



August 30, 2005

Division of Dockets Management (HFA-205)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Draft Guidance: Emergency Use Authorization for Medical Products
[Docket No. 2004D-0333, 70 *Federal Register*, 38689, July 5, 2005]

Dear Dockets Management:

BioRosetteX, a Division of the Sarnoff Corporation, commends the Emergency Use Authorization (EUA) Principals Group and Working Group for developing guidance on this topic. Anticipating the precise nature of biological, chemical, radiological, and nuclear agents is extremely difficult and will likely grow more so in the future. The FDA has correctly identified the importance of a flexible and highly responsive review process as a crucial component of the rapid pharmaceutical response necessary to maintain national security and public health.

As an organization dedicated to accelerating the biodefense medical countermeasure development process, we appreciate the opportunity to provide comments on this draft guidance. Additionally, we would invite direct dialog with the Agency if you would consider the opportunity valuable.

Sincerely,

Lynne Gilfillan, Ph.D.
Managing Director

General Comments:

This draft guidance is reasonable and welcomed. It appropriately reflects the necessary flexibility with which FDA will regard submissions that do not and, for reasons of national security and public health, cannot follow the usual submission guidelines and usual timelines, but are instead provided to the agency under the conditions of a declared emergency.

1. The need to provide for the use of information and knowledge derived from in silico procedures and experiments to be considered as pertinent to the determination of safety and efficacy of unapproved drug and biologic products

In particular, we appreciate the emphasis on reviewing the totality of scientific evidence available in determining whether a product is likely to be effective as a biodefense medical countermeasure and whether the known and potential benefits outweigh the known and potential risks. We suggest a clarification in the guidance that such scientific evidence may include data, information and knowledge derived primarily from computational biology and/or chemistry approaches, often referred to as *in silico* data. Increasingly, information and knowledge pertinent to the determination of safety and efficacy of an unapproved drug and biologic products are derived from *in silico* procedures and experiments. For example, computation-based approaches can be useful in informing:

1. The characterization of the mechanism of action;
2. The prediction of human toxicity and effectiveness;
3. The selection of appropriate animal pharmacology and toxicology test species;
4. The prediction and selection of clinical trial parameters such as human dosing regimens (loading and maintenance doses, dose frequency, dose duration, drug-drug interactions, etc.), directly from animal pharmacology results;
5. The identification of critical design criteria for clinical trials that will provide reliable and convincing data;
6. The prediction of the likely clinical trial outcomes and results;
7. The determination of the potential risk associated with certain manufacturing processes and approaches.

Such *in silico* “tools” are now routinely used in pharmaceutical development settings, and numerous groups including the FDA have suggested that these *in silico* techniques will become increasingly important sources of evidence that will be acceptable for inclusion in regulatory reviews in the future. Under the conditions of a declared national emergency, the judicious application of *in silico* techniques could provide substantial evidence for risk-benefit determinations in much shorter timeframes than would be possible with data derived from human or animal clinical trials or animal and *in vitro* experimentation. Our recommendation is that the document be edited to incorporate the Agency’s intent to review and consider *in silico* data as an important and significant part of the overall evidence database.

2. The need to include explicit wording that provides the authority for the use of the product for certain investigational uses, such as those that may be critically important to providing sufficient evidence for a sound risk-benefit determination

The conditions of authorization of emergency use are reasonable, and sufficiently flexible to provide for a variety of circumstances while protecting the basic rights of patients. However, the conditions, as well as the process associated with determining eligibility and granting of an EUA, appear to be focused primarily on the dissemination and application of unapproved products or unapproved uses of approved products to a broad population of patients under conditions of mass dispensing or physician-managed hospital care. We are concerned that the authority for the emergency use of the product for certain investigational uses, such as those that may be critically important to providing sufficient evidence of for a sound risk-benefit determination, may not be considered under this procedure or anywhere else. For example, the authorization to proceed with a well-controlled human safety and/or efficacy clinical trial, or initiate exploratory clinical trials such as those considered under the “Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies” could face unnecessary delay during a declared emergency due to a lack of pre-existing guidance for such consideration. Our recommendation is that the draft guidance be amended, particularly in sections III “Eligibility for an EUA” and VI “Conditions of Authorization,” to reflect that an EUA may be granted and conditions set for investigational uses under the procedures set forth in this guidance.

3. The need to develop the infrastructure to support streamlined and substantive mechanisms for continuous review of potentially important biodefense products

The establishment of a process for receiving requests for the consideration of a prospective EUA is a proactive mechanism for increasing the Agency’s awareness of potentially important biodefense products in development, as well as providing the Agency with data and information on the safety, effectiveness, and manufacturing characteristics of these products, including those data and information produced by novel

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Comments from BioRosettex

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discovery and development tools and processes. This will serve to make these products available much more quickly should they be needed in the event of an emergency. In addition, we believe this procedure could become a useful mechanism for supporting important Agency initiatives, such as the “Critical Path Initiative,” designed to stimulate the development, application, and ultimate validation of new, improved tools and processes for safety and efficacy determination and industrialization. The guidance does support these functions by recommending that data from ongoing or later testing that becomes available during the review or term of the EUA be submitted.

However, we believe that without a streamlined and substantive mechanism for such submissions, developers may neglect to provide such information to the agency. Such a mechanism could also support the submission of data in a reviewable and sufficiently complete format to permit timely and substantive review, including consultation with working and expert technical groups within and outside the Agency, even under rapidly developing or unexpected emergency circumstances. We propose that the Agency make the development of such a mechanism, in partnership with other government agencies, academic centers, and industry organizations, a clear goal, with guidance for continuous submissions of relevant data via that mechanism the subject of future guidance. BioRosettex is particularly interested in working with FDA towards this goal.