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Re: NAS 0; Not Product Specific
**General Correspondence: Comments on Draft "Guidance for Industry:
Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers
Enrolled in Preventive Vaccine Trials"**
[Docket No. 2005D - 0155]

Dear Sir or Madame:

Reference is made to the notice published by the FDA in the Federal Register on May 2, 2005, to invite written comments on a new draft guidance for industry ("Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"). The purpose of this letter is to provide comments on this new draft guidance.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, happier, healthier, and more productive lives. GSK has a long history of productive research and development of vaccine products and our clinical development group has been involved in vaccine testing throughout the development of our approved products and maintains continued interest and expertise in this area. In addition, we have ongoing activities to develop new vaccines for a variety of uses. In view of our longstanding work in this field and our substantial interest in the topic in this new draft guidance, we welcome this opportunity to provide comments for FDA's consideration.

We value the benefit of guidance and standardization from the perspective of FDA for the identification and grading of adverse events following vaccination. GSK endorses further collaborations to reach a universal standardization for this purpose, and we urge that such guideline is reviewed and agreed upon by other main regulatory bodies, including ICH endorsement. For this purpose, we propose contacting the European Authorities through the European Vaccines Manufacturers. We also recommend that the guidelines are

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aligned with the Brighton Collaboration definitions
[<http://brightoncollaboration.org/en/index/aeft.html>].

General Comments

The final Guidance should very clearly state that not all events listed in the Toxicity Grading Scale tables provided in the draft guidance need to be solicited or recorded in every trial. It is our understanding that sponsors will not be required to justify the lack of inclusion.

Although it can be clinically relevant to use an intensity grading system for a specific event by collecting information on multiple variables, we recommend this information be collected separately. For example, swelling uses **both** a measurement **and** an assessment of degree of functional impairment; headache uses **both** interference with activity **and** use of pain reliever; clinical illness uses **both** interference with activity **and** requires medical attention. Compound criteria could then be developed at the stage of the analyses.

The Grade 4 category is seen as problematic for numerous reasons:

- GSK Biologicals will lose the ability to reference our extensive experience with clinical toxicity grading in vaccine development programs, as the change to a four-grade scale will not be in line with our current system with 3 grades.
- Some events might reach a Grade 4 without being "potentially life threatening". Naming those events as "potentially life threatening" in clinical reports might lead to misinterpretation.
- The ranking of life-threatening events does not appear to be consistent. For example, >2+ proteinuria is indicated as Grade 4 (potentially life-threatening) while the corresponding Grade 4 adverse event for respiratory rate is intubation. One can argue that the Grade 2 respiratory rate represents a potentially greater risk to health than the Grade 4 proteinuria.

In summary, we recommend elimination of category "Grade 4"; AEs that result in hospitalization are SAEs, so they will otherwise be captured.

Implementation of this Guideline could be potentially disruptive for ongoing clinical development and we suggest that at the time of implementation, the Guidance be applicable to new programs but not those already underway.

The concept of a toxicity table for unsolicited AEs can be very useful when studying vaccines administered to populations other than healthy persons (e.g., Staph Mab in NICU patients, or Cancer vaccines, or vaccines studied for the elderly). Otherwise, the

occurrence of unsolicited AEs is so uncommon and the diversity so great that standardization may be of limited value because clinical context is so critical in judging the impact of AEs after vaccination.

Section III. Toxicity Grading Tables

Part A: Tables for Clinical Abnormalities - "Local Reaction to Injectable Product" (page 3)

Clarification is needed on the definitions of "pain" and "tenderness". In the past, it was difficult to understand reactogenicity results across studies where symptoms with similar (but slightly different) meaning were solicited in the same protocol and/or different protocols (i.e. fatigue and malaise, irritability and fussiness) without clear definitions. It will be difficult to differentiate pain and tenderness in a standardized way and we suggest merging those 2 symptoms to one.

There is no grading for very mild events (redness or swelling < 2.5 cm or temperature < 38°C) that are currently captured.

Exfoliative dermatitis and necrosis appear distinct from redness and swelling, i.e. clinically separate entities.

Use of anti-inflammatory agents or other pain relievers may reflect physician preference and not severity.

Table footnotes:

Clarification is needed for "** In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable".

Please clarify the "functional" scale for "*** Swelling should be evaluated and graded using the functional scale as well as the actual measurement".

Part A: Tables for Clinical Abnormalities - "Vital Signs" (page 4)

For the measurement of vital signs (even though rarely used for vaccine studies), a time period "at rest" should be consistent. Pharma studies usually require at least 5 minutes at rest and at least 5 minutes between repeat measurements.

Grade 1 and 2 cardiovascular symptoms are too stringent. They are still within the margin of values of subjects that would be included as "normal healthy volunteers" in clinical trials (as long as they do not have significant symptoms)

Arrhythmia cannot be considered as severe tachycardia or bradycardia.

PSVT routinely exceeds 150 beats/minute; almost no such occurrence would be graded more than 2.

The hypertension scale is inflated for adults.

Part A: Tables for Clinical Abnormalities - "Systemic (General)/Systemic Illness" (page 5)

We note that rash, urticaria and arthralgia are not listed, whereas the Agency has asked us to add those symptoms to the list of solicited symptoms in recent studies. What is FDA's position on those symptoms?

The definition for severe nausea is unclear: "prevents daily activity, requires outpatient IV hydration". Does this mean AND or OR?

The CDC case definition of diarrhea is '3 or more looser than normal stools'.

Unless the subjects are meant to be kept in the clinic, weighing stools is not a practical criterion for grading diarrhea.

Part B: Tables for Laboratory Abnormalities (pages 6 and 7)

In general, the guidelines are too stringent to be used to characterize the "normal healthy volunteers" included in our preventative vaccine trials. Some of those volunteer subjects might have slight laboratory abnormalities without clinical symptomatology, which should be considered as normal, for participation in clinical trials (for example, studies in an elderly population). Examples are provided, below:

Serum

- Lower limit of toxicity Grade 1 should be moved up for alkaline phosphatase, ALT, AST, bilirubin. As currently listed, 1.1 x ULN, the noise to signal ratio would be quite high. Consider 1.2 or 1.25 ULN; a similar line of thinking may also apply to the lower limit for Grade 1 for creatinine.

- BUN scale sets threshold for grades 2-4 too low.
- Calcium scale without reference to serum protein is misleading - suggest deletion.
- Dynamic range for cholesterol is too narrow.

Hematology

- Lower limit of toxicity grade 1 should be moved up for hemoglobin.
- Leukocyte thresholds for grades 1 & 2 are too low (especially WBC counts in view of normal levels for Blacks).

This submission is provided in electronic format according to the instructions provided at <http://accessdata.fda.gov/scripts/oc/dockets/commentdocket.cgm?AGENCY=FDA>.

Please contact me at (919) 483-6405 if you require clarification or have any questions about these comments. Thank you.

Sincerely,



Anne N. Stokley, M.S.P.H.
Director, Policy, Intelligence & Education
US Regulatory Affairs