

## **ONLINE SUPPLEMENT**

### **Supplementary Methods**

BARDA's underlying statute (PAHPA, PL 109-417) defines "advanced development" as activities that "predominantly are conducted after basic research and preclinical development of MCMs and are related to manufacturing MCMs on a commercial scale in a form that satisfies regulatory requirements." Such activities include: clinical testing; the design and development of tests and animal models for clinical testing; activities to facilitate MCM manufacture on a commercial scale and to foster the creation of new technologies to increase manufacturing surge capacity; and activities to improve the shelf-life of a product (42 USCS § 247d-7e). For the purposes of this analysis, the activities that BARDA would support under its "advanced development" mission are equivalent to "clinical development" activities.

Candidates identified in this survey as being in preclinical development were all confirmed candidates deemed to have the potential to enter clinical trials in FY2009. The survey excluded products that are already under an HHS Project BioShield procurement contract, and assumed that included products would have their clinical development costs fully funded by BARDA, while BioShield contracts will cover manufacturing costs. Because biodefense medical countermeasures will likely be purchased solely by the US government (with essentially no commercial sales), it is reasonable to assume that the government will fund development of these products in their entirety as is done with more traditional national security requirements (e.g. aircraft, ships, tanks, missiles).

Mean development out-of-pocket costs, durations, and phase transition probabilities were obtained for small molecule drugs and for biological therapeutics, based on published estimates.<sup>1,2</sup> These estimates have been corroborated with other datasets.<sup>3</sup> Previous studies have found that clinical development costs and timelines for vaccines are similar to those for small molecule drugs;<sup>4,5</sup> here they are assumed to be identical. The transition probabilities for preclinical development were taken from other published sources.<sup>6,7</sup> Out-of-pocket costs were updated to 2008 dollars first by applying U.S. Bureau of Economic Analysis' GDP price deflation indices, and second by applying the annual growth rates in the real costs of clinical development observed between 1987 and 2000.<sup>1,8</sup>

Most biodefense MCMs will be evaluated for efficacy using the FDA's Animal Efficacy Rule instead of traditional human clinical trials. However, there are insufficient public data on the costs, timelines, and success rates of Animal Efficacy Rule development, so standard, aggregate human clinical trial data were used. To date, only two products have been approved via the Animal Efficacy Rule<sup>9</sup> and both of these were preexisting products that were receiving approval for new indications. It is likely that the process, costs, timelines, and success rates for approval using the Animal Efficacy Rule for a truly new product will be substantially different than for these first two products. Three MCM candidates currently in Phase II trials involve a larger number of human subjects than is typical; thus our estimates may underestimate Phase II and III development costs for MCMs.

Six caveats should be noted about our analysis. First, because our analysis presumes that clinical development would be funded by the U.S. government, our cost estimates include

only out-of-pocket costs; capitalized costs would be significantly higher.<sup>1-3</sup> Second, our analysis underestimates the total level of funding needed to support BARDA, whose mission includes not only the development of biodefense MCMs, but also the development of diagnostics and biosimetry assays, as well as MCMs for chemical, radiological, and nuclear threats. Third, our costs estimates are for clinical development only and do not include the substantial costs of basic research, preclinical development, large-scale manufacturing, and stockpiling in the Strategic National Stockpile (SNS), which are not explicitly part of BARDA's advanced development mission as defined by law. Fourth, these costs may increase as the number of threat agents expands with the growing accessibility of biotechnologies.<sup>10</sup> Fifth, our survey of candidates was based on publicly-available information; some existing candidates may not be included if they have not been disclosed by their developers. Sixth, industry data suggest that R&D costs for anti-infectives are higher than those for most drugs, in which case our estimates may be lower than actual costs.<sup>11</sup>

## Supplementary References

1. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *Journal of Health Economics* 2003; 22:151-85.
2. DiMasi JA, Grabowski HG. The Cost of Biopharmaceutical R&D: Is Biotech Different? *Manage. Decis. Econ.* 2007; 28:469-479.
3. Adams CP and Brantner VV. Estimating The Cost Of New Drug Development: Is It Really \$802 Million? *Health Affairs* 2006; 25(2):420-428.
4. Institute of Medicine, *Financing Vaccines in the 21st Century*, Washington DC: National Academy Press, 2004.
5. Grabowski, H., and J. Vernon. *The Search for New Vaccines: The Effects of the Vaccines for Children Program*. Washington, DC: AEI Press, 1997.
6. Struck MM, Vaccine R&D success rates and development times, *Nat Biotechnol* 1996;14:591-593.
7. Bains W, Failure rates in drug discovery and development: will we ever get any better? *Drug Discovery World* 2004;5(4):9-17.
8. DiMasi JA, Hansen RW, Grabowski HG, Lasagna L, Cost of innovation in the pharmaceutical industry. *Journal of Health Economics* 1991;10:107-42.

9. Gronvall GK, Trent D, Borio LL, et al. The FDA Animal Efficacy Rule and biodefense countermeasures: a way forward. *Nat Biotechnol.* 2007; 25(10):1084-87.

10. Petro JB, Plasse TR, McNulty JA. Biotechnology: impact on biological warfare and biodefense..*Biosecur Bioterror.* 2003; 1(3):161-8.

11. DiMasi JA, Grabowski HG, Vernon J. R&D Costs and Returns by Therapeutic Category. *Drug Information Journal* 2004; 38(3): 211-23.