatment” and “chronic treatment”. As written, “chronic treatment” appears to be described as a <i>type</i> of long-term treatment (line 175) and is subject to the more specific and expanded exposure recommendations given in lines 178-184. All other “long-term treatment” types, such as “intermittent” for example, appear to be subject to the more general exposure recommendations given in lines 176-178. If this interpretation is incorrect, please revise the paragraph to clarify the exposure recommendations for <i>all</i> types of “long-term treatment.”</p>
181-184	<p>The term “relevant dose” is unclear. Given the Agency’s emphasis on additional and late-stage dose exploration, we trust that the term “relevant dose” would <i>not</i> be limited to doses at or above the minimum dose ultimately proposed for the labeling. For the purposes of the safety database, we suggest that “relevant dose” include any dose that has been rationalized through prior testing to be a viable dose appropriate for administration periods of at least 6 months.</p>
231-234	<p>The draft guidance includes the recommendation that sponsors communicate with the review division early in the development program on the appropriate size of the safety database and again at “appropriate regulatory milestones</p>

	<p>(e.g., end-of-phase 2 and pre-NDA meetings).” This suggests that sponsors should not rely on the advice of the review division from earlier consultations. The pre-NDA meeting is very late in the pre-marketing development program to learn that the previously agreed upon safety database is now considered inadequate. The intent of this statement warrants further explanation.</p>
252-277	<p>Section IV.B.1. appears to intermingle two important concepts: long-term controlled safety studies and active comparator studies. The result is confusion; the concepts pertaining simply to long-term controlled safety studies (lines 260-265 and lines 281-285, minus the word “comparative in line 281), whether or not they pertain to active comparator studies, should remain in this section. The remaining text dealing with active comparator studies (lines 267-279), whether or not they are long-term, should be consolidated with section IV.D.</p>
256	<p>Please expand to read: “Control groups may be given an active comparator or a placebo, depending upon the disease being treated. In certain disease states the use of a placebo for long-term studies is inappropriate due, for example, to ethical considerations.”</p>
273	<p>Situations in which there are known adverse events with cumulative toxicity could be cited as an example where the use of a long-term, controlled safety study could be useful.</p>
281-292	<p>We suggest that the concepts of diversity and chronicity be kept separate. Important information about diverse populations can be obtained at various stages of product development; this section seems unduly focused on Phase III studies. This could be remedied by revising line 281 to read “Premarketing safety databases should include, to the extent possible, a diverse population.” Similarly, revise line 283 to read, “We recommend that, to the extent feasible, only patients with obvious contraindications be excluded from study entry.”</p> <p>This section should acknowledge that the inclusion of a more diverse population introduces significantly more variability and will likely increase enrollment numbers and extend the duration of the trial. Moreover, the accommodation of more diverse populations at one stage of development may necessitate difficult accommodations at other stages of development. For example, inclusion of the very elderly in Phase III will likely entail study of pharmacokinetics in Phase I. These studies may not always have a good representation of the elderly. These factors must be weighed carefully against the breadth of the inclusion/exclusion criteria, the disease state, any available pharmacogenomic information, etc., and sponsors may consider such factors when determining whether a more diverse population is feasible.</p> <p>Lines 288-290 state that “broadening inclusion criteria in phase 3 studies enhances the generalizability of study findings and may, therefore, allow the product to be labeled for broader use.” We believe this is unlikely unless the study is sufficiently powered to support the broader claims. If this statement</p>

	<p>is to be retained in the final guidance it deserves further explanation and, perhaps, an example of how a broader claim might result from a more diverse phase 3 population.</p> <p>Finally, any decision to require a highly diverse phase 3 study population should be justified by an expectation of a benefit commensurate with the increased cost of development and the delayed availability of the product.</p>
307-318	<p>The draft guidance recommends studying more than one dose level in phase 3 “in circumstances when phase 2 studies cannot reasonably be considered to have established a single most appropriate dose.” It appears that FDA is recommending a major change in the way drugs are developed. First, the guidance implies that it is no longer sufficient to identify a dose that is safe and effective under conditions of proposed labeling, but, instead, the “single most appropriate dose” must be identified. Second, the guidance indicates that data from typical phase 2 studies are an unacceptable basis for defining the single most appropriate dose, which must be based on clinical outcome data. Implementation of this recommendation will greatly slow drug development and the availability of new products to the public as well as significantly increase the costs of drug development. Given the advances in drug therapy that have been developed under the current drug development paradigm, the basis for rejecting that approach is unclear. Further, this recommendation appears counter to the philosophy expressed in the recently published “Critical Path” document. We recommend revision of this section of the guidance to clearly focus on those unique circumstances in which identification of the single most appropriate dose is critical to the safe and effective use of the drug (e.g., drugs with a narrow therapeutic index).</p>
345	<p>The conduct of product-dietary supplement interaction studies presents a myriad of problems. We suggest that the Agency delete this recommendation as they have appropriately done with product-food interactions, or that the recommendation be limited only to those dietary supplements that have been well-documented in the scientific literature to be used concomitantly with the subject drug or class of drugs. It should be noted that such studies, if conducted, would not necessarily result in generalizable results, given the unregulated nature of dietary supplements and the resultant variability in their content and performance.</p>
363	<p>Qualification/clarification of the term “biomarker” is needed. In its draft guidance “Pharmacogenomic Data Submissions” dated November 2003, the Agency proposed definitions of “known biomarker,” “known valid biomarker,” and “probable valid biomarker.” The description of “biomarker” in this guidance document should align with the Agency’s final definitions. Further, the Agency’s recommendation to study biomarkers during clinical development should be limited to “<i>known valid</i> biomarkers pertinent to a known safety concern.”</p>
453-456	<p>It should be noted that some Institutional Review Boards or Ethics Committees place limitations on sample retention. The end of the first sentence should read “...for possible assessments at a later time, subject to</p>

	any applicable Investigational Review Board or Ethics Committee approvals.” It is possible that in some circumstances sample retention will be denied by the IRB/EC.
475-498 and 512-513	<p>Much uncertainty remains with regard to the effectiveness of a MEPA due, in part, to the lack of validated measurement tools. FDA has recently announced that MEPA guidance is “up in the air” and “premature” at this time (<i>ref. Pink Sheet, June 29, 2004</i>). Accordingly, we recommend that these passages be deleted from the guidance. They may be replaced with a brief description of a MEPA, the assertion that it is a voluntary tool, and the retention of lines 513-517 that direct the sponsor to meet with the FDA for additional guidance.</p> <p>Most companies currently engage in extensive vetting of potential trademarks prior to selecting a mark for a new product. Because of the global nature of the pharmaceutical market place, this includes evaluating potential marks for confusion in multiple languages. Trademarks are reviewed for similarity with existing trademarks with both other pharmaceuticals as well as non-pharmaceutical products. In addition, the Patent and Trademark office conducts its own review of proposed trademarks for conflict with other products. These efforts have been referred to as “good naming practices” and it has been recommended that, in the absence of validation of testing methods, FDA should accept documentation of a good faith effort by sponsors to engage in such good naming practices</p>
489-491 and 508-510	Clarification of roles with regard to the above activities is needed. The Agency states that it undertakes some of these activities (line 489) yet it encourages sponsors to undertake these activities (lines 489-491 and 508-510). Certainly these activities should not be duplicated. It should be clarified that the conduct of good naming practices and any related analyses by sponsors will alleviate FDA of the need to do this. The resultant impact to review time should be addressed. Currently, the clearance of a proposed trade name through FDA can be a very lengthy one. We seek assurance that the provision of naming data in a sponsor’s application will not negatively impact review timelines and will, if anything, facilitate review.
603-604	How would recharacterization of “mischaracterized” events be orchestrated? Adverse event terms are typically clarified with the investigator. Whether or not AE terminology has been successfully reviewed with the investigator, who subsequently decides that a “mischaracterization” has occurred? The sponsor and/or FDA? When is this done? The current language is overly vague. We suggest the sentence read “If, prior to product approval and despite attempts with the investigator for clarification, the sponsor concludes that adverse events have been mischaracterized, the sponsor could consider, in consultation with FDA, recharacterizing the event to make it consistent with accepted case definitions.”
608	The document states that sponsors should <i>ensure</i> that investigators have accurately characterized adverse events. There are practical limitations to sponsors’ oversight with regard to access to all relevant data and the patients

	<p>themselves. We suggest the sentence read, “In addition to <i>checking</i> that investigators have accurately characterized adverse events, we recommend that sponsors <i>check</i> that verbatim terms used by investigators have been appropriately coded.”</p>
864-868	<p>We support the exertion of reasonable effort to obtain detailed reasons for study withdrawals. However, there will be occasions where additional information cannot be obtained and sub-optimal explanations such as “withdrew consent” must suffice. As written, the document implies that these types of explanations would not be acceptable. Please modify line 865 to read “...sponsors should make reasonable efforts to account for all dropouts...” and line 867 to read “Vague explanations such as ‘withdrew consent,’ ‘failed to return,’ or ‘lost to follow-up’ should be kept to a minimum.”</p>
874-881	<p>The terms “very long half –life” and “late safety events” warrant clarification. Currently, subjects are typically followed for five half-lives or 30 days after exposure. Monitoring subjects well after this time is both burdensome and impractical. Once subjects come off study, they may or may not be followed by the same physician and lack of oversight and loss to follow-up increases. This could result in a small group of subjects who are followed for whom a clinically or statistically meaningful conclusion cannot be drawn due to lack of sample size.</p>
950	<p>Add the qualifier “...(if performed)”</p>

ABBOTT LABORATORIES

Global Pharmaceutical Regulatory Affairs

Douglas L. Sporn
Divisional Vice President
Global Pharmaceutical Regulatory Affairs
Telephone: (847) 937-7986
Facsimile: (847) 938-3346

200 Abbott Park Road
D-RA78, AP30-1
Abbott Park, Illinois 60064-6157
E-mail: doug.sporn@abbott.com

July 2, 2004

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

Re: Docket No. 2004D-0187 Request for Comments on the Draft Guidance on Pre-Marketing Risk Assessment

Abbott Laboratories (Abbott) is pleased to have the opportunity to comment on the Draft Guidance on Pre-Marketing Risk Assessment, published in the Federal Register on May 5, 2004.

In general, Abbott supports the Pharmaceutical Research and Manufacturers of America (PhRMA) responses sent to the FDA on this draft guidance and provides the additional attached comments.

Abbott wishes to acknowledge the Agency's foresight in addressing this very important issue in a multi-step process, e.g., a Concept Paper, public workshop, and Draft Guidance. This has afforded stakeholders the opportunity to provide well-considered and thorough input. It has also provided stakeholders a prospective view of the Agency's evolving thinking so that they can begin to consider system adjustments that will meet the needs of a robust risk management approach. We urge the Agency to consider a similar transparent and multi-step commentary process for other initiatives of like stature.

Should you have any questions, please contact Jill Sackett at (847)-937-4085 or by FAX at (847) 938-3346.

Sincerely,

Douglas L. Sporn / jms

Douglas L. Sporn

2004D-0187

C6



**Abbott Comments on FDA Draft Guidance for Industry:
Pre-Marketing Risk Assessment
Docket No. 2004D-0187**

July 2, 2004

General Comments

Abbott Laboratories appreciates the opportunity to provide comments on this Draft Guidance. We are pleased to see the Agency's responsiveness to stakeholder concerns as reflected by some of the improvements made to this document in both content and clarification over the previously issued Concept Paper. In particular, we are reassured to see the Agency's improved emphasis that "routine" risk assessment and risk minimization are sufficient for most products. We are further encouraged to see risk discussed in a more balanced fashion with benefit, as both are inextricably linked.

We seek additional clarification on whether certain recommendations apply to all products or only to a subset of products that pose "an unusual type or level of risk." In addition, there remain several areas of concern that deserve specific mention as tabulated below.

The majority of this guidance relies on the collection of adverse events as the mechanism for risk assessment. The role of ancillary analyses should be acknowledged. Evaluation of controlled data points such as lab values, diagnostic imaging, and vital signs can reveal important trends and are valuable assets in the overall review of drug exposure.

Drug development is a necessarily lengthy process. Some NDAs that are submitted well after the effective date of this Guidance will contain data based upon studies that were underway prior to the genesis of the Guidance, the designs of which may not meet all new recommendations, e.g., late-stage dose finding, size of safety database, comparator use, etc. We seek clarification from the Agency that retrospective application of these new recommendations will not be applied to studies that were submitted to the Agency and underway before finalization of this Guidance.

Specific Comments

Line(s)	Comment
155, 226, 382-385	We object to the suggestion of a higher standard of approval for products that are developed in the presence of approved therapies. At line 155, the draft guidance states that the size of the safety database will depend on "the potential advantages of the product over existing therapy" (among other things). At line 226, it is further stated that a larger database may be appropriate when "a safe and effective alternative to the investigational product is already available." Line 382 indicates that when "there is a well-established related therapy," safety data with an active comparator would be desirable. This troubling theme throughout the document suggests that any

	<p>drug preceded by existing therapies would require larger subject numbers and a comparator arm. This suggests that the performance of the investigational drug will be compared, at least from a safety aspect, with at least one of its predecessors. It further implies a higher standard of approval for subsequent drugs.</p> <p>As pointed out in the draft “Guidance for Industry: Development and Use of Risk Minimization Action Plans” (lines 119-121), the statutory standard for FDA approval of a product is that the product is “safe and effective for its labeled indications under its labeled conditions of use.” There is no basis for interpreting the statutory standard for approval to require each subsequent product for a particular indication to be safer (or more effective) than available approved and marketed products. These statements suggest that the path to market is increasingly steep, not only for each follow-on product in the same class, but for each subsequent product for a given condition.</p> <p>The Agency’s recommendations for a larger safety database and comparator arm appear to apply to nearly all new drugs because, with the exception of a completely unmet need, some type of safe and effective alternative treatment usually exists.</p> <p>We suspect that these recommendations apply only to that subset of drugs that may pose “an unusual type or level of risk” (line 64-65). Even then, these recommendations would apply on a case-by-case basis, as evidenced by the Agency’s use of the word “may”. If this interpretation is correct, please clarify the referenced passages. If not, this recommendation is unreasonably broad and inconsistent in the context of the preceding text in section IV.</p>
175-184	<p>In this paragraph the Agency seems to be drawing a distinction between the terms “long-term treatment” and “chronic treatment”. As written, “chronic treatment” appears to be described as a <i>type</i> of long-term treatment (line 175) and is subject to the more specific and expanded exposure recommendations given in lines 178-184. All other “long-term treatment” types, such as “intermittent” for example, appear to be subject to the more general exposure recommendations given in lines 176-178. If this interpretation is incorrect, please revise the paragraph to clarify the exposure recommendations for <i>all</i> types of “long-term treatment.”</p>
181-184	<p>The term “relevant dose” is unclear. Given the Agency’s emphasis on additional and late-stage dose exploration, we trust that the term “relevant dose” would <i>not</i> be limited to doses at or above the minimum dose ultimately proposed for the labeling. For the purposes of the safety database, we suggest that “relevant dose” include any dose that has been rationalized through prior testing to be a viable dose appropriate for administration periods of at least 6 months.</p>
231-234	<p>The draft guidance includes the recommendation that sponsors communicate with the review division early in the development program on the appropriate size of the safety database and again at “appropriate regulatory milestones</p>

	<p>(e.g., end-of-phase 2 and pre-NDA meetings).” This suggests that sponsors should not rely on the advice of the review division from earlier consultations. The pre-NDA meeting is very late in the pre-marketing development program to learn that the previously agreed upon safety database is now considered inadequate. The intent of this statement warrants further explanation.</p>
252-277	<p>Section IV.B.1. appears to intermingle two important concepts: long-term controlled safety studies and active comparator studies. The result is confusion; the concepts pertaining simply to long-term controlled safety studies (lines 260-265 and lines 281-285, minus the word “comparative in line 281), whether or not they pertain to active comparator studies, should remain in this section. The remaining text dealing with active comparator studies (lines 267-279), whether or not they are long-term, should be consolidated with section IV.D.</p>
256	<p>Please expand to read: “Control groups may be given an active comparator or a placebo, depending upon the disease being treated. In certain disease states the use of a placebo for long-term studies is inappropriate due, for example, to ethical considerations.”</p>
273	<p>Situations in which there are known adverse events with cumulative toxicity could be cited as an example where the use of a long-term, controlled safety study could be useful.</p>
281-292	<p>We suggest that the concepts of diversity and chronicity be kept separate. Important information about diverse populations can be obtained at various stages of product development; this section seems unduly focused on Phase III studies. This could be remedied by revising line 281 to read “Premarketing safety databases should include, to the extent possible, a diverse population.” Similarly, revise line 283 to read, “We recommend that, to the extent feasible, only patients with obvious contraindications be excluded from study entry.”</p> <p>This section should acknowledge that the inclusion of a more diverse population introduces significantly more variability and will likely increase enrollment numbers and extend the duration of the trial. Moreover, the accommodation of more diverse populations at one stage of development may necessitate difficult accommodations at other stages of development. For example, inclusion of the very elderly in Phase III will likely entail study of pharmacokinetics in Phase I. These studies may not always have a good representation of the elderly. These factors must be weighed carefully against the breadth of the inclusion/exclusion criteria, the disease state, any available pharmacogenomic information, etc., and sponsors may consider such factors when determining whether a more diverse population is feasible.</p> <p>Lines 288-290 state that “broadening inclusion criteria in phase 3 studies enhances the generalizability of study findings and may, therefore, allow the product to be labeled for broader use.” We believe this is unlikely unless the study is sufficiently powered to support the broader claims. If this statement</p>

	<p>is to be retained in the final guidance it deserves further explanation and, perhaps, an example of how a broader claim might result from a more diverse phase 3 population.</p> <p>Finally, any decision to require a highly diverse phase 3 study population should be justified by an expectation of a benefit commensurate with the increased cost of development and the delayed availability of the product.</p>
307-318	<p>The draft guidance recommends studying more than one dose level in phase 3 “in circumstances when phase 2 studies cannot reasonably be considered to have established a single most appropriate dose.” It appears that FDA is recommending a major change in the way drugs are developed. First, the guidance implies that it is no longer sufficient to identify a dose that is safe and effective under conditions of proposed labeling, but, instead, the “single most appropriate dose” must be identified. Second, the guidance indicates that data from typical phase 2 studies are an unacceptable basis for defining the single most appropriate dose, which must be based on clinical outcome data. Implementation of this recommendation will greatly slow drug development and the availability of new products to the public as well as significantly increase the costs of drug development. Given the advances in drug therapy that have been developed under the current drug development paradigm, the basis for rejecting that approach is unclear. Further, this recommendation appears counter to the philosophy expressed in the recently published “Critical Path” document. We recommend revision of this section of the guidance to clearly focus on those unique circumstances in which identification of the single most appropriate dose is critical to the safe and effective use of the drug (e.g., drugs with a narrow therapeutic index).</p>
345	<p>The conduct of product-dietary supplement interaction studies presents a myriad of problems. We suggest that the Agency delete this recommendation as they have appropriately done with product-food interactions, or that the recommendation be limited only to those dietary supplements that have been well-documented in the scientific literature to be used concomitantly with the subject drug or class of drugs. It should be noted that such studies, if conducted, would not necessarily result in generalizable results, given the unregulated nature of dietary supplements and the resultant variability in their content and performance.</p>
363	<p>Qualification/clarification of the term “biomarker” is needed. In its draft guidance “Pharmacogenomic Data Submissions” dated November 2003, the Agency proposed definitions of “known biomarker,” “known valid biomarker,” and “probable valid biomarker.” The description of “biomarker” in this guidance document should align with the Agency’s final definitions. Further, the Agency’s recommendation to study biomarkers during clinical development should be limited to “<i>known valid</i> biomarkers pertinent to a known safety concern.”</p>
453-456	<p>It should be noted that some Institutional Review Boards or Ethics Committees place limitations on sample retention. The end of the first sentence should read “...for possible assessments at a later time, subject to</p>

	<p>any applicable Investigational Review Board or Ethics Committee approvals.” It is possible that in some circumstances sample retention will be denied by the IRB/EC.</p>
<p>475-498 and 512- 513</p>	<p>Much uncertainty remains with regard to the effectiveness of a MEPA due, in part, to the lack of validated measurement tools. FDA has recently announced that MEPA guidance is “up in the air” and “premature” at this time (<i>ref. Pink Sheet, June 29, 2004</i>). Accordingly, we recommend that these passages be deleted from the guidance. They may be replaced with a brief description of a MEPA, the assertion that it is a voluntary tool, and the retention of lines 513-517 that direct the sponsor to meet with the FDA for additional guidance.</p> <p>Most companies currently engage in extensive vetting of potential trademarks prior to selecting a mark for a new product. Because of the global nature of the pharmaceutical market place, this includes evaluating potential marks for confusion in multiple languages. Trademarks are reviewed for similarity with existing trademarks with both other pharmaceuticals as well as non-pharmaceutical products. In addition, the Patent and Trademark office conducts its own review of proposed trademarks for conflict with other products. These efforts have been referred to as “good naming practices” and it has been recommended that, in the absence of validation of testing methods, FDA should accept documentation of a good faith effort by sponsors to engage in such good naming practices</p>
<p>489-491 and 508-510</p>	<p>Clarification of roles with regard to the above activities is needed. The Agency states that it undertakes some of these activities (line 489) yet it encourages sponsors to undertake these activities (lines 489-491 and 508-510). Certainly these activities should not be duplicated. It should be clarified that the conduct of good naming practices and any related analyses by sponsors will alleviate FDA of the need to do this. The resultant impact to review time should be addressed. Currently, the clearance of a proposed trade name through FDA can be a very lengthy one. We seek assurance that the provision of naming data in a sponsor’s application will not negatively impact review timelines and will, if anything, facilitate review.</p>
<p>603-604</p>	<p>How would recharacterization of “mischaracterized” events be orchestrated? Adverse event terms are typically clarified with the investigator. Whether or not AE terminology has been successfully reviewed with the investigator, who subsequently decides that a “mischaracterization” has occurred? The sponsor and/or FDA? When is this done? The current language is overly vague. We suggest the sentence read “If, prior to product approval and despite attempts with the investigator for clarification, the sponsor concludes that adverse events have been mischaracterized, the sponsor could consider, in consultation with FDA, recharacterizing the event to make it consistent with accepted case definitions.”</p>
<p>608</p>	<p>The document states that sponsors should <i>ensure</i> that investigators have accurately characterized adverse events. There are practical limitations to sponsors’ oversight with regard to access to all relevant data and the patients</p>

	<p>themselves. We suggest the sentence read, “In addition to <i>checking</i> that investigators have accurately characterized adverse events, we recommend that sponsors <i>check</i> that verbatim terms used by investigators have been appropriately coded.”</p>
864-868	<p>We support the exertion of reasonable effort to obtain detailed reasons for study withdrawals. However, there will be occasions where additional information cannot be obtained and sub-optimal explanations such as “withdrew consent” must suffice. As written, the document implies that these types of explanations would not be acceptable. Please modify line 865 to read “...sponsors should make reasonable efforts to account for all dropouts...” and line 867 to read “Vague explanations such as ‘withdrew consent,’ ‘failed to return,’ or ‘lost to follow-up’ should be kept to a minimum.”</p>
874-881	<p>The terms “very long half –life” and “late safety events” warrant clarification. Currently, subjects are typically followed for five half-lives or 30 days after exposure. Monitoring subjects well after this time is both burdensome and impractical. Once subjects come off study, they may or may not be followed by the same physician and lack of oversight and loss to follow-up increases. This could result in a small group of subjects who are followed for whom a clinically or statistically meaningful conclusion cannot be drawn due to lack of sample size.</p>
950	<p>Add the qualifier “...(if performed)”</p>