Dear Reviewers and the BMJ Review Committee:

Thank you for reviewing the submission and your thoughtful comments on this paper. We value your suggestions for improving the manuscript and appreciate this opportunity to address your comments/suggestions. Before we address each comment in turn, we would like to provide some overarching comments.

The reviewers suggest that the paper needs to take a stronger stance on its policy implications and next steps. We agree with the reviewers that the data are clear: the press releases (PRs) are a poor substitute for the FDA complete response letters (CRLs). However, this paper’s primary purpose is to provide a novel analysis of previously unavailable data to quantify the differences between the CRLs and the PRs. While this analytical paper could inform subsequent policy-making, and we identify the array of available policy options, we regard strong policy recommendations as beyond its scope.

Nonetheless, based on the advice of the reviewers, we have sharpened the public health arguments in a number of locations:

1. Added to the Discussion, p. 15: “[The disclosure of CRLs] would also allow for broader and more informed public discussion by relevant stakeholders (such as patients, clinicians, researchers, and public health advocates) of the reasons for FDA’s actions.”

2. Added to the Discussion, pp. 15-16: “Three potential approaches to reducing the gap between the information provided in CRLs and that provided in PRs are: 1. Sponsors could release the CRLs themselves, although they did not choose to do so for any of the CRLs in this study; 2) Sponsors could release more complete PRs; and 3) FDA could itself make the CRLs public, although this would likely require a change in FDA’s regulations. A thorough discussion of these options is beyond the scope of this paper.”

3. Added to the Conclusion, p. 17: “The potential benefits of publicly disclosing the Agency’s detailed rationale for refusing approval include better informing the development of new drugs, facilitating a richer public health discourse, and countering misconceptions regarding FDA’s reasons for denial of applications.”

In the following pages, we address each of the comments by Reviewer #1, Reviewer #2 and the BMJ Committee, in that order.

**Reviewer #1 Comments:**

**Reviewer 1, Comment 1:** The authors should make a stronger public health case as to why the
information in the CRL is useful and needs to be faithfully reported to the public (rather than simply its financial implications for investors). …. The information in the CRL can be immediately clinically relevant.

Authors’ Response: We have made the changes indicated above to address this comment. In addition, on p. 3, we noted that the information might be useful to clinicians.

Reviewer 1, Comment 2: The paragraph, for example, on transparency in the Discussion is not precise enough--can the FDA now act to improve transparency as the authors suggest? Will this require N&C rulemaking? Does Congress need to get involved?

Authors’ Response: The edits described in the introduction to this letter address this comment. Please note that on pp. 15-16 we note that one of the policy options would likely require FDA rulemaking.

Reviewer 1, Comment 3: I would recommend subsections [in the Results] to help orient the reader, since the denominator changes a lot among your various analyses.

Authors’ Response: To address this concern, per the reviewer’s recommendation, we have created subsections within both the Methods and Results sections to help orient the reader. Please note that the addition of subsections required rearranging the text in some areas to fit under the subheadings. These changes are indicated in track changes in the resubmitted manuscript.

Reviewer 1, Comment 3 (continued): There were some analyses that were superfluous like whether NDAs vs BLAs were more likely to have PRs (who cares?). It’s also not clear why having “at least one matching PR statement” is a relevant comparison.

Authors’ Response: We would prefer to include the NDA/BLA comparison as it takes up little space in the table and is actually one of the variables that is a statistically significant predictor of releasing a PR (see p. 10). We also favor retaining the analysis regarding “at least one matching PR statement.” From a disclosure perspective, there is little difference between not issuing a PR and issuing a PR with so little information that no statements in the CRL are matched. However, to save space, we have combined the discussion of the predictors of issuing a PR with at least one matching statement and the predictors of matching when measured at the statement level, since they are similar.

Reviewer 1, Comment 3 (continued): I was confused by the 11 PR statements that did not occur in CRLs -- what does that mean, and is that relevant, particularly if the PR was intended to provide information about other stuff as well as the CRL?
Authors’ Response: We conducted this analysis to classify statements in the PR that go beyond the CRL. We think this addresses a question many readers would have once they learn that certain information is not included in the PRs: Did the companies add information that was not in the CRLs? We believe our findings emphasize that companies at times use the PRs to make additional statements that may alter the context in which CRLs are viewed, such as emphasis of non-primary endpoints or referrals to favorable decisions by a foreign regulatory agency.

Reviewer 1, Comment 3 (continued): Similarly, is it relevant that 27/50 PRs don't explicitly state that marketing cannot commence?

Authors’ Response: This statement was deleted.

Reviewer 1, Comment 4: It would be extremely helpful, and I think would make the paper even more powerful, to present examples or quotes from the PR and CRLs. You do this once in the Discussion, omitting the drug names, but since the PRs are not CCI, I would think that would give you license to create a table of PR statements with a second column providing your interpretation about whether these statements were in the CRL, or did not match, or whatever. It would also be useful to provide more redacted CRL statements, if you indeed feel like they should be redacted. Arguably, if a company is issuing a PR about the information in a CRL, doesn't that mean that the company doesn't think that the information is protected, and would give you license to show examples of matching vs. non-matching statements in another qualitative-style table?

Authors’ Response: We do not consider ourselves limited by the CCI issue, as no drug or company would be identified. In fact, prior to submission, we prepared the table suggested, comparing CRL and PR statements. However, the findings were not particularly interesting. This is because, in general, PRs tend to omit information in the CRL; they do not generally misrepresent.

Reviewer #2 Comments:

Reviewer 2, Comment 1: Choosing 750 employees as the cutoff separating larger from smaller sponsors seems odd and is never justified. In order for this result to be at all credible, two things must be supplied. First, a prima facie justification for the 750-person cutoff. Second, a robustness check that tells us whether the finding is still significant when the cutoff is 500, or 900, or 1000, or something else. Far superior to these, in my opinion, would be an analysis using the log of the employees variable, as it would exploit the monotonicity required by the hypothesis.

Authors’ Response: We have modified the submitted version to explain that is was Dun and Bradstreet that characterized the companies as large and small (using the Small
Business Administration’s approach), not us (p. 5): “We used the Dun & Bradstreet Business Information database, *which* characterizes sponsors as either “large” or “small” *using the cutoff of 750 employees used in the Small Business Administration classification of business size."

**Reviewer Comment 2:** Relatedly, the authors test a number of hypotheses in these differences, and it is not clear whether the reported differences satisfy a Bonferroni-like correction.

**Authors’ Response:** The reviewer raises a valid point. However, there is considerable debate about multiplicity correction, with the Bonferroni, in particular, being criticized as too conservative. In this paper, we took the approach of examining our results for overall consistency and only emphasizing those results that recurred in multiple analyses. In particular, small firms and those that were public traded were more likely to match, no matter how we measured matching. However, given the consistency in our results, it is unlikely that what we have observed is due to chance.

**Reviewer Comment 3:** Finally, one policy issue raised by this paper is why the FDA or another public health organization cannot do more to publicize the CRLs. I assume that this is a trade information restriction (exemption to FOIA), but I have not kept up with the latest regs on this. The answer to this question would seem to have great weight for the question of "where to go from here."

**Authors’ Response:** Thank you for this comment. As noted in the introduction to this letter, we have made the appropriate changes to the paper to reflect this concern. In particular, we have noted that FDA release of CRLs would likely require a change in FDA’s regulations.

**Comments by the BMJ Committee:**

**BMJ Comment 1:** Please explain the choice of cut-off dates as Aug 11, 2008 to June 27, 2013.

**Authors’ Response:** CDER begin issuing CRLs in the current form in August 2008, the first CRL issued in our sample was August 11, 2008. Prior to this, the Center issued “Approvable” and “Non-Approvable” letters. The end date of June 27, 2013 is the close-out date for data collection for this study. We have clarified the reasoning behind the start/end dates in the Methods section of the paper (p. 4) by adding the following text: “The study covered NDA and BLA applications from August 11, 2008, when CDER begin issuing CRLs, through June 27, 2013.”

**BMJ Comment 2:** We would like you to mention in the abstract that CRLs are not made public and also that press releases are not mandatory.
Authors’ Response: We have added text to the background section of the Abstract (p. 2) to clarify these two points. The text now reads: “The US Food and Drug Administration (FDA) issues *non-public* Complete Response Letters (CRLs) to sponsors when FDA determines that it cannot approve their marketing applications. Thereafter, sponsors may choose *but are not required* to issue press releases (PRs), often the only public source of information describing FDA’s decisions and rationales.”

BMJ Comment 3: Methods - What is the chance that the matching was over-specified - in that they created so many categories - driven from details in the CRLs - that there really wasn't a chance that PRs could match the CRLs on all points?

Authors’ Response: We considered the risk of over-specification during study design. Much of our thinking is described in the first full paragraph on p. 16. These and some additional considerations follow:

1. The seven domains (based on ICH classification and CRL review) were necessary to adequately capture the breadth of topics covered in the CRLs, which often use these names as subheaders. We used a similar approach to identify the 64 sub-domains, attempting to capture the richness of the material in the CRLs without creating an unmanageable number of sub-domains.

2. Note that, although the overall number of domains and sub-domains is not small, CRLs contained statements coded to a median of only four domains and eight subdomains.

3. If several sentences in a CRL (even those pages apart) addressed a single subdomain, they were combined into a single statement.

4. A single sentence in a PR could be matched to several CRL statements.

5. We also limited the number of sub-domains in CMC (4) and Labeling (3) to more general categories. This was also done to prevent over-specification, particularly in the case of CMC, a field which lends itself to granularity, maximizing the probability of matching.

6. To avoid overemphasizing CMC and Labeling statements, which can be lengthy and may be of less concern and more easily addressed, each CRL was limited to one statement for each CMC and Labeling subdomain. (In contrast, several distinct CRL statements could be coded to the same subdomain for the other five domains). This increased the probability of matching in the CMC and Labeling domains.
7. When matching PR statements to CRL statements, we were very generous. The PRs only needed to mention, in very general terms, the essence of a CRL statement at a high level. For example, a CRL might mention in some detail what the design of a new clinical trial should be. However, we coded the PR as having a matching statement if there was any reference to the need for a trial whatsoever.

8. Despite the generous matching, the overall matching did not exceed 15% (even when considering SEC documents). We believe it is doubtful that, even if the number of sub-domains were reduced substantially, the matching percentage would increase in any significant manner.

**BMJ Comment 4:** Results: Please share how many statements were made on average per CRL. As CRLs are much longer than press releases, it raises questions about the expectation that a press release could convey as much information as a CRL.

**Authors’ Response:** In the submitted manuscript, we included on p. 11: “A total of 687 statements were identified in all 61 CRLs (median 8 statements per CRL; range 1–38).” Further, we agree with the Committee’s comment that PRs cannot convey as much information as the CRLs. Indeed, this is a central argument of this analysis. Some of these issues were already addressed in the submitted manuscript:

Discussion, p. 15: “Clearly, a PR’s primary purpose is not to reveal every deficiency FDA identifies; PRs are almost always considerably shorter and less technical than CRLs. Nonetheless, they remain the predominant source of publicly available information regarding CRLs …”

However, we have further clarified that the central theme of this analysis is that the PRs are omitting (due to their very nature) the FDA concerns cited in the CRL. We have added the following text to the last paragraph of the Introduction (p. 3) to further clarify this: “Given the distinct purpose and frequent brevity of PRs, it is not expected that they would necessarily cover all components of FDA-issued CRLs.”

**BMJ Comment 4 (continued):** It also raises the question of how many press releases for approved drugs mentioned the negative information and other caveats in approval letters.

**Authors’ Response:** While an interesting question, it is beyond the scope of this study. We did not review PRs related to approval letters. Furthermore, approval letters, unlike CRLs for drugs under premarket review, are publicly accessible.

**BMJ Comment 5:** Please share how many of the new molecular entities were rejected with a CRL are now approved and on the market.
Authors’ Response: This information was provided in the submitted manuscript in Table 1 (3rd and 4th rows from the bottom). Twenty-five of 61 products issued CRLs were approved by the study close date.

BMJ Comment 6: The methods section may be made clearer and abbreviations are to be avoided.

Authors’ Response: Thank you for this helpful suggestion. We realize the methodology is lengthy and involves multiple aspects – in an attempt to make the methods easier to follow we have introduced the sub-headings into the methods section: 1) Identification of CRLs; 2) Identification of PRs; 3) Coding of CRL Statements; 4) Identification of Matching Statements; and 5) Data analysis. All abbreviations are for terms used repeatedly. We certainly defer to the editors’ specific suggestions in this regard.

BMJ Comment 7: We would like you to reduce the length of the paper.

Authors’ Response: Please see our response to Reviewer 1, Comment 3, in which some of the text about predictors of matching has been consolidated and shortened. Should it be necessary to reduce the length of the paper further, the Editors may wish to consider moving some of the Methods into an online supplement. We think the following two sections from the Methods section may be suitable for an online supplement:

1. The section on categorization of public vs. private entities and large vs small businesses (paragraph beginning “We categorized ...” on p. 4).
2. The section on the use of FDA document archiving and orphan drug databases to collect information on application characteristics (paragraph beginning “We used … on p. 5).

BMJ Comment 7 (continued): Currently the paper seems to suggest that sponsors are manipulating by issuing misleading press releases. However, press releases are not mandatory, and the FDA being a public body, one may question why information from the CRLs is not made public. This has patient safety implications. We feel the issue is not that press releases fail to summarize CRLs but that the CRLs are not made public despite the fact that a public agency spent a lot of time and money on the analysis. The reasons for this should be made clearer. The focus might rather be to document the extent to which PRs match CRLs, and to suggest how the process may be made more transparent.

Authors’ Response: See response of BMJ Comment 4. We also feel that the added material mentioned in the second point at the beginning of this letter (relating to Discussion, pp. 15-16) provides suggestions as to how the process may be made more transparent. Material in the submitted manuscript (Discussion, p. 14) is also relevant: “Statements that were included in PRs were typically accurate, even though they were generally less detailed than CRL statements.”
**BMJ Comment 8:** Some companies might go off and reformulate drugs or do additional things to try to gain approval, and do not want competitors to know details while they are doing that. These letters are not necessarily the end of the development story for all of these drugs or classes of drugs. But the arguments for this should be made clearer.

**Authors’ Response:** We feel we have acknowledged these possibilities but enumerating the fraction of drugs that received CRLs that were later approved (see response to BMJ Comment 5) and by explaining in the Introduction (p. 3) that “Some members of the pharmaceutical industry … have suggested that the release of CRLs would provide an advantage to competitors.”

There are a small number of additional minor edits, all indicated in track changes. Once again, thank you for the opportunity to submit to the BMJ. Please let us know if there are any issues that require further clarification.

Sincerely,

Peter Lurie, MD, MPH
Associate Commissioner for Public Health Strategy and Analysis
U.S. Food and Drug Administration