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**Date:** ► June 2, 2005

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

**Subject:** **Docket No. 2005D-0112**  
*Draft Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*

Dear Sir/Madam:

Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA. We are pleased to provide the following attached comments on the draft FDA guidance, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*.

If you have any questions regarding our comments, or how we may assist with further development of this guidance, please contact Jenny Peters at 805-447-8840.

Sincerely,

Linda J. Paradiso, DVM, MBA  
Senior Director  
Oncology Therapeutic Head  
Amgen Regulatory Affairs



## General Comments

The draft guidance focuses upon strategy that has been used successfully for development of cytotoxic agents for the treatment of cancer. Thinking to the future, we suggest more focus upon targeted agent development and approval strategies. Next-generation guidance also should address targeted therapy strategies to approvals; can multiple clinical studies in one or more tumor types expressing a particular receptor or target be deemed '*adequate and well-controlled*' for a pan-indication for "*treatment of cancers expressing X receptor or target*"? Under what circumstances will changes in clinically meaningful biomarkers and/or functional imaging be utilized as primary endpoints for approval? After established correlation with standard efficacy endpoints? Which types of approvals? "*Accelerated*" for the biomarker change with "*regular*" approval to follow on establishment of positive standard efficacy endpoints?

This guidance is focused on cancer therapeutics. We suggest another guidance addressing the unique needs of supportive care agents would be very helpful to drug developers.

PRO section needs expansion. See specific comments below for details.

A glossary of abbreviations would be helpful.

Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed Text Change
Line 148	Major	<p>Language is soft with respect to when the Agency strongly recommends a particular strategy. Table would be more beneficial if more definitive. The softer the endpoint, the stronger the recommendation for blinded study designs and objective measures of outcome. The flexibility of this section is helpful, however, could be problematic with respect to sponsor interpretation of Agency guidance.</p> <p>Wording in Symptom Endpoint section under Assessment inaccurate.</p>	<p>Suggestion to tighten the wording where possible.</p> <p>Change from: <i>"Usually needs randomized blinded studies (unless endpoints have an objective component and effects are large – see text)"</i> to <i>"Usually needs randomized blinded studies (unless endpoints have a <b>measurement error</b> and effects are large – see text)"</i>.</p>
Lines 201 – 208 and 264 – 285	Major	<p>In what specific situations would ORR be allowable/acceptable for a primary endpoint and approval? What situations would lead to accelerated versus regular approval?</p>	<p>Clarify and expand the language to address.</p>
Lines 250 – 253	Minor	<p>Description of limitations of death analysis assumes a certain analysis approach.</p>	<p>Not all methods for analysis are affected.</p>
Lines 274 – 275	Major	<p>Appears to be a recommendation for RECIST criteria in assessment of tumor response.</p>	<p>While the intent was, perhaps, not to exclude other acceptable response measures, the document should state more definitively that other methodologies may be acceptable and more appropriate for particular tumor types and should be discussed, in advance, with the Agency.</p>
Lines 349-351	Minor	<p>The Agency is inferring that a Special Protocol Assessment (SPA) is strongly suggested for PFS trial designs. If absolutely required, the guidance should state directly.</p>	<p>Clarify in what particular situations a SPA is strongly recommended or required.</p>
Lines 452 – 454	Minor	<p>Erroneous conclusion that less toxicity might not translate into more effectiveness of an agent. For example, a less toxic drug might allow for more drug to be delivered on schedule, with less missed doses.</p> <p>Also, it is the impact of the effect of symptoms on a patient that is important in QOL measures, not the severity of symptoms themselves.</p>	<p>Modify wording in this section to state accurately intended meaning.</p>



Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed Text Change
Lines 474 – 475	Major	The term ' <i>validated instrument</i> ' is ill-defined.	Provide guidance on what constitutes validation. Should use the psychometric definitions accepted in the field. Change to, " <i>Symptom data should be carefully collected using a validated instrument according to a schedule detailed in the protocol.</i> " To be validated, the instrument should be performing as you expect it to perform in this patient population.
Lines 510 – 528	Minor	Not very specific with respect to allowance of biomarkers in assessment of effectiveness of new therapies.	Provide more specific guidance and more specific scenario examples where changes in biomarkers may lead to accelerated or regular approval.
Lines 570 – 571	Minor	Clarification of wording	Change, " <b>would have no effect at all</b> " with " <b>might have no effect at all</b> ".
Lines 577 – 578	Minor	Clarification of wording	Change from, " <i>Moreover a critical assumption is that the treatment effect of the active control that was observed historically will also <b>be observed</b> in the current population...</i> ," with, " <i>Moreover a critical assumption is that the treatment effect of the active control that was observed historically will also <b>exist</b> in the current population...</i> ".
Lines 639 – 640	Major	An inappropriate use of the word, ' <i>noninferiority</i> '	A noninferiority trial is one in which efficacy is established by demonstrating that a new therapy has an effect similar to that of a control that is known to be effective. While the trial described in this section has some similarities to noninferiority trials, there are also important distinctions. To avoid confusion, it would be better to avoid the use of the term ' <i>noninferiority</i> '.
Line 642	Minor	Clarify definition of ' <i>drug</i> '	Add the word ' <i>control</i> ' to ' <i>drug</i> ' for clarity
Lines 729 – 742	Major	Using date of scheduled visit for all missing data, especially date of progressive disease.	Agree with using schedule visit date to reduce bias.



Comments on FDA draft guidance, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*

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Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed Text Change
Line 773	Major	Guidelines on PFS.	Agree with recommendations in Table.
Lines 792 -793	Minor	<i>"Limited"</i> number of images is vague	How many images constitute a <i>"limited"</i> number? What is considered an appropriate number/percentage of patients imaged? Seek more definitive use of the term <i>"limited"</i> , or definition of how many images are acceptable.