



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

The Honorable Joseph R. Pitts  
Chairman  
Subcommittee on Health  
Committee on Energy and Commerce  
House of Representatives  
Washington, D.C. 20515-6115

FEB 18 2015

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the November 19, 2014, hearing before the Subcommittee on Health entitled "Examining Medical Product Development in the Wake of the Ebola Epidemic." This is the response for the record to questions posed by several Committee Members, which we received on January 8, 2015.

Please let us know if you have any further questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Thomas A. Kraus", with a stylized, flowing script.

Thomas A. Kraus  
Associate Commissioner for Legislation

cc: The Honorable Frank Pallone, Jr.  
Ranking Member  
Subcommittee on Health

We have restated each Member's questions below in bold, followed by our responses.

**The Honorable Joseph R. Pitts**

- 1. Given the long time line required to develop new vaccines and therapeutics and then demonstrate clinical safety, what initiatives are underway at the Department of Health and Human Services (HHS) to improve care for patients who are infected with Ebola today?**

BARDA is responding to this question. Please see BARDA QFR 16.

- 2. Given many of the well-reported supply challenges with mass-producing and manufacturing Ebola drug treatments, such as ZMapp and others, in the near-term pipeline of Ebola experimental and investigational treatments, do you see potential paths forward that could have the drug supply available to actually treat thousands of Ebola patients in West Africa?**

BARDA is responding to this question. Please see BARDA QFR 17.

- 3. What is the role and pathway to join the global coalition of clinical trials for finding effective new experimental therapies in patients with Ebola Virus Disease in West Africa?**

Properly designed and conducted clinical trials are the fastest and most effective way to determine if investigational products for Ebola are safe and effective. FDA strongly favors international collaboration in the design and conduct of clinical trials to ethically generate interpretable data showing whether proposed treatments are safe and effective for patients with Ebola virus disease. FDA welcomes submissions of proposals for and data from such trials for review. The infrastructure to conduct clinical trials in affected West African countries is limited and efforts are underway, including by the U.S. government, to build the infrastructure required for the conduct of critical clinical trials. FDA is providing scientific and technical assistance to the World Health Organization (WHO), which is helping to coordinate international efforts to develop medical products to prevent and treat Ebola virus disease, and is helping affected countries prioritize the investigational products for clinical testing. Medical product sponsors who want to conduct a clinical trial with an investigational product for Ebola in West Africa should work with their local regulatory authority (e.g., FDA or the European Medicines Agency) as well as with WHO and the relevant authorities in the country in which they wish to conduct a trial.

- 4. How would a treatment that focused on surviving the deadly complications of Ebola rather than the virus itself be tested in the coalition forming for clinical trials in West Africa?**

Sponsors and developers of products focused on specific complications of Ebola virus disease are welcome to submit proposals for review and feedback for how they would show benefit against such complications.

**5. For experimental treatments that are available today, what funds are being made available to rapidly test them to improve outcomes in patients in West Africa for patients with Ebola?**

BARDA is answering this question. Please see BARDA QFR 20.

**The Honorable Marsha Blackburn**

**1. How many companies have requested the ability to export investigational new drugs pursuant to the U.S. Food and Drug Administration's ("FDA") investigational new drug emergency export provisions (21 C.F.R. § 312.110 (b)(5))?**

There are several FDA provisions applicable to the export of investigational drugs. Most frequently, drugs are exported under an Investigational New Drug application (IND) for clinical trials, when the sponsor can provide to FDA data that support the ethical study of the drug in humans or are exported under provisions of the law that permit export for investigational use to a country with an advanced regulatory system (21 USC 382(c), 21 CFR 312.110(b)(1) or (3)). Even in situations in which the exporter is seeking to export to a country without an advanced regulatory system, and is unable or chooses not to submit data to FDA to justify human use of its product, FDA regulations permit export based on simple requirements that the drug comply with the laws of the country to which it is being exported, requirements of certification concerning proper manufacture and lack of adulteration, requirements of approval of clinical studies by an independent ethics committee, and requirements that test subjects be afforded informed consent before use of the drug (21 CFR 312.110 (b)(4), 312.120).

The provision found in 21 CFR 312.110(b)(5)(ii) is intended for a sudden and immediate national emergency in a foreign country in which not even the certifications designed to protect patients and test subjects identified under (b)(4) are required. This provision is not an alternative to regulatory review of the product for companies that simply choose not to, or are unable to, make the certifications required by (b)(4). Instead, it is a rarely used provision that would be expected to be applied only in those circumstances in which there was an established basis for use of the investigational drug but there was not time to utilize the usual processes for export. This provision requires a determination by the Secretary of Health and Human Services, or her designee, that prompt export is necessary, based on information provided by an authorized official of the importing country's government.

This provision has been used in one circumstance, making available to health care workers in Liberia afflicted with Ebola the few available doses of a drug with reported activity against Ebola in animal models and that had been provided to persons with the Ebola virus in the United States under an expanded access individual IND. One other request to use this provision for export of a different drug did not result in a Secretarial determination because the public health authorities of the country of intended export withdrew the request.

**2. When were those requests received by the Department of Health and Human Services ("DHHS")?**

One request under 312.110(b)(5) was received August 8, 2014, and the other, October 24, 2014.

**3. When were those same requests forwarded to the FDA for advice and consultation?**

Any requests received by HHS under 312.110(b)(5) have been forwarded to FDA within the same day of receipt.

**4. If any of those requests have been supported by DHHS to date, when was the respective company notified?**

For the request meeting the requirements of 312.110(b)(5)(ii), the requesting country and respective company were notified on August 11, 2014.

**5. Please explain the nature of DHHS's consultations with FDA. Which divisions of DHHS and FDA have primary authority in such consultations?**

HHS and FDA are in daily communications about Ebola response efforts. Communications about export requests occur within the Ebola Response working group structures and at leadership levels.

**6. If DHHS or FDA needs more information in order to complete their consultation, will they consult with the respective company?**

If more information is needed from the respective company, FDA will request such information.

**7. Have any countries made requests [to] import investigation[al] new drugs pursuant to FDA's investigations new drug emergency export provisions? If so, have they been notified of the timeline for consideration of their request?**

The U.S. government is working with the international community, including the affected countries' ministries of health, and companies that have submitted data to FDA that show some promise of effectiveness to facilitate clinical trials in affected countries, for the best candidates available. FDA has received and granted one request under 21 CFR 312.110(b)(5)(ii). In one circumstance, HHS received a request from an official not otherwise engaged in the international response efforts. HHS and FDA responded promptly to address this request through appropriate government and diplomatic communication channels. The request was ultimately withdrawn.

**The Honorable Michael C. Burgess**

**1. As the FDA fails to consider all options when it comes to vaccine, diagnostic, and drug development, how will you assess studies performed outside of the United States *not* under FDA's guidance if they prove to be safe and efficacious?**

Product sponsors and developers should submit all relevant data to FDA concerning their products, when they seek development advice and/or approval for U.S. marketing. Criteria

for accepting foreign clinical studies not conducted under an IND are outlined in 21 CFR 312.120 and focus on ensuring ethical conduct and scientific quality of the trials.

**2. How are you evaluating the risk profile of therapeutics given the high mortality rate from Ebola?**

FDA review takes into account the balance between risks and benefits for the populations in which use of a product is anticipated. This includes recognizing that greater risks of adverse events may be considered acceptable if a product shows substantial benefit in treatment of a serious life-threatening condition without other treatment options, than for a product that is likely to be given to persons with minor self-limiting illness or to healthy persons at low risk of illness.

**3. How are you ensuring that you are prioritizing the right, and the most promising, vaccines, therapeutics, and diagnostics?**

FDA is providing scientific and regulatory advice to U.S. government agencies that are supporting medical product development for Ebola and product sponsors to clarify regulatory requirements, review and provide input on pre-clinical and clinical trial designs, and expedite the regulatory review of data as they are received from product developers. Facilitating the development and availability of investigational medical products for Ebola is a high priority for FDA, and the Agency reviews all proposals and data from product sponsors and developers based on the information available for each. We give high priority to supporting the U.S. government pipeline of investigational medical products for Ebola, which is prioritized through a well-established, inter-agency process to identify and support the most promising candidates.

**4. Currently, there are six rapid diagnostics that have been approved for Emergency Use Authorization. What is the plan for providing a pathway to approval for these diagnostics when the Ebola crisis winds down?**

FDA issued a seventh Emergency Use Authorization (EUA) on December 23, 2014. FDA encourages and expects sponsor/applicants who have received an EUA for their diagnostic device to pursue clearance or approval of their device at a later date. If an authorization has been in effect for more than a year, FDA is required to provide an explanation of the scientific, regulatory, or other obstacles to the approval of the product. FDA will work closely with these device sponsors/applicants and will identify in writing any potential obstacles to approval and actions to be taken by FDA and sponsors/applicants to overcome them.

**5. False negatives are a real concern in testing for Ebola. In the case of the physician from Maryland who was treating patients in Sierra Leone, treatment was delayed because of a false negative on his initial Ebola test. How are you combatting confounding false negatives?**

As part of the EUA process, FDA reviews the totality of scientific evidence, including data on the device performance, before it can determine that the product may be effective in diagnosing Ebola infections and can conclude that the known and potential benefits of the

product outweigh the known and potential risks. To date, FDA has not received reports of false-negative results obtained with an FDA authorized Ebola test. However, it should be noted that no diagnostic test is 100 percent accurate, and there are factors such as quality and timing of specimen collection that will influence test results.

#### **6. How is the efficacy of the tests receiving Emergency Use Authorization being tested?**

There are two types of diagnostic tests being developed for Ebola; molecular and serologic. Molecular tests analyze variations in the sequence, structure, or expression of genetic material (i.e., deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)) in order to diagnose a disease or medical conditions. Serologic tests detect antibodies and antigens specific to an identifiable pathogen in order to diagnose a disease or medical conditions.

Typically, molecular Ebola diagnostics receiving EUA undergo the following testing:

- Limit of Detection (LoD) - This study determines the lowest detectable concentration of Ebola Virus at which at least 95 percent of all replicates test positive. The LoD is determined by limiting dilutions of titered or otherwise quantified Ebola virus materials in a relevant clinical matrix.
- Reactivity - These studies show whether the device can detect multiple strains of Ebola virus at concentrations near the limit of detection.
- Cross Reactivity - These studies test the assay's ability to exclusively identify Ebola virus with no cross-reactivity to other organisms that might be present in the relevant clinical specimen types and can cause symptoms similar to those observed at the onset of an Ebola infection, and
- Mock Clinical Evaluation - The performance characteristics of this test are established using contrived specimens (individual negative clinical specimens spiked with different dilutions of Ebola virus material) when positive clinical specimens are not available.

Testing for serologic Ebola diagnostics include:

- Limit of Detection (LoD),
- Reactivity
- Cross -reactivity
- Interfering substances that may have the ability to generate false-positive and false-negative results
- High-Dose Hook Effect –refers to the false-negative result, which can be seen when very high levels of target are present in a tested sample, and
- Mock Clinical Evaluation - The performance characteristics of this test are established using contrived specimens (individual negative clinical specimens spiked with different dilutions of Ebola virus material), when positive clinical specimens are not available.

**The Honorable Eliot L. Engel**

- 1. I have frequently said that the U.S. cannot meet the challenge that Ebola presents alone. Ebola is a global challenge requiring a global response. Can you discuss how the FDA is working with our international partners to facilitate collaboration and the exchange of important information on investigational products for Ebola?**

FDA is collaborating with the World Health Organization (WHO) and international regulatory counterparts to exchange information about investigational products for Ebola in support of international response efforts and to achieve regulatory harmonization, when possible. These collaborations are supported by confidentiality commitments, when necessary, to enable the sharing of non-public information. FDA international collaborations include:

- Participating in a WHO consultation to develop guidance on the ethical considerations for use of investigational interventions for Ebola
- Providing technical assistance to WHO on the development of convalescent whole blood or plasma for the treatment of Ebola
- Participating in several WHO consultations to discuss leading investigational treatments and vaccines for Ebola and key considerations for clinical testing and deployment
- Participating in a WHO-sponsored regulatory working group of international health regulators
- Participating in the WHO Scientific and Technical Advisory Committee for Ebola Experimental Interventions to help facilitate and accelerate appropriate clinical testing of investigational products for Ebola
- Participating in numerous engagements with our international regulatory counterparts — including the European Medicines Agency, Medicines and Healthcare Products Regulatory Agency (UK), Paul-Ehrlich-Institut (Germany), Health Canada, and others — to exchange information on investigational products for Ebola.