as a top priority and condition for receiving further funding after FY2010. Congress should also mandate that BARDA submit five-year funding projections with each budget proposal, so as to better align appropriations with actual and projected funding needs.

On the basis of the analysis of Matheny *et al.*[1] the Center for Biosecurity recommends $1.7 billion for BARDA to develop biodefense countermeasures in FY2010 (refs. 5,6). Our analysis suggests that figure is too high. Thus, in addition to taking the actions above, BARDA should prepare a budget request based upon the actual and projected number of countermeasures that will require funding in FY2010. In this time of national fiscal uncertainty, Congress should closely oversee BARDA and require substantial justification for its yearly budget.

Note: Supplementary information is available on the Nature Biotechnology website.

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Matheny *et al.* reply:

We are grateful to Klotz and Pearson for projecting BARDA's biodefense medical countermeasure (MCM) advanced development funding needs using separate methods from our own analysis[1] and confirming our finding that these needs are considerably higher than BARDA's current funding. We do not, however, agree with all of the assumptions used in their analysis, for reasons we describe below. Nevertheless, whether one accepts our $904 million estimate of fiscal year (FY) 2009 costs for the existing MCM pipeline or Klotz and Pearson's range of $476–977 million, in FY09 BARDA received $275 million for its advanced development mission—much lower than either of our estimates. Moreover, both we and Klotz and Pearson projected only BARDA's biodefense costs, ignoring the development costs of diagnostic tests and chemical, radiological and nuclear medical countermeasures for which BARDA is also responsible. Consequently, both we and Klotz and Pearson have likely underestimated BARDA's total funding needs.

As Klotz and Pearson note, the most important differences between our two analyses depend on the development phase of candidates, the assumed inflation rate of clinical trial costs, and how one 'rounds-off' the number of additional drug and vaccine candidates needed for BARDA to meet its requirements.

They appear to have used our pipeline data verbatim, except for one of the products, cethromycin, which they place in phase 3. Given cethromycin's success in advanced development for community-acquired pneumonia since the time of our original analysis, we agree that cethromycin should now be considered a phase 3 product for anthrax (its sponsor now lists cethromycin in phase 3 (pre-new drug application animal studies) for anthrax). For consistency, it would have been useful for Klotz and Pearson to update the status of all 32 products in our pipeline scan. We have done so, and since our original analysis, the development status of approximately one-third of the pipeline has changed: three products have changed phase, four products have been discontinued and four products have been added. Updating our own model using the latest publicly available information on product status, we estimate that BARDA's costs for supporting the 32 existing biodefense candidates through advanced development will be $904 million for FY09. This is an increase over our original estimate of $817 million. Similarly, we estimate that satisfying each MCM requirement with 90% probability will cost BARDA $13.2 billion from FY09–15.

Regarding inflation of clinical trial costs, Klotz and Pearson defend using a lower inflation rate by arguing that "there is considerable effort within the pharmaceutical industry…to reduce drug development costs." We know of no evidence that the pharmaceutical industry is succeeding in this effort. Although Klotz and Pearson suggest that there has been a reduction in the number of clinical trial personnel from 2003 to 2006, the same data show an increase in phase 1, 2 and 3 personnel. Moreover, the number of personnel only partly explains clinical trial costs, which also depend on the number of trial sites and subjects, as well as the cost per staff, site and subject. At the moment, their assertion that "…cost-saving efforts could bring inflation rates down to well below 10%" seems entirely speculative. We stand by our assumption that for the next seven years, clinical trial costs will continue to increase at their historical rate.

Regarding 'rounding-off', Klotz and Pearson suggest in their **Supplementary Analysis** that "rounding-off should take place after computing the total number of additional candidates required across all countermeasure classes." This would be the case if BARDA's objective were to have a 90% probability of satisfying its requirements, on average. But under this approach, the probability of filling a particular requirement could be much less than 90%. Our approach applies to a different (and we believe more accurate) objective for BARDA: to ensure for each requirement at least a 90% probability of developing one approved product. This objective requires rounding up to the nearest whole number of products per requirement.

Despite these differences, whether one accepts our '90% success' estimate of $13.2 billion for FY09–15, based on the latest pipeline, or Klotz and Pearson's range of $6.3 to $11.6 billion, it is clear that both groups concur that BARDA's mission will require far more funding than it is currently receiving. Drug and vaccine development is a long, high-risk and expensive endeavor—there is no avoiding this. Until the US government begins funding MCM development at an appropriate level, we will not have the medicines and vaccines needed to protect the health and security of the American people.

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