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

**RE: [Docket No. 2005D-0155] – Draft Guidance for Industry: Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; Availability**

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 or biologic 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 vaccine product candidates through developmental testing and clinical trials, Merck scientists address issues affected by this proposed Guidance. We have extensive experience in the clinical development of vaccine candidates and have utilized that experience to author the comments below.

**General Comments**

We commend the Food and Drug Administration (FDA or Agency) for its efforts in the development of guidance for industry establishing a toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. The proposed guidance is clear in that the parameters described as clinical abnormalities are *not necessarily warranted for every clinical trial of health volunteers* (Section III. Toxicity Grading Scale Tables). We encourage the Agency to reinforce this point in the final guidance document and in subsequent training of review staff.

Harmonization of the grading of adverse events is critical for the efficient clinical development of vaccine candidates for worldwide use. Slight discrepancies in categorization of adverse events may have major impact on clinical development; we encourage the Agency to work with its international (and domestic) colleagues to promote harmonization. The Brighton Collaborative referenced in Section II. (Background) has been developing similar standards for case definitions and adverse event evaluations. We have identified areas of disparity between this draft guidance and the work of the Brighton Collaborative. For instance, the Brighton classifications often include Grade 0 categories. In our experience, CBER has explicitly asked sponsors to follow the Brighton Collaborative classification scheme when reporting fevers. We request that contradictions between the work of the Agency and the Collaborative be avoided. This could be accomplished by harmonizing the guidance with the work of the Collaborative; in this example, by adding a category of Grade 0 for reporting fevers.

### **Specific Comments**

**I. Introduction:** *“Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies.”* We agree that uniform criteria will facilitate comparisons of safety data but we do not believe the Agency is indicating that comparisons between sponsors can be made. We suggest that the sentence be modified to read *“Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies conducted by the same sponsor”*.

**III. A. Tables for Clinical Abnormalities, Table for Local Reaction to Injectable Product:** Although the Potentially Life Threatening (Grade 4) descriptions (e.g., emergency room visit or hospitalization) clearly represent more extreme events than Grade 3, for several of the events (particularly local reactions, but also some others), it seems rather inappropriate to use the label *“potentially life threatening”*. We suggest that the most severe Local Reactions Grade 4 be changed from *“Potentially Life Threatening (Grade 4)”* to *“Most Severe (Grade 4)”*. In addition, local reactions are often poorly characterized such as differentiation between allergic reaction and cellulitis resulting from the injectable. We request that text describing characterization of local reactions be added to the guidance to indicate that the cause of the local reaction should be noted, such as, allergic reaction, cellulitis or undifferentiated.

**III. A. Tables for Clinical Abnormalities, Table for Vital Signs and Table for Systemic (General).** The vital signs section must allow for flexibility with respect to normal ranges. Toxicity should relate to an abnormality, reflecting a negative change from baseline. Many young people have a resting pulse in the 50s. According to the Systemic Table in the draft guidance, a pulse between 50 – 54 would be considered abnormal; the draft guidance does not seem to allow NOT calling a resting pulse in the

50s an adverse event. In addition, the concept of baseline condition or normality can apply to some systemic events as well, either due to chronic conditions (e.g., back pain) or normal events (e.g., lower abdominal pain with menstruation). We agree that a change from the baseline condition would be important to capture. We suggest that explanatory text be added to the guidance reflecting that toxicity should relate to an abnormality, reflected by a change from baseline. *If the healthy volunteer exhibits vital signs or signs/symptoms at baseline that would meet the criteria for mild or moderate clinical abnormalities, then an adverse change from the baseline condition, if present, determines categorization of the adverse event.*

**III. A. Tables for Clinical Abnormalities, Table for Vital Signs.** Depending on the populations involved, there may need to be some latitude in the specified categories for fever. Some sponsors may wish to use a more stringent cut-off of 100.0 °F (instead of 100.4), 101.0 °F (instead of 101.2), or some other cutoff when describing Mild or Moderate fever, respectively. We request that the value ranges for Mild, Moderate and Severe fever be *suggested* ranges, with the option of more stringent values clearly described in the text of the guidance. In addition, Grade 4 fever would be better defined not by a number alone, but by the presence of accompanying symptoms indicating a life-threatening situation.

**III. B. Tables for Laboratory Abnormalities, Serum, Hematology, Urine.** As mentioned in the General Comments, the parameters listed in these Tables should be considered examples of parameters and not necessarily indicate that each parameter needs to be followed in every vaccine clinical study. In addition, as noted in the footnote, the guidance should be based on local (institutional or central laboratory) normal ranges; the ranges provided in the tables are viewed as examples. This is a critical point that requires additional emphasis.

The laboratory values that are followed for safety should be limited to select, important parameters including an assessment of the variability of the values in the normal population. For example, regional or racial differences in some laboratory values, such as in white blood cell (WBC) count may need to be considered. Also, because (as noted in the Introduction) the grading system provided in the table can be useful in defining stopping rules for the clinical study, we wish to point out that the variability of certain laboratory parameters may limit the usefulness of the parameters in clinical design. For example, although it may be reasonable to follow creatine phosphokinase (CPK) values, the variability of this parameter in a normal active population makes it difficult to use as a basis for stopping rules.

## **Conclusion**

In summary, we support the development of this guidance document. We have identified 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. It will be important for the Agency to foster international harmonization with the definitions of clinical abnormalities, while continuing to recognize that each vaccine development program is unique.

We appreciate the opportunity to share our comments with respect to the FDA Draft Guidance for Industry: Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Please do not hesitate to contact me, should you have any questions.

Sincerely,



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