

BARDA FY09 ADVANCED DEVELOPMENT COST ESTIMATES FOR MEDICAL COUNTERMEASURES AGAINST BIOLOGICAL THREATS

(WORKING DRAFT – updated January 29, 2008)

FY08 BARDA advanced development appropriation..... **\$102M**

FY09 advanced development funding required for BARDA to have a 90% chance of ultimately developing one successful medical countermeasure (MCM) for each requirement set forth in the PHEMCE

Implementation Plan¹..... **\$3,390M**

- This analysis addresses only PHEMCE requirements for MCMs against biological threats. It does not include countermeasures against radiological, nuclear, or chemical weapons, nor does it include diagnostics, biodosimetry tests, or CHEMPACKS.
- These estimates include ONLY advanced development costs – not the costs of basic research, pre-clinical development, manufacturing, stockpiling, or maintaining these MCMs.
- These cost estimates are for FY09 only. Sustained funding – for many years – of a similar magnitude would be required to successfully develop any MCMs, given the long timelines of biopharmaceutical development.
- Definitions, assumptions, data, and methods used in this analysis are described on pages 2-3.

Number of MCMs currently in development yields low probability of success:

One option for the country would be to budget for advanced development funding for only the candidate MCMs currently in development. Based on our survey of MCMs in development, one year of BARDA advanced development funding for them would cost \$817 million in FY09.

However, biopharmaceutical development has very high failure rates. On average, for every five small molecule drugs, or every three biological therapeutics, that enter advanced development, only one ultimately attains FDA approval.^{2,3} Therefore, \$817 million of advanced development funding for only the candidate MCMs currently in development would give the country the following probabilities of ultimately developing successful, PHEMCE-required MCMs:

Anthrax vaccine:	85%	Filovirus antiviral:	41%
Anthrax antitoxin:	72%	Junin virus antiviral:	23%
Filovirus vaccine:	63%	Gram(+) broad-spectrum antibiotic:	12%
Smallpox antiviral:	53%	Gram(-) broad-spectrum antibiotic:	12%

Substantial increase in BARDA funding needed to increase probability of success:

The current level of funding, \$102 million, if continued on an annual basis, is sufficient to support only two individual MCM candidates in advanced development, with only a 30% chance of either candidate ultimately being successful.

To have at least a 90% probability of one successful product for each PHEMCE biological threat requirement, the portfolio of candidate MCMs would need to be expanded. One year of BARDA advanced development funding for this larger MCM portfolio would cost \$3,390 million in FY09.

DEFINITIONS, ASSUMPTIONS, DATA, AND METHODS

Definition of “advanced development”:

- BARDA’s underlying statute (PAHPA, PL 109-417) defines advanced development as work “conducted after basic research and preclinical development of the product.” For the purposes of this analysis, the activities that BARDA would support under its “advanced development” mission are equivalent to “clinical development” activities.

PHEMCE Implementation Plan MCM requirements:

Small Molecule Drugs: 5

Vaccines: 2

Biological Therapeutic: 1

Assumptions:

- These requirements are based on Table 2 of the plan.¹
- This analysis includes only MCM requirements for biological threats. It does not include countermeasures against radiological, nuclear, or chemical weapons, nor does it include diagnostics, biodosimetry tests, or CHEMPACKS.
- "Filovirus MCM" category was assumed to include one vaccine and one small molecule drug.
- Requirements for broad-spectrum antivirals were assumed to represent three small molecule drugs – one for filoviruses, one for junin, and one for smallpox. (Requirements for filovirus and smallpox antivirals also appear separately in Table 2 – these were only counted once.)
- The requirement for smallpox vaccine was assumed to have been fulfilled by previous HHS procurements and a recent BioShield contract.
- Requirements for broad-spectrum antibiotics were assumed to represent two small molecule drugs – one for Gram-positive bacteria, and one for Gram-negative bacteria – with biodefense indications.

Survey of candidate MCMs in advanced development:

- The survey identified products that could fulfill a PHEMCE requirement¹ and that are currently in advanced development (Phase I-III of clinical development) or have the potential to enter Phase I of clinical development in FY09.
- The survey drew from publicly available information from US government and private sector sources and was not limited to products currently receiving US government support.
- The survey excludes products that are already under a BioShield contract.

Data for costs, timelines, and success rates of advanced development:

- Advanced development (i.e. clinical development) data for small molecule drugs² and biological therapeutics³ were obtained from peer-reviewed publications.
 - Costs were updated to 2008 dollars using the U.S. Bureau of Economic Analysis’ GDP price deflation indices and historical clinical cost growth rates.²

- Probabilities of success for MCMs were based on historical, aggregate data, and are not judgments of the merits of specific candidate MCMs currently in development.
- Many MCMs will have to be evaluated using the FDA's Animal Efficacy Rule instead of traditional human clinical trials for efficacy (i.e. Phases II and III). Human safety trials will still be required.
 - There are not sufficient public data to support an analysis of the actual costs, timelines, and success rates of Animal Efficacy Rule development.
 - In the survey of current MCM candidates used in this analysis, the majority of MCMs would be expected to be in Phase I during FY09. Therefore, for the purposes of these cost estimates, all data used are based on traditional human clinical trials.
- Clinical development costs, timelines, and success rates for vaccines were assumed to be the same as those for small molecule drugs – based on a survey of the literature.^{4,5}

Methods:

- FY09 clinical phases were projected by assuming that candidate MCMs now in preclinical development will enter Phase I trials for FY09 with probability equal to the average preclinical development to Phase I transition probability^{5,6}; those now in Phase I will enter Phase II trials for FY09 with probability equal to the average Phase I-II transition probability;^{2,3} and those now in Phase II trials will remain in Phase II trials for FY09.
- FY09 costs of advanced development for existing candidate MCMs were calculated by multiplying the number of candidate MCMs projected to be in each clinical phase by the respective annual cost per phase.
- FY09 costs to fulfill all PHEMCE Implementation Plan requirements were calculated by first, as above, calculating the costs of advanced development for existing candidate MCMs; and second, by adding the annual costs of Phase I trials for the additional candidates needed to yield, with 90% probability, one successful product per requirement – based on the published success rates of the stages of biopharmaceutical development.
- The probability of at least one approved product per requirement was calculated as:

$$1 - \prod_i 1 - \Pr\langle Approval | i \rangle^{N_i}; \text{ where } N_i \text{ is the number of candidates at stage } i.$$

References:

1. U.S. Department of Health and Human Services. Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), Implementation Plan for Chemical, Biological, Radiological, and Nuclear Threats. April 2007.
2. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *Journal of Health Economics* 2003; 22:151-85.
3. DiMasi JA, Grabowski HG. The Cost of Biopharmaceutical R&D: Is Biotech Different? *Manage. Decis. Econ.* 2007; 28:469-479.
4. Institute of Medicine, Financing Vaccines in the 21st Century, 2003: "verifiable, quantitative information on [vaccine] costs, revenues, and profits is lacking," but "Total development costs of bringing a vaccine to market are roughly similar to those for drugs and can be higher (Grabowski and Vernon, 1997)."
5. Grabowski, H., and J. Vernon. 1997. *The Search for New Vaccines: The Effects of the Vaccines for Children Program*. Washington, DC: AEI Press.
6. Struck MM. Vaccine R&D success rates and development times. *Nature Biotechnology* 1996; 14:591-593.
7. Nwaka S and Ridley RG. Virtual drug discovery and development for neglected diseases through public-private partnerships. *Nature Reviews Drug Discovery* 2003; 2:919-928.