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Re: Docket No. 2005D-1022
Draft Guidance for Industry, Investigators, and Reviewers - Exploratory IND Studies

Dear Madam or Sir:

Enclosed please find comments from GlaxoSmithKline, including general and specific comments for the Draft Guidance for Industry, Investigators, and Reviewers - Exploratory IND Studies. These comments are presented for consideration by the FDA. The general comments are presented first, with the specific comments presented in order by line number and section in the draft guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this draft guidance. I am submitting the comments for this draft guidance by hardcopy. Therefore, you will receive this letter with two copies of the comments.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

A handwritten signature in black ink that reads "Mary Faye S. Whisler".

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

2005D-0122

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GENERAL COMMENTS

At GlaxoSmithKline, we discover, develop, manufacture, and distribute prescription and non-prescription drug products for the treatment of many diseases. In our work, we sponsor the conduct of many clinical investigations including "first in human" clinical trials of new molecular entities. Our comments on this draft guidance are based on our extensive experiences and knowledge of this field. GlaxoSmithKline supports development of the Guidance and appreciates the opportunity to provide comments for consideration.

GlaxoSmithKline is supportive of the exploratory IND concept and appreciates the Agency's effort to clarify how sponsors may meet regulatory requirements and maintain human subject protection while moving forward development of promising candidate products with greater efficiency. In our suggestions, we have described areas where we feel that specific guidance from the Agency will facilitate increased development efficiency, ensure consistency of expectations for content/format across the CDER review Divisions, and allow the greatest opportunity for sponsors to avoid providing more supporting information than is required by regulations. Provided below are both general and specific, annotated, suggestions that we believe will further improve the Guidance.

- It would be helpful if the Guidance included a tabular summary that contrasts the Agency's expectations for data/documentation needed in the Phase I IND and the Exploratory IND. This information could be provided in an appendix and would include: the clinical development plan and associated document requirements, Chemistry, Manufacturing and Controls (CMC) information, Pharmacology and Toxicology information, and Previous Human Experience. Use of examples would facilitate an understanding of areas where FDA will allow the greatest opportunities for development efficiency.
- We suggest that the Guidance specify that a molecule that is already the subject of an active IND may be utilized as a direct comparator in an exploratory IND and that data may be incorporated by cross-reference (e.g. head to head comparison of pharmacodynamic (PD) or pharmacokinetic (PK) parameters of a lead or reference molecule versus follow-on compounds).
- We suggest that the Guidance specifically address Annual Report requirements for the exploratory IND.

SPECIFIC COMMENTS

Line 23 - GSK suggests that as long as the supporting data requirements have been met, the exploratory IND should allow comparison of molecules for pharmacodynamic effects via different pharmacologic mechanisms. Accordingly, we suggest that the requirement for “closely related” drugs be clarified or the term deleted from the Guidance. GSK also feels that the Guidance should also make clear that an exploratory IND may cover multiple formulations and multiple routes of administration (e.g. metered-dose inhalers, dry powder inhalers, nebulized solutions, intranasal solutions, iv formulations, tablets, capsules, etc.).

Lines 37, 188, 342 - The draft guidance describes an intent of limited duration of clinical exposure and gives 7 days as an example of this intent. Please clarify if this is the maximum duration of exposure based on the recommended repeated dose toxicity studies described in each of the scenarios described in Section C. Specifically, please clarify if this means 7 consecutive calendar days or days on which a clinical dose is administered (e.g. every other day single doses for 2 weeks). We also suggest that the Guidance address if 14 day repeat dose studies are conducted in rodent and non-rodent species (e.g. scenario described on lines 361 to 363 when rodent is not the most sensitive species), that clinical dosing up to 14 days can be supported.

Lines 105 to 106 – GSK suggests that the Guidance specify that the exploratory IND will allow for first time in human (FTIH) studies in the intended use population (patients) via comparative assessment of specific biomarkers at doses below those expected to be therapeutically active (i.e. FTIH studies in patients in an early Phase 1 setting).

Lines 176 to 178 – GSK suggests that the Guidance describe a specific mechanism to facilitate continuity of the administrative record by allowing the exploratory IND to transition to support traditional studies. We note that line 176 alludes to this option by supplementing the IND but more detail regarding Agency expectations would be helpful and allow for consistency between review Divisions. Such a mechanism would allow all data for the molecule that is taken forward to reside with one application. This application could be referenced in the future should a molecule not initially advanced become the subject of a subsequent IND. We feel it would be more efficient for a sponsor to submit an amendment to the IND with a declaration of future intent to focus on a single identified molecule rather than withdraw or inactivate the exploratory IND. This declaration would certify that any future investigations for other molecules would not be conducted until a separate IND had been submitted. As indicated on lines 177 and 178, additional data would be required to be submitted to FDA in order to support clinical investigations intended to evaluate traditional dose escalation, safety and tolerance. We propose that the Guidance make clear that all usual data requirements would be expected at the point that a clinical study protocol is submitted to evaluate dose escalation, safety and tolerance objectives. Importantly, FDA should address whether a mandatory review period would be required at the time the exploratory IND is transitioned to support traditional Phase 1 study objectives.

Lines 181 to 190 – GSK suggests the Guidance address whether clinical studies to assess multiple drugs within the same study allow for both parallel dosing and cross-over dosing designs. GSK also suggests the Guidance address any limitations applicable to situations where more than one drug may be administered to a single subject following an appropriate wash-out period (e.g. maximum number of agents, total exposure per agent etc).

Line 182 - Footnote 9 states that unless an IND is in effect, before you can conduct a radiolabeled study, you need to have first time in human results published in a medical journal. FTIH studies are not usually published as they are so early in the development and do not generally offer insight into efficacy. Also radiolabeled studies are conducted under the auspices of the local IRB and the Radioactive Drug Research Committee (RDRC). Supporting data can include published data but also 'other human data' provided it supports calculation of the non-pharmacologically active dose. The footnote requires clarification; a suggested change: "...following the initial publication in the medical literature of a first in human experience with that radiolabeled compound." to: "...based on published literature or other human data with the radiolabeled compound."

Lines 217 to 289 – It is noted that there is no distinction between drug substance and drug product in this guidance. However, it would be helpful to organize CMC information such that items typically for active ingredient only are grouped together and items that are typically for drug products are also grouped together.

Lines 227 to 228 – In the sentence: "For products intended for ophthalmic, inhalational, or parenteral administration, sterility must be ensured," GSK recommends addition of the word "by nebulization" after inhalation. Typically, MDIs are not sterile. We suggest that the specific text should read: "For products intended for ophthalmic, inhalational by nebulization, or parenteral administration, sterility must be ensured."

Lines 259 to 260 – The inhaled products should be defined as this statement assumes that it is a nebulized solution for inhalation.

Lines 268 to 269 – Please clarify the degree of impurity characterization required for an exploratory IND. It appears that FDA would not usually require characterization at the time of an exploratory IND. This should be clarified and examples given when FDA would expect data to support characterizations prior to a traditional IND. GSK suggests that this guidance reference applicable ICH/FDA guidance documents.

Lines 291 to 425 (Section III C.) – The Guidance gives little if any specific insight as to the flexibility FDA will allow with respect to the content/format for non-clinical data presented for safety studies. Based on the draft guidance, one would expect to provide data in the same level of detail as described in Section G. of FDA's Guidance "*Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized Therapeutic Biotechnology-derived Products*". Since the regulations do not specifically require that individual study reports must be submitted, we suggest that additional flexibility with respect to the content of toxicology data is within the spirit and intent of the exploratory IND. Accordingly, we suggest that the Guidance describe how the Clinical Investigator's Brochure might be utilized to serve as the basis for summarized/tabulated toxicology data required under 21 CFR312.23(a)(8)(ii)(b). We propose that the requirements for individual draft and final reports would not apply for an exploratory IND but would apply when a traditional dose escalation, safety, or tolerance studies are submitted.

Lines 342-343 – This line states 'Repeat dose clinical trials lasting up to 7 days can be supported by a 2-week repeat dose toxicology study in a sensitive species accompanied by toxicokinetic evaluations.'

It would be useful if the rationale for selecting the high dose for the rat 2-week study could be given. We would like to propose that this should normally be a dose that produces some evidence of target organ toxicity, but for compounds of low toxicity a maximum dose of 1000 mg/kg could be used.

Lines 346-347 – These lines state 'If a rodent species is used, additional studies in non-rodents, most often dogs, can be used to confirm that the rodent is an appropriately sensitive species. This confirmation can be approached in a number of ways.' In Europe, discussions are ongoing between EFPIA and the CHMP Safety Working Party to support such exploratory clinical studies by conducting toxicology studies in which the doses used are selected to produce an overage of the intended clinical exposure. A quite extensive FTIH database has been collected by EFPIA that provides support for an overage-based approach. In order to create a degree of harmony between the US and European approaches we would like to propose the following sentence (italics) be inserted (lines 355 - 358). 'Alternatively, the test in the second species could be incorporated as part of an exploratory, dose escalating study culminating in repeated doses equivalent to the rat NOAEL. *Another approach could be to conduct an overage-based study in the non-rodent, with doses selected to achieve exposures at least 10-fold higher than the highest human exposure in the proposed clinical study.* In all cases the number of repeat administrations in the non-rodent should, at a minimum, be equal to the number of administrations, given with the same schedule, intended clinically.'

Lines 349-351 – This line states 'The number of animals used in the confirmatory study can be fewer than normally used to attain statistically meaningful comparisons, but of sufficient number to meaningfully identify a toxic response.'

It would be useful to state a minimum number here to avoid confusion.

Lines 366-370 – This line states 'If an exploratory IND study is designed to elicit pharmacological effects, each candidate product to be tested should be evaluated for safety pharmacology¹⁷. Evaluation of the central nervous and respiratory systems can be performed as part the rodent toxicology studies while safety pharmacology for the cardiovascular system can be assessed in the non-rodent species, generally the dog.'

GSK does not understand why safety pharmacology studies are only required if the clinical study is designed to elicit pharmacological effects. The objective of the clinical study might be around a toxicokinetic (TK) endpoint, e.g. half life, but the dose administered could still achieve exposures that might produce unwanted pharmacological effects. Furthermore, safety pharmacology studies are conducted to identify effects that are not necessarily related to the intended target pharmacology. It would also be useful to provide some guidance on how the doses should be used if the dog CV study should be selected.

Lines 381 - 385 – These lines state 'The maximum clinical dose would be the lowest of the following: (1) $\frac{1}{4}$ of the 2-week NOAEL; (2) $\frac{1}{2}$ of the AUC at the NOAEL in the 2-week rodent study, or the AUC in the dog at the rat NOAEL, whichever is lower; or (3) the dose that produces a pharmacological response or at which target modulation is observed in the clinical trial.'

However, in the flow diagram in the attachment, one option (bottom right) for the calculation of clinical stop dose is 'Clinical equivalent of $\frac{1}{2}$ of rat or non-rodent AUC - whichever is lower.' This seems to contradict the text - if the stop dose is based on the non-rodent study, please clarify whether it should it be the AUC or $\frac{1}{2}$ the AUC.

Lines 417 to 418 – GSK suggests that expectations for GMP compliance should be specified in a manner consistent to the description for GLP.