



March 2, 2015

Manon Ress, PhD
The Union for Affordable Cancer Treatment (UACT)
1621 Connecticut Avenue, N.W.
Washington, D.C. 20006

Dear Dr. Ress:

Thank you for your letter of February 3, 2015 regarding the release of key results from our most recent Tufts Center for the Study of Drug Development (CSDD) study on the R&D costs of new drug development. We welcome the opportunity to engage in an open and candid discussion of the methodology and results of our study. You had previously sent a similar letter to Tufts University President Anthony Monaco on November 24, 2014. Because that letter encapsulates the process, data, and methodology questions that you pose in your letter to me, and because your letter to Dr. Monaco contains additional characterizations of our study, my responses, which are provided below, are directed to the contents of that letter.

Comparison of Our Current Estimate to Our Past Estimate: In your letter to Dr. Monaco, you overstate the difference in estimated total cost for our current study compared to that for our prior (*Journal of Health Economics*, 2003) study. Your assertion is that the current estimate is 3.2 times that of the prior estimate. However, you have compared our earlier figure, which is in year 2000 dollars, to our more recent figure, which is in year 2013 dollars. That is an apples-to-oranges comparison. Our press release, our slides, and my presentation of those slides make clear what the real (constant dollar) increase in the cost estimates is in percentage terms overall and on a compound annual growth rate basis. Media accounts of our release that I have seen that noted the extent of the increase in cost described the differential correctly.

Comparison of Our Current Estimate to an OHE Estimate: Your letter suggests that our cost estimate is extraordinary when compared with a \$1.5 billion (in year 2011 dollars) Office of Health Economics (OHE) estimate, which they published in a late 2012 OHE report. Your letter is worded in a way to suggest that their figure and ours are estimates of nearly contemporaneous development, and so are conflicting. However, the OHE report used data on drugs that were in some phase of clinical development during 1997 to 1999, whereas our data are generally much more recent, and therefore our results cannot be said to be inconsistent with their results. Indeed, the timing of the development data effectively places the OHE report analysis period between those for our 2003 study and our current study.

Drug Development “Costs” versus Drug “Prices”: Our study is focused on drug development costs, rather than drug prices. Expectations about R&D and other company costs and the prices that can be obtained for drugs that make it to market together help determine the incentives for developers to invest in new drug innovation. We have not linked industry R&D cost estimates, or the R&D costs of specific drugs, to how individual drug prices are either established or can be “justified.” I discussed this topic in response to a question posed during the webcast in which I

presented our study results, as well as in several media interviews in the days following the presentation.¹

Information on Study Methodology: Your letter to Dr. Monaco claims that we provided little information in the “few PowerPoint slides” presented. It should be noted, however, that the slide-deck we presented consisted of 30 slides, including nine slides dealing with data and methodology. We also provided a methodology background. Moreover, I noted during the presentation that the methodology we used in the current study was the same as in our prior study. The interested reader could also go to the exposition of methodology in our 2003 paper published in the *Journal of Health Economics* for further discussion. There is no mystery over how we determined our results. The methodology has been clearly and comprehensively described.

Funding: You ask in your letter about any funding I or my co-authors received to conduct our study, as well as funds to pay for the press release and conference. Neither Tufts CSDD nor I received outside funding of any sort earmarked to conduct our study, or to pay for the press release, the press conference, or any related activities or events. Similarly, my coauthors, who are at different universities, did not receive any outside funding in support of their work on the study (including any funds from Tufts CSDD). Tufts CSDD is transparent about its funding model. It is described under “Financial Disclosure” on our website (http://csdd.tufts.edu/about/financial_disclosure). If you have additional questions about Tufts CSDD funding, feel free to contact Tufts CSDD’s director, Dr. Kenneth Kaitin <kenneth.kaitin@tufts.edu>.

Peer Review: You asked in your letter whether the peer reviewers who were assigned by the journal to review the study manuscript have any potential financial conflicts of interest. It is not possible for us to answer this question because, in a blinded journal review process, we have no way of knowing who the referees are.

Undisclosed Study Data: Your letter addressed to me asks for information on individual clinical trials. The data that we collected are at the molecule level, not at the level of individual clinical trials. It is also not possible to assess the “reasonableness” of the estimates for particular drugs, or even in the aggregate, with clinical trial size information for the molecules, as published information on per patient costs does not cover all of the costs we measured during clinical testing (which include costs for chemistry, manufacturing, and controls (CMC) R&D and animal testing conducted concurrently with clinical testing, overhead from operating an ongoing R&D organization, and any other R&D-related costs during the clinical testing period). We do not have the granularity in the data to distinguish among all these different types of expenditures. In addition, publicly reported per patient costs do not cover all costs directly related to clinical trial testing. Typically, they only include investigator fees and central laboratory costs. Thus, it is not possible to make the type of reasonableness assessments that you suggest are possible with additional information from the study.

¹ See, e.g., Cathy Kelly, Cost of New Drug Development Pushed to \$2.6 Bil. By High Failure Rates – Study, *The Pink Sheet Daily*, November 18, 2014; Don Seifert, Studies show increase in drug prices outpace increase in development costs, *Boston Business Journal*, November 18, 2014.

Analysis of Clinical Trial Sizes: Your letter asserts that the number of subjects enrolled in industry-sponsored clinical trials for cancer drugs is typically low in comparison to those for non-cancer drugs. Given the apparent nexus between UACT and Knowledge Ecology International (KEI) (same street address, a video narrated by a KEI staffer announcing that UACT would be directing its questions to me), it seems fair to presume that the basis for your claim that Food and Drug Administration (FDA) Medical Reviews demonstrate that clinical trial sizes are substantially lower for cancer drugs compared to non-cancer drugs is based on information contained in two spreadsheets created by the KEI staffer noted above and one other KEI staffer. One spreadsheet examined cancer drugs approved in the United States since 2005, and the other looks at all 2010 approvals.²

It is not possible to know the total number of subjects that were in clinical trials for approved drugs by examining the Medical Reviews available at the FDA website. The one drug mentioned in your original letter (sorafenib [Nexavar™]) illustrates how the number of subjects in trials discussed in the Medical Reviews can vastly understate the number of subjects in clinical trials funded by pharmaceutical firms. Nexavar™ was first approved in the United States for an orphan drug cancer indication (advanced renal cell carcinoma). The reviews will contain discussions of trials that the medical reviewer considered pivotal to the decision to approve the drug for the specific indication for which it was approved. They do not necessarily contain information on all clinical trials conducted by a sponsor pre-approval (and, of course, they do not contain information on post-approval trials). The extent to which the reviews understate the number of subjects in clinical trials will also vary depending on the drug. This can hold true for groups of drugs, as well. Cancer drugs, in particular, may be especially sensitive to this undercounting as cancer drug development often involves testing in multiple cancers. Thus, Medical Reviews do not provide an accurate assessment of either absolute or relative clinical trial sizes.

Pre-Approval Trials: For example, the KEI spreadsheet value for the number of subjects in clinical trials prior to first U.S. approval of sorafenib is 1,233. This is an accurate count of numbers presented in sorafenib's Medical Review. In the review, one Phase 2 and one Phase 3 trial were discussed. Seven Phase 1 trials were also noted. However, it is easily demonstrated that the number of subjects enrolled in industry-funded clinical trials prior to approval greatly exceeds the number used by KEI. ClinicalTrials.gov is a publicly available searchable registry of clinical trials. It is well known that this registry undercounts clinical trials. This is particularly true for Phase 1 trials, as hypothesis-generating, as opposed to hypothesis-testing, studies need not be included. In any event, a search of the registry for trials initiated prior to sorafenib's original U.S. approval that were industry-sponsored and for which Bayer was a sponsor/collaborator indicates that 5,558 subjects were enrolled in 14 trials for six cancers. These include two Phase I trials, eight Phase II trials, and four Phase III trials. The fact that only two Phase I trials were found in the registry, while the Medical Review notes seven trials, underscores the fact that not all trials make it into the registry. Using the number of subjects reported in the Medical Review for Phase I trials increases the pre-approval number of subjects

² See <https://docs.google.com/spreadsheets/d/1z0pLyTIEMSHF7xwOFPxiJk-bkg3YLZbXlmK-pbbH41U/pubhtml> and <http://keionline.org/node/2124>.

to 5,670.³ Thus, the actual number of subjects enrolled in pre-approval sorafenib trials was nearly five-fold the value that KEI uses. As noted, the registry may not cover all trials. Our pre-approval cost estimates include expenditures on all indications pursued prior to approval.

Post-Approval Trials: R&D on approved compounds often continues post-approval. Our lifecycle R&D cost estimate includes post-approval costs. Such development is extensive for some drugs. This is certainly the case for sorafenib. A further search of the registry for all industry funded trials where Bayer was a sponsor/collaborator shows 160 clinical trials for which a total of 22,316 subjects were enrolled (1,073 in Phase 1, 1,923 in Phase 1/2, 6,460 in Phase 2, 13,249 in Phase 3, and 611 in Phase 4).⁴ This number is 18 times larger than the KEI number obtained from examining the FDA's Medical Review. Of course, there can be continued development of sorafenib, and so even more subjects in clinical trials.

Cancer Drugs: You ask in your letter about cancer-specific drug development costs. With regard to development costs of drugs for particular therapeutic classes, as we have done with past cost study analyses, we will follow-up with an additional paper that will provide a detailed look at clinical period costs by therapeutic class, including metrics for development times and risks. As in the past, we will restrict the analysis to therapeutic classes for which there are sufficient data.

Orphan Drug Tax Credit: Your letter asks how orphan drug tax credits were accounted for, if at all, in our analysis. In our slides, and in my oral presentation of those slides, we clearly stated that the R&D cost estimates are pre-tax. We were interested in measuring the resources expended by private sector developers (regardless of who ultimately pays). Including tax credits can distort the picture of how resource costs have changed over time, because tax structures can change over time. This is no different than what we did in our previous studies. We have not made statements about individual drugs. We are looking at industry spending as a whole in relation to the output generated by that spending. While orphan drug tax credits may be important for particular drugs, in the aggregate these credits are not empirically significant. Tax expenditure data available from the U.S. government on the size of orphan drug tax credits, along with external estimates of aggregate biopharmaceutical R&D expenditures, indicate that U.S. orphan drug tax credits amount to a small share of U.S. aggregate R&D spending by the biopharmaceutical industry.

Public Funding of Research: You ask what role National Institute of Health (NIH) funding plays in our analysis. What we measured for our study is what private developers actually spent on development. NIH research is complementary. If the NIH does any basic research, or even clinical research, that has findings that developers find useful, then the cost of that NIH research is part of the social cost of drug development. The social cost is the private cost plus what governments and non-profits spend that contributes to the discovery and development of new

³ KEI submitted comments in a dispute regarding the compulsory licensing of Nexavar™ in which it claimed that 424 patients were included in Phase 1 trials related to the U.S. approval of the compound for renal cell carcinoma. Using this figure for Phase 1 increases the pre-approval number of subjects to 5,897 (KEI, Comments on the Bayer appeal of the compulsory license on Nexavar patents, February 17, 2013, paragraph 50; found at <http://keionline.org/node/1657>).

⁴ Data accessed from clinicaltrials.gov on December 29, 2014.

drugs. If private developers spend less than they otherwise would as a consequence of NIH research, then the resultant lower costs would be captured by our estimate, because we are only measuring what private developers spent. The sample selection criteria do not preclude cases where companies take advantage of knowledge generated by NIH research in guiding their own research.

Again, thank you for your interest in our study on the R&D costs of new drug development. The research enterprise, and our understanding of what that research is intended to illuminate, is enhanced by informed discussion and debate.

Sincerely,

A handwritten signature in black ink that reads "Joseph A. DiMasi". The signature is written in a cursive, flowing style.

Joseph A. DiMasi, PhD
Director of Economic Analysis
Tufts Center for the Study of Drug Development
Tufts University School of Medicine