19 December 2008

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

Re: Docket No. FDA–2008–D–0530: Draft Guidance for Industry on Tropical Disease Priority Review Vouchers; Availability

Dear Sir or Madam:

AVI BioPharma, Inc. (AVI) is pleased to have this opportunity to respond to the Request for Comments included in Docket No. FDA–2008–D–0530, which has been titled "Draft Guidance for Industry on Tropical Disease Priority Review Vouchers." AVI is encouraged by, and strongly supports, the Food and Drug Administration (FDA) in its efforts to create incentives that promote the development of new therapies for underserved diseases.

On 12 December 2008, the FDA held a public hearing, which AVI attended, to obtain input on adding additional diseases to the list of tropical diseases recognized under the Food and Drug Administration Amendments Act. AVI plans to submit a separate response to the Request for Comments (Docket No. FDA-2008-N-0567) to address specific points that were raised at that hearing, the most significant of which is the clear definition of what constitutes a "market."

In this docket response, AVI outlines why it believes that Ebola hemorrhagic fever (EHF) and Marburg hemorrhagic fever (MHF) should be added to the list of qualifying tropical diseases that may be eligible for a priority review voucher (PRV) according to Section 524(a)(3)(Q) of the Federal Food, Drug, and Cosmetic Act (the Act).

AVI also proposes criteria and a process that could be used when determining whether an unlisted infectious disease qualifies to be designated by the Secretary of Health and Human Services (HHS) to be listed according to Section 524(a)(3)(Q) of the Act. Finally, AVI requests clarification on two specific points in the draft guidance.

INTRODUCTION

AVI is an emerging biopharmaceutical company focusing on the development of novel, RNA-based therapies designed to target several important diseases, including the hemorrhagic fevers that can result from infection with viruses such as Ebola, Marburg, Junin, and Dengue. EHF, MHF, and Junin hemorrhagic fevers are tropical diseases that primarily affect individuals in developing countries located in Africa and South America. The incentives created by tropical disease PRVs are profound if they are successful in promoting development of new therapies and prophylactic measures that will have a beneficial effect on the overall health of individuals affected by tropical diseases and living in developing nations. PRVs provide additional incentives to small companies to parlay their drug development efforts

in support of a larger world health mission to treat tropical diseases. Furthermore, such incentives may encourage larger Pharma companies, currently without a significant presence in this sector, to invest resources in the development of agents for neglected tropical diseases.

At present, the draft guidance contains a list of 16 specifically named diseases, including Dengue hemorrhagic fever, that are eligible for priority review, as well as a final provision allowing diseases that are not currently on the list to be added, if so designated by the Secretary of HHS. A final provision states that in order for a disease to qualify to be added to the list of named diseases, it must meet the following criteria:

1. There must be no significant market in developed nations;
2. The disease disproportionately affects poor and marginalized populations

As written, the draft guidance contains a high-level summary of the process whereby a tropical disease can be added to the list; however, some elements of the decision-making paradigm are vague and currently open to interpretation. In this docket response, AVI presents evidence that EHF and MHF qualify for inclusion on the list of tropical diseases eligible for PRVs under the provisions stated above, and also proposes a decision-making framework, by using MHF as the example, that can be applied to naming additional tropical diseases to the list.

EBOLA AND MARBURG VIRUSES

Ebola virus and Marburg virus, the only known members of the Filoviridae family of viruses, are two of the most virulent pathogens known to infect humans. Infection with either virus has been shown to result in a devastating multisystem syndrome collectively known as viral hemorrhagic fevers (VHFs). VHFs caused by either the Ebola virus or the Marburg virus are almost clinically indistinguishable from each other and result in damage to the overall vascular system, which is so severe that it ultimately impairs the body's ability to regulate itself; consequently, infection often has a fatal outcome. Despite the fact that both EHF and MHF are rare, each disease has been associated with dramatic outbreaks resulting in high mortality. Human illness and death resulting from infection with either the Ebola virus or the Marburg virus have in large part been confined to persons living in developing nations in equatorial and subequatorial Africa, although a small number of cases have been reported in individuals visiting these regions of Africa. No cases of EHF or MHF have been documented in the United States or other developed nations (as defined by the United Nations Human Development Index [HDI]). At present, there are no preventative or curative treatments for VHFs resulting from infection by either the Ebola virus or the Marburg virus marketed anywhere in the world. Therefore, AVI is requesting that Ebola/EHF and Marburg/MHF be added to the list of tropical diseases that qualify for PRV based on the following criteria:

1. There must be no significant market in developed nations;
2. The disease disproportionately affects poor and marginalized populations

It should be noted that Dengue hemorrhagic fever, a type of VHF that is less severe, has a lower mortality rate when compared with that of either EHF or MHF, and a greater geographical distribution including the United States, is already included on the list of diseases that qualify for PRVs.

According to Section 524(a)(3)(Q) of the Act the Secretary of HHS may designate any infectious disease as eligible for PRV consideration if the aforementioned criteria listed above are met. AVI's argument justifying inclusion for each disease is presented in further detail below.

Ebola Virus

Four distinct subtypes of Ebola virus have been identified: Zaire, Sudan, Côte d'Ivoire, and Reston. Three subtypes have been found Africa, the Zaire, Sudan, and Côte d'Ivoire subtypes. Each of these subtypes has been identified as causing illness in humans. Death occurs in 50% to 90% of all clinical cases of EHF resulting from infection with one of the three African subtypes. The fourth subtype, Ebola Reston, is isolated to the Western Pacific, and has resulted only in development of antibodies, but not hemorrhagic fever, following human infection. The natural reservoir of the Ebola virus is unknown; however, given the geographic regions where outbreaks have occurred, the reservoir is believed to reside only on the African continent and in areas of the Western Pacific.

Both the World Health Organization (WHO) and the American Society for Tropical Medicine and Hygiene consider EHF to be a tropical disease. Although isolated cases of EHF have resulted from accidental needle-stick injury in laboratory workers located in England and Russia, the only confirmed outbreaks of EHF have been isolated to developing nations on the African continent including the Democratic Republic of Congo, Côte d'Ivoire, Congo, Gabon, Sudan, and Uganda. Table 1 details the total number of human infections and fatalities resulting from Ebola virus by the continent where the infection occurred.

Table 1. Total Number of Human Infections and Fatalities from Ebola Hemorrhagic Fever by Continent

Continent	Human Infections	Fatalities
Africa	2,245	1,507
Europe	1[a]	0
North America	6	0
Australia	0	0
Asia	2	0
South America	0	0

Source: Centers for Disease Control, updated January 2008; does not include Bundibugyo recent outbreak.

[a] Infection of a laboratory worker by accidental needle stick with a contaminated needle.

Furthermore, it has been verified that the outbreaks in the Democratic Republic of Congo, Côte d'Ivoire, Congo, Gabon, Sudan, and Uganda resulted from infection with one of the three African subtypes of Ebola, further supporting classification of EHF as a tropical disease.

Ebola-Reston, the fourth subtype of the Ebola virus, was originally detected in a colony of cynomolgus monkeys that had been imported from the Philippines and were housed in Reston, Virginia. During November 1989, the Ebola-Reston subtype was detected in a second colony of cynomolgus monkeys that were housed in Philadelphia but had also been imported from the same supplier in the Philippines. In the interim, three additional outbreaks of Ebola-Reston have been reported in nonhuman primates in the United States, two in 1990 (Reston, Virginia and Alice, Texas) and again in 1996 (Alice, Texas). Ebola-Reston was also detected in a colony of monkeys in Italy (Sienna) during 1992. The source of each of these outbreaks of Ebola-Reston has been traced to a single supplier, an export facility in the Philippines (Laguna Province); however, the investigation was unable to determine the mode of contamination of the facility. Despite the fact that Ebola-Reston is highly pathogenic for nonhuman primates, no human cases of hemorrhagic fever or death resulting from infection with the Reston subtype have been reported (humans infected with Ebola-Reston do develop antibodies against the virus, but do not progress to hemorrhagic fever).

A fifth subtype – Bundibugyo- was just recently confirmed and demonstrates the potential of ongoing mutation of these types of viruses and the potential introduction of new strains that may pose greater future threats in terms of geographic expansion or transmission.

At present, there is no approved therapy to prevent or cure infection with Ebola virus anywhere in the world. Although EHF has been described for over 30 years, a standard treatment for EHF does not currently exist. The only treatment options available to patients involve supportive therapy consisting of balancing the patient's fluids and electrolytes, maintaining the patient's oxygen status and blood pressure, and treatment of any complicating infections.

Designing primary measures to prevent infection with Ebola virus in Africa is challenging because the identity and location of the natural reservoir are not yet known. Once cases of EHF do appear, treatment is further complicated by the poor socioeconomic conditions within healthcare facilities in Africa that often favor spread, rather than containment, of the epidemic. Transmission of the virus can occur in several ways, including direct contact with the blood, body fluids, or secretions from an infected patient or contact with contaminated objects, including needles and syringes that are re-used without proper sterilization techniques. The spread of Ebola virus to families and friends of patients with EHF occurs frequently since they often come in contact with bodily secretions from the infected individual while caring for them. In addition, in many African healthcare facilities, EHF patients are not isolated, and healthcare workers treat EHF patients without the use of proper barrier nursing techniques, including the use of a mask, gown, goggles, or gloves. As a result, nosocomial transmission of EHF has been repeatedly documented in African healthcare workers. In addition, certain social practices, including burial practices that involve washing the body and touching the deceased on the face or elsewhere (called a love touch) have contributed to the spread of Ebola virus.

The lack of available preventive or curative therapies for EHF in any market worldwide, inclusive of developed and developing nations, meets the first criterion for inclusion in the list of diseases that qualify for PRVs as stated in Section 524(a)(3)(Q) of the Act. Secondly, as shown in Table 1 above, EHF cases have in large part been limited to persons living in Africa where socioeconomic factors contribute to the spread of EHF between friends and families and within healthcare facilities, satisfying the second criterion that the disease disproportionately affects poor and marginalized populations.

Marburg Virus

The Marburg virus belongs to the same family as Ebola; however, only a single subtype of the Marburg virus has been identified to date. There are numerous parallels between EHF and MHF. Like EHF, MHF is a severe form of hemorrhagic fever that damages the overall vascular system; however the case fatality rate is approximately 25%, lower than that for EHF. The natural reservoir of the Marburg virus is also unknown; however, it is believed to be indigenous to parts of Africa, including Uganda, Western Kenya, and perhaps Zimbabwe.

MHF is listed by both WHO and the American Society for Tropical Medicine and Hygiene as a tropical disease.

Simultaneous outbreaks of hemorrhagic fever in laboratories in Marburg and Frankfurt, Germany, and Belgrade, Yugoslavia, in 1967 led to the first identification of the Marburg virus. The initial infections occurred in laboratory workers who had been exposed to African green monkeys or tissues from African green monkeys imported from Uganda that were ultimately determined to be the source of the infection. During the initial outbreak, a total of 32 individuals developed MHF, seven of whom died, including the laboratory workers, medical personnel, and family member who cared for the sick. Since 1967, there

have been outbreaks or sporadic cases of MHF in several developing nations on the African continent, including Angola, Democratic Republic of Congo, Kenya, and South Africa (in an individual who had recently traveled to Zimbabwe). Table 2 details the total number of human infections and fatalities resulting from Marburg virus and the continent on which the infection occurred.

Table 2. Total Number of Human Cases of Marburg Hemorrhagic Fever by Continent

Continent	Human Infections	Fatalities
Africa	414	360
Europe	31	7
North America	0	0
Australia	0	0
Asia	2	0
South America	0	0

Source: Centers for Disease Control updated July 2008

The fact that infection with Marburg virus has been limited to persons living in or visiting developing nations on the African continent (with the one exception of the laboratory workers in Europe who were infected following exposure to infected green monkeys imported from Africa) provides support for the classification of MHF as a tropical disease.

At present there are no therapies to prevent or cure infection with Marburg virus marketed anywhere in the world. Additionally there is no standard treatment for MHF beyond supportive therapy such as balancing the patient's fluids and electrolytes, maintaining the patient's oxygen status and blood pressure, replacing lost blood, and treatment of any complicating infections.

As with Ebola, the primary measures designed to prevent infection with Marburg virus in Africa are limited since the identity and precise location of the natural reservoir is unknown. Once cases of MHF do appear, treatment is plagued by the same poor socioeconomic conditions within healthcare facilities in Africa that complicates the treatment of EHF. Transmission of the Marburg virus from person to person can occur; however, it requires close contact with a patient. This is evidenced by the fact that, on several occasions, isolated cases of MHF have been transmitted to the primary care physician or nurse, without an accompanying widespread outbreak. It is believed that infection results from contact with blood or other bodily fluids that contain a high concentration of the Marburg virus, and patients are believed to be most contagious when hemorrhagic symptoms are present. Transmission of Marburg virus also occurs through the use of non-sterile reused needles and medical equipment, and to medical workers not practicing proper barrier nursing techniques. Social practices including the burial practices may also contribute to the spread of Marburg virus.

The lack of available preventive or curative therapies for MHF in any market worldwide, inclusive of developed and developing nations, meets the first criterion for inclusion in the list of diseases that qualify for PRVs as stated in Section 524(a)(3)(Q) of the Act. Secondly, as described previously, documented cases of MHF have been shown to have occurred in or originated from individuals or monkey in Africa. Within Africa various socioeconomic factors are known to contribute to the spread of MHF, including poor medical facilities, improper barrier nursing techniques, and burial practices that involve touching the dead, satisfying the second criterion that the disorder disproportionately affects poor and marginalized populations.

Conclusions: Ebola and Marburg

As described above, there is no significant market for EHF and MHF in developed nations. In addition, epidemiological data have demonstrated that both EHF and MHF disproportionately affect populations

living in Angola, Côte d'Ivoire, Congo, Democratic Republic of Congo, Gabon, Kenya, Sudan, and Uganda. Each of these nations lies on the African continent, and based on several socioeconomic measures, all are considered to be developing countries by the United Nations and the International Monetary Fund. The citizens of the aforementioned countries in large part represent poor and marginalized populations as defined by low income per capita and low Human Development Index (United Nations index combining normalized measures of life expectancy, literacy, educational attainment, and gross domestic product per capita for countries). These populations typically endure unsanitary health care practices and practice social norms that contribute to the spread of EHF or MHF outbreaks.

With the creation of BioShield, an argument could be made that a biodefense related program aimed at developing a vaccine or curative treatment for EHF or MHF may have a significant market should the United States Department of Defense choose to stockpile the treatment as a countermeasure for bioterrorism. Indeed, this issue was raised at the 12 December 2008 public hearing (Docket No. FDA-2008-N-0567). As stated above, AVI plans to submit a written response to Docket No. FDA-2008-N-0567 to address items discussed at that hearing in full. Briefly, however, the issue hinges on how "significant market" is defined. AVI does not believe that an argument can be made that the potential for a one-time or limited purchase of a product by the Department of Defense constitutes a "significant market". The list of tropical diseases eligible for PRV should not be biased against diseases that are also on the list of priority pathogens under BioShield as long as the diseases meet the criteria for inclusion as specified by law in Section 524(a)(3)(Q) of the Act.

AVI believes there is a considerable weight of evidence for inclusion of both Ebola/EHF and Marburg/MHF on the list of tropical diseases that qualify for PRV according to Section 524(a)(3)(Q) of the Act and respectfully requests that both diseases be added.

PROPOSED CRITERIA AND PROCESS FOR DESIGNATING NEW DISEASES THAT ARE ELIGIBLE FOR TROPICAL DISEASE PRIORITY REVIEW VOUCHER

AVI recognizes that the spectrum of tropical and infectious diseases is too broad to be amenable to a simple checklist to determine whether or not a disease should be listed as eligible for PRV consideration. Furthermore, AVI notes the remarkable success of the Office of Orphan Products Development (OOPD) within the FDA in dealing with similar issues. Therefore, per Q23 (Lines 340 to 346) of the draft guidance, AVI proposes several criteria, based on the OOPD model, that could be used to designate other infectious diseases as eligible according to Section 524(a)(3)(Q) of the Act.

Criteria to Consider regarding Section 524(a)(3)(Q) of the Act

Section 524(a)(3)(Q) of the Act allows the Secretary of HHS to designate any infectious disease as eligible for PRV consideration if both of the following conditions apply:

1. There is no significant market in developed nations.

2. The disease disproportionately affects poor and marginalized populations.

Below, AVI proposes criteria that the Secretary of HHS should consider when determining if an infectious disease is eligible according to these two conditions.

AVI also proposes a "weight of evidence" approach for evaluating these criteria when deciding whether or not to designate a disease as eligible. In other words, if a disease does not meet one of these specific criteria, it is not automatically excluded from eligibility. For example, AVI suggests, as part of its proposed paradigm, that the intermittent and unpredictable nature of zoonotic disease outbreaks should be weighted when considering the criteria of Section 524(a)(3)(Q). This does not imply that non-zoonotic diseases should be excluded. .

Criteria for Determining if There Is No Significant Market in Developed Nations

1. *Is the disease not present at significant prevalence in developed nations?*
   As defined by the "rare disease or condition" criteria in the United States Orphan Drug Act (fewer than 200,000 persons) or in the European Regulation on Orphan Medicinal Products (fewer than 5 in 10,000 persons), it is anticipated a tropical disease will not have a significant market in developed nations (as defined by HDI). Indeed, the draft guidance states that it is anticipated "that many tropical disease applications may qualify for designation as orphan drug products" (Lines 134 to 135 of draft guidance).

2. *Is the disease incidence intermittent or unpredictable?*
   Some diseases have low steady state prevalence, with occasional spikes in incidence (i.e., "outbreaks"). However, others (e.g., some zoonoses) are not generally present in human populations, but can suddenly appear. It is difficult to create a valid business model around treatments to the former in particular, which limits their market potential. Issues of drug warehousing and delivery to affected regions are among the logistical considerations that complicate healthcare delivery for such diseases.

3. *Is there no reasonable expectation that costs of research and development of the drug for the disease can be recovered by sales of the drug in developed nations?*
   A sponsor who develops a therapy for an eligible disease may reasonably expect the drug to generate relatively small sales in comparison to the cost of development and, consequently, to incur a financial loss. Sponsors should present an analysis of their potential market to demonstrate why they are unlikely to recoup development expenses.

4. *Is the disease identified by WHO as a neglected disease?*
   As part of its process in identifying neglected diseases, the WHO considers the lack of a significant market in developed nations. In addition to recognition by WHO, recognition of a disease as underserved or neglected by another authoritative organization (e.g., The Global Network for Neglected Tropical Diseases, The Bill and Melinda Gates Foundation, The Rockefeller Foundation) should be considered.

Criteria for Determining If a Disease Disproportionately Effects Poor and Marginalized Populations

1. *Does the disease primarily affect underdeveloped countries?*
   Several diseases that are listed, as well as others that may qualify, are present in developed nations, but the majority of cases are from underdeveloped nations. Also, the relative financial burden of such diseases is likely to be greater in an underdeveloped country. AVI suggests that when considering this criterion, a disease should be shown to have a prevalence or incidence in affected underdeveloped nations that is at least 50 times that in developed nations. This numeric cutoff is somewhat arbitrary and the final definition of disproportion may be more complex. The public health effect of many listed and potentially qualifying diseases is notoriously hard to extrapolate because of systematic underreporting in poor countries. AVI proposes that the

Secretary of HHS assess other factors, for example, the overall burden of disease assessed by using the disability-adjusted life year (DALY) when determining the degree of disproportion.

2. *Does the disease primarily affect areas with minimal healthcare infrastructure?*
This is implicit under criterion 1 of this section, but also extends to developed countries that have large areas that are either poor or have minimal health care infrastructure or both. For example, tuberculosis, which is a qualifying disease under Section 524(a)(3), is endemic in rural areas of some developed nations.

3. *Are health care works at higher risk?*
In underdeveloped countries, diseases that pose an increased risk for health care workers can present a particularly devastating problem. The loss of health care workers exponentially compounds the existing problems of treatment and management. These have a high potential to further impoverish or marginalize a population.

4. *Is the disease zoonotic?*
In addition to the distinct epidemiology of zoonotic disease mentioned above, other characteristics of zoonoses should be considered. Poor and marginalized populations are more at risk of contracting zoonoses because of the strong association with poverty and living in close proximity with animals that are potential disease reservoirs. The animals in and around these populations are less likely to have adequate veterinary care, increasing the chance for them to serve as disease vectors. Additionally, an often overlooked factor of zoonotic diseases is that, in underdeveloped countries, livestock is a critical financial resource. A zoonotic disease could attack both human health as well as resources that could be used to combat or control the disease.

This criterion does not imply that non-zoonotic diseases should be excluded. Rather, for diseases characterized by this epidemiologic pattern, the Secretary of HHS should decide if, after considering the weight of <u>all</u> criteria, reasonable evidence supports a determination as to whether an infectious disease has both no significant market in developed nations and disproportionately affects poor and marginalized populations.

5. *Is the diseases identified by WHO as a neglected disease?*
As part of its process in identifying neglected diseases, the WHO considered whether a disease primarily affected poor populations or whether it primarily affected disadvantaged populations. In addition to recognition by WHO, recognition of a disease as primarily a disease of the poor or as primarily a disease of the disadvantaged by another authoritative organization (e.g., The Global Network for Neglected Tropical Diseases, The Bill and Melinda Gates Foundation, The Rockefeller Foundation) should be considered.

<u>Decision Algorithm for Determining if Diseases Qualifies under Section 524(a)(3)(Q) of the Act</u>
AVI is proposing that a "weight of evidence" approach be used when deciding whether a disease should be designated as eligible. AVI believes that the intent of Section 524(a)(3)(Q) of the Act is to give the Secretary of HHS the discretion to consider multiple factors in this process.

Using the criteria proposed above, a decision algorithm to aid in determining if an unlisted disease should be designated as eligible under Section 524(a)(3)(Q) of the Act is proposed in Figure 1.

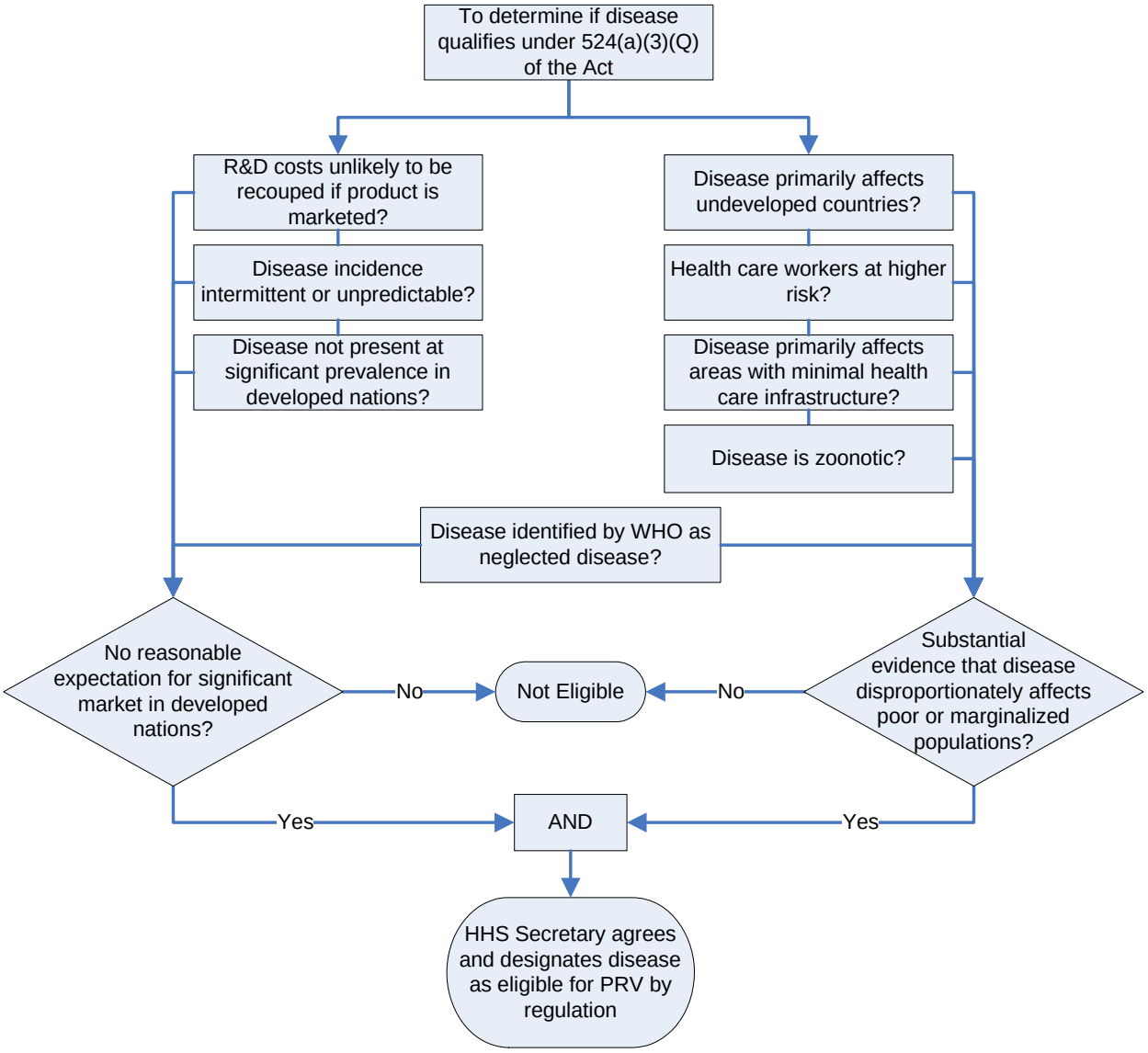

Figure 1. Proposed process for determining if disease qualifies to be listed per Section 524(a)(3)(Q) of the Act.

Proposed Format for Submitting Request

AVI proposes a format modeled after the OOPD process for orphan drug designation requests for the submission of a request for an infectious disease to be added to the list of those eligible for PRVs according to Section 524(a)(3)(Q) of the Act.

A sponsor should submit a formal request to the Secretary of HHS. The request must be submitted before the submission of a marketing application to the FDA, but sponsors are encouraged to submit a request during early development, including before the submission of an IND. Early communication with the FDA about the sponsor's intention to pursue adding a disease to the list of those eligible for PRVs is preferable and will facilitate product development.

The request should be submitted in duplicate, be in the form of an information package that does not exceed 20 pages (excluding references), and should include the following:

1. A cover letter with the following:

    a. A heading that includes "REQUEST FOR DISEASE LISTING UNDER SECTION 524(a)(3)(Q) OF THE FFDC ACT"

    b. A statement that the sponsor requests infectious disease priority review voucher eligibility for a specific disease per Section 524(a)(3)(Q) of the Act

2. The name and address of the sponsor; the name of the sponsor's primary contact person and/or resident agent including title, address, and telephone number

3. A description of the disease, reasons why therapies are needed, and other pertinent facts

4. Documentation, with appended authoritative references, to demonstrate the following:

    a. The disease has no significant market in developed nations that (i) may include an assessment of historical market of the previous 20 years and (ii) may include an assessment of predicted market for the next 10 years.

    b. The disease disproportionately affects poor and marginalized populations.

5. A summary of the regulatory status and marketing history of any drugs in the United States and in foreign countries (e.g., IND and marketing application status and dispositions as available) used to treat the disease, if any

Proposed Process for Request Review

AVI proposes the following process, modeled after the OOPD process for reviewing orphan designation requests, for the review of a request for an infectious disease to be added to the list of those eligible for PRVs according to Section 524(a)(3)(Q) of the Act.

1. A request for disease listing is submitted as described above.

2. The Secretary of HHS has 60 days to review the request and respond to the sponsor

a. If the Secretary of HHS judges the request to be without merit, the Secretary may send a "Refuse to Review" letter to the sponsor

b. If the Secretary of HHS judges the request to be incomplete or requests more information, the review clock stops and the sponsor has 30 days to respond and submit additional information

c. The review clock resumes after the Secretary of HHS receives the requested information.

3. After the review the Secretary of HHS has the following options:

a. Disapprove of the request and notify the sponsor

b. Call for a public Advisory Committee to gain additional input on the request (After the Advisory Committee meeting, the Secretary of HHS has 30 days to announce a decision.)

c. Approve the request, notify the sponsor by letter, and designate by regulation the disease as eligible for PRV consideration.

EXAMPLE OF PROPOSED DECISION PROCESS

The following figure illustrates AVI's proposed decision algorithm as applied to EHF and MHF.

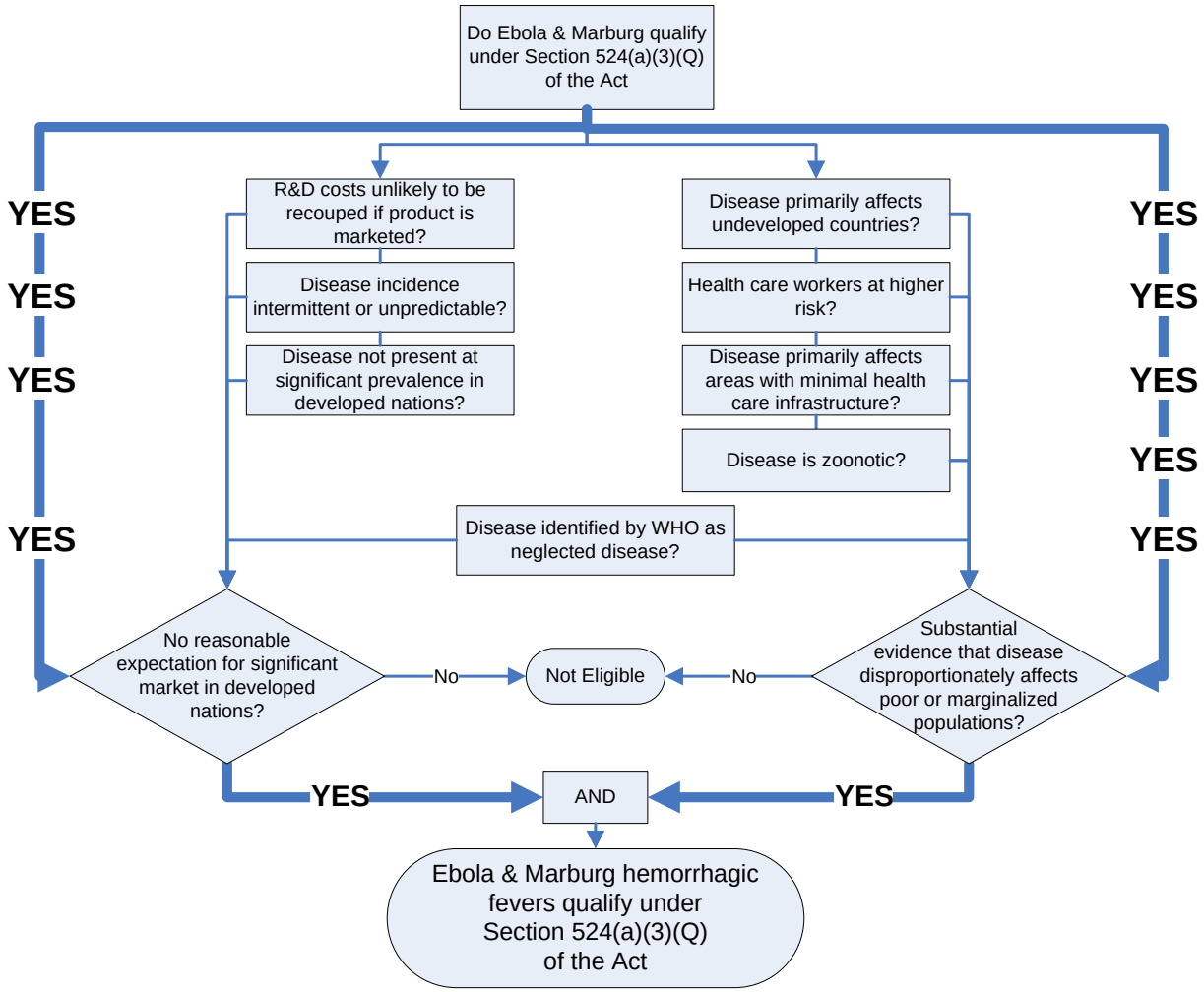

Figure 2. Applied process: determining if Ebola hemorrhagic fever and Marburg hemorrhagic fever qualify to be listed per Section 524(a)(3)(Q) of the Act.

Letter to: Division of Dockets Management
Re: **Docket No. FDA–2008–D–0530**
From; AVI BioPharma, Inc.
Date: 19 December 2008

REQUESTS FOR CLARIFICATION

AVI respectfully requests that the FDA provide clarifications on the following:

1. PRV Guidance Document, Lines 186 to 197 (Q8): To what extent does the FDA define "transfer"? If a sponsor company changed its name after receiving a PRV, would the FDA consider it a transfer? Additionally, if a sponsor company was acquired by another company after receiving a PRV, would the FDA consider it a transfer?

2. PRV Guidance Document, Lines 207 to 215 (Q9): Does the FDA plan to specify content (i.e., language) that should be included in the letter ("redeeming letter") notifying the FDA that a sponsor intends to use a PRV?

Respectfully submitted,

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