

June 3, 2005



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

**Re: [Docket No. 2005D-0112] – Draft Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics**

Merck & Co., Inc. is a leading worldwide human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck candidates for cancer therapy through developmental testing and clinical trials, Merck scientists address issues affected by this proposed Guidance. We have extensive experience in clinical development including the use of oncology endpoints and have utilized that experience to author the comments below.

Merck commends the Food and Drug Administration (FDA) for issuing the draft guidance on cancer clinical trial endpoints to support effectiveness claims. It is critically important that the development of new, effective therapies be fostered by updated, science-driven approaches as many patients are not adequately served by existing medicines. As noted in the draft guidance, this is to be the first in a series of cancer endpoint guidances; followed by guidance for specific types of cancer. We fully support the development of these guidance documents and encourage ongoing dialogue between FDA, NCI (National Cancer Institute), industry and academia to aid in the drafting of these documents. We encourage continued workshops such as the planned FDA Workshop on Clinical Trial Endpoints in Acute Leukemia, scheduled for June 24, 2005 in Washington, DC.

At this time, both the FDA and the European regulatory authority are working toward finalization of guidance documents concerning the development of anticancer medicinal products. In order to facilitate the development of medicines for patients who often have no alternatives and little time available to wait for new treatments, regulatory authorities should capitalize on their contemporaneous efforts and develop harmonized guidance. In particular, placebo-controlled oncology trials or controlled trials using comparator agents (whether or not approved for that indication) which may provide the required basis for approval in one region, may be an unacceptable clinical strategy in other regions. It is imperative that agreement on the requirement for placebo-controlled or comparator-controlled oncology trials be reached. Disharmony between two regions could result in multi-year delays in new medicines for patients while clinical studies are redesigned and conducted. We have expanded on the need for harmonization in the section titled General Comments.

The draft guidance document is clearly written and it provides useful definitions of endpoints and relevant aspects of endpoints and clinical trial design. In particular, the extensive discussion of time to event progression endpoints (such as Table 1, A Comparison of Important Cancer Approval Endpoints) and the progression free survival (PFS) sensitivity analysis examples in Appendix 3 (Example Tables for PFS Analysis) are particularly useful. With respect to overall substance, the document is a very general, but useful, compilation of approaches to designing clinical trial endpoints. Overall, the draft guidance adds little new information to overall knowledge, existing guidance or current practice for anticancer drug development leading to regulatory approval. This document provides an excellent foundation but it will be important for FDA to develop the detailed guidance documents for various specific cancers and their therapies.

### **General Comments**

We have two general comments on this draft and the overall regulatory approach for the development of guidance concerning cancer therapeutics. In Europe, the CHMP (Committee for Medicinal Products for Human Use) recently issued (17 March 2005) a draft Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev. 3). As both the FDA and CHMP are developing guidance in the field of oncology, we encourage the regulatory authorities to harmonize their approach. There would be tremendous advantage to cancer patients, sponsors and the regulatory agencies if there were a more explicit harmonization and cross-reference of these guidelines. Especially in the case of rare cancers, in order to offer the therapeutic benefit investigational products may provide it is important that patient participation in a clinical trial be maximized. Divergent agency (US, EU, Japan) expectations for global oncology drug development result in inefficient use of resources that may delay the effective development of oncology medicines.

In particular, this draft guidance calls for controlled oncology trials in advanced disease using an add-on design to standard therapy (i.e. standard therapy plus investigational agent versus standard therapy and placebo or nothing) or investigational agent versus BSC (best supportive care) that may or may not include a matched image placebo (e.g.

tablet). In contrast, the CHMP draft guideline is calling for controlled oncology trials in less advanced disease against a standard comparator with support from single arm trials in more advanced disease. In addition, the CHMP draft guideline goes further in providing parameters for acceptable comparators for controlled trials. For these issues, harmonization would make the development process for oncology drugs more efficient by allowing one trial design and acceptable control arms to satisfy both agency requirements. Consistency of requirements may provide more meaningful results in the long-term.

Our second general comment addresses evolving clinical practice in the field of oncology. Changes in clinical practices may occur prior to completion of the clinical trial. Such changes may subsequently have an effect on the ability of the sponsor to effectively complete ongoing comparator or placebo controlled studies. Thus, guidance should incorporate flexibility in proposed clinical trial design. One possible mechanism to address this is for the Agency to be receptive to adaptive trial designs, such as incorporation of interim analyses and other modification of trial design.

### **Specific Comments**

Our specific comments on the draft guidance follow below. We present the section description and subject line from the guidance document followed by our recommendation.

#### **Section II Background B Endpoints Supporting Past Approvals in Oncology**

Line 122 *"Finally, if the ORR is high enough and the responses are of sufficient duration, ORR does indeed seem reasonable likely to predict clinical benefit"*. The justification of objective response rate (ORR) to reasonably predict clinical benefit based on "[response rates] *high enough and...of sufficient duration*" appears rather arbitrary. We are requesting more detail around the magnitude of the response or the duration of response; an example would be helpful while recognizing that final decision will always be handled case by case.

#### **Section III General Endpoint Considerations**

It would be helpful if the guidance provided examples of cancer types for which surrogate clinical endpoints would be acceptable for *accelerated approval* or *regular approval* (Line 190) of a drug<sup>1</sup>. We acknowledge that specific examples are cited in the draft guidance, such as using DFS (disease free survival) and ORR for approval of hormonal therapies for breast cancer (Line 112); we suggest other examples be provided as well (e.g., hematological response rate in acute leukemia; DFS as an acceptable endpoint for colon cancer drugs in the surgical adjuvant setting). The Agency should consider broadening the acceptability of DFS and be more willing to accept this measure as an endpoint in appropriately designed clinical trials.

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<sup>1</sup>Herein, our use of the term "drug" implies drug, biologic or any combination of the two.

It would also be helpful if guidance were provided as to how a sponsor can determine what is considered a meaningful “*clinical benefit*” (Table 1) for specific clinical endpoints. We recognize that providing specific guidance will be difficult because it will depend on cancer type, stage of disease, and alternative therapies but some guidance on the general approach for determining a meaningful clinical benefit would be useful.

### **Section III B Endpoints Based on Tumor Assessments**

This section and Appendix 4 (Independent Review of Tumor Endpoints) suggest implementation of a central review mechanism will minimize purported bias in tumor assessment (Line 203). Tumor assessment using centralized, independent review, which is being emphasized by the FDA in this and other guidance documents (e.g. draft guidance for medical imaging products), has not been validated in any meaningful way. Before recommending central independent review, the assessment should be validated. The implementation of an independent endpoints review committee (IRC, line 797) seems attractive on face value, but it is not clear how this review adds to final conclusions regarding tumor response or progression. Specifically, if discordance between Investigator, IRC and FDA Medical reviewer assessments were to occur, it would be impossible to determine which of these assessments - all of which contain bias - provides the most accurate assessment. In the absence of fully validated tumor assessments, it may be more appropriate to recommend the following steps:

1. sponsors verify tumor endpoint assessments for ORR and PFS prior to submission and
2. sponsors apply the recommended sensitivity analyses in Appendix 3 to PFS assessment

It would be helpful if the guidance listed examples of acceptable tools for measuring clinical endpoints, especially those for tumor assessments. For example, RECIST criteria were referenced (Line 275). We suggest that other response criteria be referenced (e.g., Cheson criteria for lymphoma response).

### **Section III B 3 Time to Progression and Progression-Free Survival e Future methods for assessing progression**

This section raises a provocative method of using a single time point assessment as a surrogate endpoint. This approach is also suggested in the draft European CHMP guideline referenced herein and it has particular appeal for targeted, non-cytotoxic agents where growth inhibition is anticipated to be the predominant pharmacological effect on tumor. It would be useful for the FDA to put more emphasis on guidance to develop and validate this methodology.

### **Section III C Endpoints Involving Symptom Assessment**

Line 465: “*First, because few cancer trials are blinded, assessments can be biased and therefore unreliable*”. It is clear that the most important problem in oncology is that few trials are blinded so that the possibility of observer bias is difficult to exclude. This creates issues in the analysis of symptom data. In general, there is a lack of validated PROs (patient reported outcome) for many measures of oncology-related symptoms.

This may be addressed if validation of PROs could be incorporated earlier in the drug development process, or in a single study rather than in separate studies. One possibility to address this would be to link specific quantitative measures with the more qualitative PRO measure. For example, in measuring symptoms associated with pulmonary function, evaluation of forced vital capacity may be coupled with a PRO measure of dyspnea. If the sponsor can justify the rationale for the measure and establish a relationship between a quantitative and qualitative measure, observer bias should be eliminated. We encourage the Agency to consider this approach in both the planned draft guidance for industry Patient Reported Outcome Measures: Use in Medicinal Product Development to Support Claims and in this guidance.

#### **Section IV Endpoints and Clinical Trial Design; Selected Issues B Studies Designed to Demonstrate Noninferiority (NI)**

Line 592: *“Because of the difficulties with the design, conduct, and analysis of non-inferiority trials, a single NI trial seldom provides sufficient evidence of efficacy to support approval.”* We believe that the adequacy of the evidence should be driven by the indication and suggest that this sentence be modified to reflect that, in some cases, a single study based on NI should be acceptable, especially if the endpoint is overall survival and the value of the comparator agent is well established.

#### **Section IV C No Treatment or Placebo Control**

Line 612 *“Placebos (identically appearing inactive controls) are generally preferred to no-treatment controls because they permit blinding”*. Placebo-controlled trials have an impact on the ability to effectively enroll patients in clinical trials. In addition, blinding issues remain even though the FDA also states that, *“newer interventions, many of them much less toxic, are increasingly being studied in blinded trials”*. In another example of the need for harmonization, placebo-controlled oncology trials are generally not recommended in the EU. It would be beneficial to patients and sponsors if the acceptability of placebo-controlled trials were harmonized.

#### **Section IV D Isolating Drug Effect in Combination**

There are specific clinical considerations for the development of a drug/drug combination. Section IV D. is very brief and does not address the myriad questions; we are requesting more detail be provided in Section IV D. Certain questions can be addressed in the expanded section, such as “Are there scenarios where an experimental drug intended only for combinations (e.g., a chemotherapy sensitizer) can be evaluated for toxicity using exclusively the “add on” approach referenced, or it is absolutely necessary that the experimental drug be evaluated first or simultaneously as a monotherapy?” “How much monotherapy data are required before combination studies are initiated in clinical trials?” We anticipate that answers to these questions would be of general value to sponsors developing drug/drug combination therapies for cancer.

**Conclusion**

In summary, we support the development of this general guidance document describing clinical trial endpoints for the approval of cancer drugs and biologics. As FDA has indicated, we agree it is important to follow this general guidance with disease-specific guidance documents. We hope these are developed using a transparent, participatory process with input from NCI, academia and industry. Additionally, as regulatory authorities in various regions of the world are also in the process of developing oncology guidance, we strongly encourage a harmonized approach to foster efficiency in the development of much needed medicines to treat cancer. We have identified specific areas for further clarification and have commented on specific potential issues. To address the need for further clarification of these points, we recommend the guidance be revised as noted herein.

We appreciate the opportunity to share our comments with respect to the FDA Draft Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Please do not hesitate to contact me, should you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Taryn Rogalski-Salter". The signature is fluid and cursive, with a long horizontal stroke at the end.

Taryn Rogalski-Salter, PhD

Director

Regulatory Policy