

Comments from the Center for Biosecurity of UPMC

on

Docket No. FDA-2008-N-0567: Designating Additions to the Current List of Tropical Diseases in the Food and Drug Administration Amendments Act

February 6, 2009

Overview

The Center for Biosecurity is an independent, nonprofit organization of the University of Pittsburgh Medical Center (UPMC). The Center works to affect policy and practice in ways that lessen the illness, death, and civil disruption that would follow large-scale epidemics, whether they occur naturally or result from the use of a biological weapon. Experts at the Center publish research findings regularly and have been consulted by government agencies, businesses, academia, and the media for independent analyses of issues pertaining to national and global epidemic preparedness and response.

We applaud the U.S. Food and Drug Administration's (FDA) efforts to develop priority review vouchers (PRVs), which are high-value, low-cost incentives for encouraging innovation and investment in medicines and vaccines against infectious diseases. The PRV program established under the FDA Amendments Act of 2007 (Pub. L. No. 110-85) lists 16 diseases that are "PRV-eligible" – pharmaceuticals that are developed to target one of these diseases have the potential to be rewarded with a PRV. According to 21 U.S.C. § 360n, the law also includes a provision to expand the list of PRV-eligible diseases with:

“Any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary”

The Center for Biosecurity of UPMC appreciates the opportunity that FDA has provided to submit public comments for designating additions to the current list of tropical diseases, and proposes that a set of diseases be added to the list. This proposed list includes diseases that have no significant market in developed nations, disproportionately affect poor and marginalized populations, and have been identified as potential biosecurity threats by the U.S. government:¹

- Viral hemorrhagic fevers: Ebola, Marburg, and Junin viruses
- Typhus (*Rickettsia prowazekii*)
- Plague (*Yersinia pestis*)
- Glanders (*Burkholderia mallei*)
- Melioidosis (*Burkholderia pseudomallei*)
- Tularemia (*Francisella tularensis*)
- Anthrax (*Bacillus anthracis*)

There is an urgent public need to develop new medicines and vaccines (i.e., medical countermeasures or “MCMs”) for all of these diseases. All would appear to satisfy the requirements under 21 U.S.C. § 360n: there is “no significant market in developed nations” for these diseases, and they “disproportionately affect poor and marginalized populations.” Adding these diseases to the FDA PRV program’s list of eligible diseases would improve both global health and security.

¹ U.S. Department of Health and Human Services. *Public Health Emergency Medical Countermeasure Enterprise Implementation Plan for Chemical, Biological, Radiological and Nuclear Threats*. April 2007. http://www.hhs.gov/aspr/barda/documents/phemce_implplan_041607final.pdf. Accessed February 3, 2009.

No Significant Market in Developed Nations

The FDA Amendments Act does not define the term “significant market.” “Market” could mean only the commercial market, or could mean both the commercial market and non-commercial funding from governments and foundations. Whether a market is “significant” could be assessed relative to product development costs, or relative to the market size of other products.

We are cautious when determining Congressional intent, but it seems reasonable to interpret the phrase “market” used in 21 U.S.C. § 360n to refer only to commercial markets, since many of the tropical disease products eligible for PRVs in the statute already receive non-commercial funding from governments and foundations.² All of the diseases we are proposing above occur at low levels in the developed world (as will be discussed below) and, as a result, have no commercial market in developed countries. Therefore our above interpretation of the law would mean that biodefense MCMs have no “market.”

Even if non-commercial funding is to be considered as part of the “market,” the biodefense MCM market would still not be “significant.” As we explain below, the non-commercial market for biodefense MCMs has been insignificant compared both to development costs and to the market size for other diseases.

Although the diseases proposed above have been determined by the U.S. government to be “material threats” to the country and in need of new medicines and vaccines,³ the non-commercial funding provided by current U.S. policies to develop new products has thus far induced insufficient engagement by industry. This lack of engagement is, in part, because biodefense MCMs share the same disincentives to investment inherent in all anti-infective products, and their biodefense status actually adds new costs and barriers.⁴ With the U.S. government as the primary purchaser of MCMs, sales are heavily dependent on evolving threat assessments and government policies. This introduces a new, unfamiliar risk factor that private sector companies can do little to control. There is also significant regulatory uncertainty for biodefense MCMs, since many cannot be ethically tested for efficacy in humans and therefore must be evaluated using the FDA’s new and relatively untested Animal Efficacy Rule.

Market size compared to development costs

There are three main sources of government investment in civilian biodefense MCM development: the National Institute of Allergy and Infectious Diseases (NIAID), which funds basic research and early-stage development; the Biomedical Advanced Research and Development Authority (BARDA), which funds advanced development of chemical, biological, radiological, and nuclear (CBRN) MCMs; and BioShield, which procures CBRN MCMs for the U.S. national stockpile. Collectively, these offices are responsible for the research, development, and purchase of approximately 11 CBRN MCMs required under the U.S. Department of Health

² Moran M, Guzman J, Ropars AL, et al. Neglected disease research and development: how much are we really spending? *PLoS Med* 2009;6(2):e30. [Epub ahead of print]

³ U.S. Department of Health and Human Services. *Public Health Emergency Medical Countermeasure Enterprise Implementation Plan for Chemical, Biological, Radiological and Nuclear Threats*. April 2007. http://www.hhs.gov/aspr/barda/documents/phemce_implplan_041607final.pdf. Accessed February 3, 2009.

⁴ Matheny J, Mair M, Mulcahy A, Smith BT. Incentives for biodefense countermeasure development. *Biosecure Bioterror* 2008;5:228-238.

and Human Services' (HHS) Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) Implementation Plan.⁵ The annual funding for MCM research and development is \$155 million per product per year, on average;⁶ while the total funding available for MCM purchasing is \$336 million per product, on average.⁷

By comparison, the cost to develop a *single* new drug or vaccine is estimated to be more than \$1 billion.⁸ In an analysis performed by the Center for Biosecurity, the annual advanced development funding provided to civilian biodefense is less than 10% of what would be required to satisfy the HHS PHEMCE requirements for new products.⁹

Market size compared to tropical disease markets

The market size for some tropical diseases is larger than that for biodefense diseases. For instance, in 2007, \$468 million was spent on malaria R&D, while \$410 million was spent on tuberculosis R&D.¹⁰ Compare these figures to the \$155 million biodefense R&D figure above. The commercial market for purchasing malaria drugs in developed countries has been estimated at \$750 million in net present value of revenues.¹¹ The commercial market for tuberculosis drugs sold in developed countries has been estimated at between \$42 to 56 million per year, or around \$400 million in net present value of revenues.¹² Compare these figures to the \$336 million biodefense procurement figure above. These figures for malaria and tuberculosis markets do not include purchases by governments or foundations of tropical disease products that are ultimately used overseas as part of foreign aid programs or global health charities. We do not mean to suggest that tropical disease markets are of sufficient size given their grave impact on human health. We only mean to illustrate that biodefense MCM markets are similarly limited, compared to those for tropical diseases.

Thus, the market for biodefense MCMs is not significant, both by comparison to typical product development costs, and by comparison to tropical disease markets.

Disproportionate Impact on Poor and Marginalized Populations

While the diseases we propose here are largely thought of in the U.S. as potential bioterrorism threats, they do have a disproportionate, daily impact on poor and marginalized populations in

⁵ U.S. Department of Health and Human Services. *Public Health Emergency Medical Countermeasure Enterprise Implementation Plan for Chemical, Biological, Radiological and Nuclear Threats*. April 2007.

http://www.hhs.gov/aspr/barda/documents/phemce_implplan_041607final.pdf. Accessed February 3, 2009.

⁶ NIAID and BARDA R&D funding is approximately \$1.7 billion per year, combined. \$1.7 billion divided by 11 PHEMCE required products equals \$155 million per product per year.

⁷ The BioShield Special Reserve Fund has \$3.7 billion unobligated. \$3.7 billion divided by 11 PHEMCE required products equals \$336 million per requirement.

⁸ DiMasi JA, Grabowski HG. The cost of biopharmaceutical R&D: is biotech different? *Manage Decis Econ* 2007;28:469-479.

⁹ Matheny J, Mair M, Smith BT. Cost/success projections for US biodefense countermeasure development. *Nature Biotechnology* 2008;26:981-983.

¹⁰ Moran M, Guzman J, Ropars AL, et al. Neglected disease research and development: how much are we really spending? *PLoS Med* 2009;6(2):e30. [Epub ahead of print]

¹¹ Berndt ER, Glennerster R, Kremer MR, et al. Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness. *Health Econ* 2007;16(5):491-511.

¹² Schwalbe NR, Wells WA, Geaneotes AP, et al. Estimating the market for tuberculosis drugs in industrialized and developing nations. *Int J Tuberc Lung Dis* 2008;12(10):1173-81.

developing nations. While data on many of these diseases are limited, it is estimated that over 95% of human cases of these diseases occur in developing countries.¹³ In developed countries, their incidence is well under 10,000 cases per year. The diseases are largely associated with poor living conditions, agricultural work, and/or close proximity to wildlife rarely found in the developed world. While the case rates for the diseases being proposed are lower than most of the 16 tropical diseases that current qualify for PRVs, they do have a debilitating impact on the overall health status of individuals, worker productivity, poverty, and education in the affected countries.

As an illustration, Ebola has a mortality rate up to 90% and occurs predominantly in African nations.^{14,15} Transmission of Ebola has been associated with poor health care practices (e.g., use of improperly sterilized needles), direct contact with non-human primates, and human burial practices. According to the World Health Organization, since the Ebola virus was discovered, approximately 1850 cases, resulting in over 1200 deaths, have been documented.¹⁶ No treatment or vaccine currently exists.¹⁷ In addition, melioidosis is predominantly a disease of tropical climates,¹⁸ and thus disproportionately impacts poor and marginalized populations. Thailand, for example, reports 2,000-3,000 cases per year; 20% of community-acquired septicemic cases (39% of fatal septicemias and 36% of fatal community-acquired pneumonias) are caused by melioidosis in the northeast region of the country.^{19,20} Septicemia associated with melioidosis has a case fatality rate of up to 90%.²¹ Endemic in Southeast Asia,²² melioidosis has also been observed in Africa, India, the Middle East, Central and South America, and the Northern Territory of Australia.²³

Another example is epidemic typhus, which is contracted through lice bites and can be found worldwide (e.g., Asia, Central and East Africa, Mexico, Central and South America), but is endemic in the Peruvian Andes, Burundi, and Rwanda.^{24,25,26} Typhus is associated with poor

¹³ In the U.S., for example, the incidence of tularemia, plague, botulism, and anthrax is less than 200 cases per year. Chang M, Glynn MK, Groseclose SL. Endemic, notifiable bioterrorism-related diseases, United States, 1992-1999. *Emerg Infect Dis* 2003;9(5). <http://www.cdc.gov/ncidod/EID/vol9no5/02-0477.htm>.

¹⁴ World Health Organization. Viral haemorrhagic fever. Fact sheet no. 103. December 2008. <http://www.who.int/mediacentre/factsheets/fs103/en/>.

¹⁵ Peterson AT, Bauer JT, Mills JN. Ecologic and geographic distribution of filovirus disease. *Emerg Infect Dis* 2004;10(1):40-47. <http://www.cdc.gov/ncidod/eid/vol10no1/03-0125.htm>.

¹⁶ World Health Organization. Viral haemorrhagic fever. Fact sheet no. 103. December 2008. <http://www.who.int/mediacentre/factsheets/fs103/en/>.

¹⁷ Ibid.

¹⁸ U.S. Centers for Disease Control and Prevention, Division of Foodborne, Bacterial and Mycotic Diseases. Melioidosis: general information. http://www.cdc.gov/nczved/dfbmd/disease_listing/melioidosis_gi.html.

¹⁹ Currie BJ. *Burkholderia pseudomallei* and *Burkholderia mallei*: Melioidosis and Glanders. In *Principles and Practice of Infectious Diseases*. Churchill Livingstone, 2004.

²⁰ Vietri NJ, Deshazer D. Melioidosis. In *Medical Aspects of Biological Warfare*. Borden Institute, 2007.

²¹ American Veterinary Medical Association. Background: Glanders and Melioidosis. August 23, 2006. http://www.avma.org/reference/backgrounders/glanders_melioidosis_bgnd.asp.

²² U.S. Centers for Disease Control and Prevention, Division of Foodborne, Bacterial and Mycotic Diseases. Melioidosis: general information. http://www.cdc.gov/nczved/dfbmd/disease_listing/melioidosis_gi.html.

²³ Ibid.

²⁴ Raoult D, Walker DH. *Rickettsia prowazekii* (Epidemic or Louse-Borne Typhus). *Principles and Practice of Infectious Diseases*. Churchill Livingstone, 2004. Chapter 187.

²⁵ Mooty M, Lutwick LI. Epidemic Typhus Fever. *Beyond Anthrax*. Humana Press, 2009. Chapter 8.

sanitation, crowding, and malnutrition and in conditions such as war, refugee camps, natural disasters, and mass human migrations.^{27,28,29} In modern outbreaks, epidemic typhus has affected tens of thousands of individuals, with mortality reaching as high as 20% without treatment.^{30,31,32} In 1997, an estimated 100,000 cases occurred in refugee camps in Burundi.³³ According to one source, “it is highly likely that the prevalence and mortality of this important infection is significantly underestimated.”³⁴

Conclusion

As the diseases discussed above have no significant market in developed nations, and disproportionately affect poor and marginalized populations, we hope you will consider their inclusion in the PRV program. Adding them to the program’s list of eligible diseases would improve both global health and security.

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²⁶ Raoult D, Woodward T, Dumler JS. The history of epidemic typhus. *Infect Dis Clin North Am* 2004;18(1):127-40.

²⁷ Raoult D, Walker DH. *Rickettsia prowazekii* (Epidemic or Louse-Borne Typhus). *Principles and Practice of Infectious Diseases*. Churchill Livingstone, 2004. Chapter 187.

²⁸ Mooty M, Lutwick LI. Epidemic Typhus Fever. *Beyond Anthrax*. Humana Press, 2009. Chapter 8.

²⁹ Raoult D, Woodward T, Dumler JS. The history of epidemic typhus. *Infect Dis Clin North Am* 2004;18(1):127-40.

³⁰ Raoult D, Walker DH. *Rickettsia prowazekii* (Epidemic or Louse-Borne Typhus). *Principles and Practice of Infectious Diseases*. Churchill Livingstone, 2004. Chapter 187.

³¹ Mooty M, Lutwick LI. Epidemic Typhus Fever. *Beyond Anthrax*. Humana Press, 2009. Chapter 8.

³² Raoult D, Woodward T, Dumler JS. The history of epidemic typhus. *Infect Dis Clin North Am* 2004;18(1):127-40.

³³ Ibid.

³⁴ Ibid.