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Management Dockets
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Food and Drug Administration
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Re: Docket No. 2005D-0112: Comments on the “Draft Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics,” Federal Register, Volume 70, No. 63, Page 17095, April 4, 2005

Dear Sir or Madame:

Reference is made to the notice, as published by the Food and Drug Administration in the Federal Register on April 4, 2005, to invite written comments on a new draft guidance for industry (“Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics”). The purpose of this letter is to provide comments on this new draft guidance.

GlaxoSmithKline is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacture, and distribution of medicines and vaccines that enable people to lead longer, healthier, and more productive lives. GlaxoSmithKline has a long history of productive research and development of products for the treatment of cancer. In these efforts, we have worked constructively with the Division of Oncology Drug Products and other groups within FDA.

GlaxoSmithKline holds FDA-approved New Drug Applications for a number of products to treat cancer patients, including Hycamtin[®] (topotecan hydrochloride) for injection, Alkeran[®] (melphalan) products, Leukeran[®] (chlorambucil) tablets, Myleran[®] (busulfan) tablets, Navelbine[®] (vinorelbine tartrate) Injection, Bexxar[®] (tositumomab and iodine I 131 tositumomab) and Zofran[®] (ondansetron hydrochloride) products. In addition, we have ongoing activities to develop new drug products in a variety of classes to treat solid tumors, hematologic malignancies, and cancer related illnesses. These include inhibitors of ErbB1 and ErbB2 tyrosine kinases receptors, inhibitors of VEGFR tyrosine kinase, and NK1 receptor antagonists. In view of our longstanding work in this field and our substantial interest in the topics in this new draft guidance, we welcome this opportunity to provide comments for FDA’s consideration.

In the following sections, we provide comments on the draft guidance.

General Comments

The draft guidance is being issued at an opportune time when many new targeted agents are under investigation. The development of such agents may carry different challenges from historical development of cytotoxic agents. Table 1 provides a useful, quick reference for comparing endpoints, and it shows not only current status of the endpoints but also provides issues that still need to be addressed, e.g., Various definitions exist for DFS and PFS; Few instruments are validated for measuring cancer-specific symptoms. It is important to acknowledge that potential future issues are included; among those are methods for assessing progression (Line 396) and the introduction of unproven analyses of symptom endpoints (Line 493).

Aspects of the guidance are most useful when examples of tumor types and settings are given showing where specific endpoints are appropriate, e.g., DFS for colon cancer (Line 224). Similarly, explanations of the difficulties with the use of HRQLs (Line 448) and historical controls in certain settings (Line 163) are valuable for those designing development programs. It is suggested that FDA post as part of the Oncology Tools website a list of validated surrogate endpoints that result from the workshops and Advisory Committee review of endpoints for different tumor types. The listing/posting could be updated more quickly than guidance documents.

The focal point of each comment that follows is identified by the line numbers in the draft guidance. We trust that this approach will facilitate your review and consideration of our comments.

II. BACKGROUND

Lines 43-44: We suggest an addition (addition in italics) for clarity. “In conventional oncology drug development, early phase clinical trials evaluate safety *and tolerability*, and identify evidence of biological drug activity, such as tumor shrinkage.”

Lines 45-46: We suggest an addition to one sentence that follows (addition in italics) for clarity. There may be other endpoints in later stage studies, e.g., safety. “Endpoints for later phase efficacy studies *primarily* evaluate whether a drug provides a clinical benefit such as prolongation of survival or an improvement in symptoms.”

A. Regulatory Requirements for Effectiveness

Line 83: We suggest providing additional detail to clarify what is meant by “highly reliable and statistically strong evidence”. For example would a significance level of 0.01 instead of 0.05 be considered “strong evidence”?

Line 91: Regarding the first sentence in the section, we suggest revised or additional wording to clarify the regulatory requirements for approval, such as the following. *FDA has interpreted the requirement for substantial evidence of efficacy to mean that the sponsors show substantial evidence of clinical benefit and for regular approval this has been an improvement in survival or in a patient's quality of life, improved physical functioning, or improved tumor-related symptoms.*

B. Endpoints Supporting Past Approvals in Oncology

Lines 107-111: Descriptors such as high or very high can be interpreted in various ways, but we agree the message from this sentence is needed and appropriate. It is suggested that very high be replaced by high. "The FDA has also considered that a *high* ORR alone might sometimes support regular approval, but...."

III. GENERAL ENDPOINT CONSIDERATIONS

Table 1: A Comparison of Important Cancer Approval Endpoints

It would be helpful to have the definitions of the endpoints included in this table.

Disease Free Survival, Assessment: To be consistent with Lines 201-204 of the Guidance, add bullet "Blinded review recommended".

Objective Response Rate and Complete Response, Assessment: Same comment as above. To be consistent with Lines 201-204 of the Guidance, add bullet "Blinded review recommended".

Objective Response, Second Bullet under Some Disadvantages: To improve clarity, reword "Usually reflects drug activity in a minority of patients" as "Not a comprehensive measure of drug activity".

Progression Free Survival, Sixth Bullet under Some Disadvantages: Suggest rewording to "Frequent radiologic *assessments* are needed."

We suggest adding time to progression (TTP) to Table 1 as it would be helpful to see how the advantages and disadvantages compare to other endpoints. We suggest listing as disadvantages informative censoring; it seems unlikely in most cancer settings that patient deaths are randomly related to tumor progression (as stated in lines 309-311).

Symptom Endpoints, Third and Fourth bullet in Some Disadvantages: “Few instruments are validated for measuring cancer-specific symptoms.” “Data are voluminous and complex compared to survival.” Although in general the comment in the guidance on the quantity of data is true, concise symptom based assessments do not always produce large quantities of data. Also, there are validated scales available for various symptom based endpoints; however surrogacy to survival and other traditional endpoints are not always validated. We suggest clarifying the sentence on existence of validated scales to reflect the precise lack of validation of surrogacy and also stating that sometimes unwieldy data may be generated by using complex QOL scales.

A. Overall Survival

Line 158: “An improvement in survival is of unquestioned clinical benefit.” This is well established, but we recommend more context be added. Consider that in some malignancies increased survival is expressed in number of days. Therapies in other tumor types may provide clinical benefit with responses or stable disease that is measured in weeks or months.

B. Endpoints Based on Tumor Assessments

Lines 194-196: We suggest removing the phrase ‘from a second trial’ from the following statement: “Drug applications using studies that rely on tumor measurement based endpoints as sole evidence of efficacy should generally provide confirmatory evidence from a second trial.” There are cases where it has been acceptable to submit for approval using a tumor measurement based endpoint with survival data from the same trial provided at a later date as confirmatory evidence.

Line 194-195: For clarity it would be helpful to add “(e.g., progression free survival or ORR)” from lines 201-202 to the following sentence “ Drug applications using studies that rely on tumor measurement based endpoints (*e.g., progression free survival or ORR*) as sole evidence. . .”

1. Disease-Free Survival

Lines 217-219: An addition to the following sentence is recommended for clarity. “Whereas overall survival is the standard endpoint for most adjuvant settings, DFS has been the primary basis of approval for hormonal therapy after initial surgery for breast cancer, *as hormonal therapy carries minimum side effects and survival is significantly extended.*”

Lines 239-241: A revision is suggested that would replace likely with possibly in this sentence. An addition of timing is suggested. "Unscheduled assessments can occur... differences between study arms in the frequency, *timing*, or reason for unscheduled assessment *may possibly* introduce bias."

2. *Objective Response Rate*

Line 279-282: "These issues...determine whether ORR will support marketing authorization,..." The guidance would be enhanced considerably if the Agency adds their views on situations, tumor types, or characteristics of responses that would support approvals based on response rates. It is understandable that this is always a review issue, but reflecting these views in the guidance will allow sponsors to approach the Agency appropriately.

3. *Time to Progression and Progression-Free Survival*

Line 289: For clarity, it would be helpful to fully define time to progression at the beginning of this section (e.g., indicate that according to TTP all deaths are censored) because there are some definitions of TTP that count death due to the cancer under study as an event.

Lines 289-291: We agree that TTP has seldom served as a primary endpoint for *initial* approval of drug products, but there is an established precedent that TTP has been an appropriate endpoint for subsequent indications. It is suggested that this caveat be added.

Lines 291-293: "Time to symptomatic progression, which would represent a clear clinical benefit, is infrequently assessed but would be a credible endpoint of a well-conducted (generally blinded) trial." Although this will vary by tumor type, we suggest inclusion of examples where this would be an appropriate endpoint.

c. PFS trial design issues

Lines 348-352: Revised wording is proposed regarding "analysis of missing data." "It is important that the FDA and the sponsor agree prospectively on the protocol, data to be recorded on the case report form, statistical analysis plan (including *methodology for handling* missing data and censoring methods), and,....

Also, the reader would be assisted if the guidance included more details on designing trials properly such that missing data are minimized. Specifically, this would address

situations, frequency of visits and how this relates to the hypothesized treatment effect.

4 Time to Treatment Failure

Lines 421-422: “Defined that way, TTF is not recommended as an endpoint for drug approval because it combines efficacy and toxicity measures.” Other endpoints also combine efficacy and toxicity measures. For example, in determining the overall response rate, if a patient discontinues study treatment due to toxicity, the patient is still part of the denominator. Hence, the reasoning for not recommending TTF is not adequately articulated.

C. Endpoints Involving Symptom Assessment

Lines 436-437: “HRQL is discussed in a separate FDA draft guidance on patient – reported outcomes (PRO)¹⁰.” The referenced footnote describes the draft guidance that is due out in the summer of 2005. GlaxoSmithKline appreciates the Agency’s efforts to issue such a guidance which will complement this guidance on endpoints.

Lines 443-445: “It seems self-evident that cancer patients will be in most cases the best source for determining effects on patient symptoms, so that PRO instruments seem most appropriate.” It should be noted that the PRO could be influenced by the way in which the questions are phrased and therefore the use of validated instruments is important.

The reader would be assisted if the guidance included examples of cases where symptom assessment endpoints have been used.

1. Specific Symptom Endpoints

It would be helpful for the guidance to include suggestions on how to account for missing data for symptom endpoints (specifically missing data due to deaths).

2. Problems Encountered with Symptom Data

Lines 503-504: “Ideally, when patients stop treatment, data collection forms should continue to gather information to inform the analysis.” It would be useful to add how long patients should be followed, e.g., 30 days post dose.

D. Biomarkers

This section states that further research is needed in this area. We agree and look forward to working with FDA as pharmacogenomics and other aspects of this field move forward. It would be beneficial for future guidances on Biomarkers to address creation of assays for surrogate markers for targeted therapies and biomarker-to-clinical benefit validation in as much detail as possible. If possible, this current guidance should provide some reference on how to develop biomarkers and criteria for establishing surrogacy.

V. SUMMARY AND CONCLUSION

Line 654-656: Revise the following sentence replacing “a single trial” with clinical trials. “Ultimately, of course, marketing approval will depend not only on the design of *the clinical trials*, but on FDA review of the results and data form all studies in the drug marketing application.”

APPENDIX 1:

Suggest adding the following:

- Details on how to handle lesion that are ‘too small to be measured’. Suggest entering ‘1mm’ to distinguish between missing data, lesions that have resolved, and lesions that are ‘too small to be measured’.
- Details on how to handle lesions that ‘split’. In order to appropriately document what is occurring with a given lesion, lesions that split need to be tracked based on all of the ‘pieces’ or ‘splits’. Most importantly ‘splits’ should not be documented as additional lesions. Suggest that any lesion which splits should have the longest diameter of both lesions measured, summed up, and recorded as the longest diameter for the originally recorded lesion with a lesion code of ‘lesion split or divided’ to document that the original lesion split.
- Details on how to handle lesions that ‘merge’. Suggest that if any existing lesion (#1) merges with another existing lesion (#2), measure the longest diameter of the confluent mass and record this measurement as the longest diameter for the (#1) recorded lesion. Record ‘0’ as the longest diameter for the (#2) lesion and record the lesion both with a lesion code of ‘Lesion Merged or Coalesced’ to document that the two lesions merged.

- Mention the types of methods that are acceptable for the evaluation of lesions, e.g., CT Scan, Ultrasound, PET scan.

Again, we thank you for this opportunity to provide comments on this important topic. This submission is provided in electronic format according to the instructions provided at

<http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm>

Please contact Robert S. Watson at (919)-483-6972 for any matters regarding this submission. If you wish clarification or further discussion of our comments, we would be pleased to schedule a teleconference or meeting in follow-up. Thank you.

Sincerely,

A handwritten signature in black ink, appearing to read "Robert S. Watson". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Robert S. Watson
Vice President
Regulatory Affairs, Oncology