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HIV VACCINE
TRIALS NETWORK

29 July 2005

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

From: HIV Vaccine Trials Network Scientific Support Unit
by Theresa Shea, PA-C, HVTN Core Medical Monitor

RE: **Docket No. 2005D-0155, CBER 200432**
Draft Guidance for Industry
Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers
Enrolled in Preventive Vaccine Clinical Trials

The HIV Vaccine Trials Network (HVTN) respectfully requests your review of the attached responses to the Food and Drug Administration's "Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."

As you know, the HVTN has worked closely with the Division of AIDS (DAIDS) over recent years, incorporating the network's existing data to develop appropriate toxicity grading scales for vaccine research participants. The HVTN and DAIDS are committed to ensuring participant safety in HIV vaccine trials. The HVTN believes the comments contained in this document, as well as the recently updated *Division of AIDS Table For Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004* are essential to guiding the industry in this commitment to safety in the pursuit of effective vaccines.

We appreciate this opportunity to work with the FDA in these important efforts.

2005D-0155

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HVTN Response to Draft Guidance for Industry
Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive
Vaccine Clinical Trials

General Comments:

- In the laboratory tables, the lower limit of each range should utilize the > or >= symbols to eliminate gap values between grades
- Functional grading criteria are more easily applied and interpreted (particularly across different countries) than types of medications used

A. Tables for Clinical Abnormalities

a. Local Reaction to Injectable Product:

- i. Pain: Because of individual variation in the threshold for use of pain relieving medicines, as well as differing medication use in different countries, we find the functional criteria to be more useful in ensuring standardization of reporting than medication use.
- ii. Tenderness: Tenderness is usually defined as pain when the area is touched. This is not clear from the definition of Grade 2 and Grade 3 events in the table. Grade 2 and Grade 3 would be more appropriately defined as "Moderate pain to the touch" and "Severe pain to the touch," respectively.
- iii. Erythema: Based upon the experience of the HVTN, the proposed grading measurements are quite narrow. Erythema is self-limited and, in the absence of other symptoms does not present a safety concern. Since the measurements are collected and available to be analyzed regardless of the assignment of grade, there is no increased safety provided by such narrow definitions of grades. Additionally, the footnote describing this measurement is not clear. We recommend the use of the definitions in the *Division of AIDS Table For Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004*.

b. Vital Signs:

- i. Fever: Based upon the HVTN experience, we believe the definitions in the current *Division of AIDS Table For Grading the Severity of Adult and*

Pediatric Adverse Events, Publish Date: December 2004, are more appropriate for injectable products.

- ii. Hypotension: Unless a participant is experiencing symptoms, hypotension is not considered adverse in a healthy population. There is no increased safety to assigning a grade to this often clinically insignificant event.
- iii. Respiratory Rate: Unless a participant is experiencing symptoms, a transiently elevated respiratory rate is not uncommon and is not considered adverse in a healthy population. There is no increased safety to assigning a grade to this often clinically insignificant event.

c. Systemic (General)

- i. All: Based upon experience in HVTN studies, we support the grading based primarily upon functional criteria as defined in the current *Division of AIDS Table For Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004*.

B. Tables for Laboratory Abnormalities

a. Serum

- i. CPK: The proposed grading of CPK does not reflect the findings consistent with a healthy, active population. In HVTN experience, an elevated CPK, in the absence of other clinically significant findings is the result of increased activity by the participant. Neither individual participant safety nor characterization of the product safety profile is enhanced by these narrow grading definitions for this test. The HVTN supports the ranges used in the updated *Division of AIDS Table For Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004*.
- ii. AST/ALT/Alkaline Phosphatase/Bilirubin: The narrow, proposed limits for these serum chemistries again do not account for common, transient fluctuations and do not enhance participant safety. The HVTN supports the ranges used in the updated *Division of AIDS Table For Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004*.

b. Hematology:

- i. Hemoglobin, absolute and delta values for both males and females: The proposed values for Grade 1 events are above the lower limit of normal for many sites, especially non-US sites. Based upon experience in HVTN studies, particularly in non-US settings, we believe the values described in the *Division of AIDS Table For Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004* are appropriate for a diverse population, and reporting and monitoring at these levels provides for participant safety.

- ii. **WBC, Lymphocytes, Neutrophils:** Similarly, experience indicates there are some populations in whom lower levels of WBCs, lymphocytes and neutrophils is a normal variant. This is documented to be the case in African American individuals and also represents the HVTN experience in African countries. We believe the *Division of AIDS Table For Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004* provides some accommodation for these variations while ensuring participant safety.