BMJ.2015.027196: Authors' Responses to Reviewers' Comments
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Editor's Comments	Authors' Responses
1.1: The authors use many different terms, some technical, and it may be helpful to the readers to add a box explaining the terminology. The box could also include some information on the legal requirements for each type of drug approval (i.e. what does the FDA require at each step of the process?). While some terms are already explained in the text, the box would be helpful for readers. The terms that could be defined are: 1. Original indication 2. Supplemental approval 2.1 New indication 2.2 Modification of approved use 2.3 Expansion of patient population 3. Orphan drug	**R.1.1:** We have created a new table (Table 1) that explains these key terms, as well as gives examples as applicable. We chose to define "supplemental application" rather than "supplemental approval" and included the other suggested terms. We also defined "supplemental indication", which is requested by drug manufacturers via a supplemental application. In addition, we have changed our usage of the term "supplemental approval" in many instances to "supplemental indication approval" to reflect the fact that supplemental approvals pertain to FDA authorization of all supplemental applications, of which supplemental indications are only a subset. The legal evidentiary standard for all drug approvals is the same, as we have mentioned in the text: *"The legal standard underlying FDA approval remains consistent for original and supplemental indications."*
1.2: We need additional information on the source of the data. What do the FDA medical reviews include? Is there a legal requirement to file these for any supplemental approval? Why were FDA medical reviews available for only 20% of supplemental approvals? Is the material in the original review sufficient?	**R.1.2:** FDA medical reviews are documents that detail the clinical evidence underlying the efficacy and safety of drug products for the proposed indications. They have served as the primary data sources in numerous prior studies examining the clinical evidence underlying original indications of novel pharmaceuticals (see, e.g., Goldberg NH, Schneeweiss S, Kowal MK et al. Availability of comparative efficacy data at the time of drug approval in the United States. JAMA. 2011;305(17):1786-1789.; Downing NS, Aminawung JA, Shah ND et al. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012.JAMA. 2014;311(4):368-377.). We are not aware of and were not

	able to identify any legal requirements to file these documents for supplemental approvals. Similarly, we are not able to identify why medical reviews were available for only 20% of supplemental approvals for new indications. We contacted the FDA regarding this issue and were told that: "Generally, posting of the FDA reviews ranges from one month to one year, depending on the degree of redaction required" and that: "In any case, you can request the review, if unposted, directly under the U.S. Freedom of Information Act (FOIA)…" The 1 month to 1 year time frame given for posting of medical reviews is inconsistent with the low accessibility of medical reviews for some of the earlier years, and, per our correspondence with FDA, "The current turn-around time for [receiving] medical reviews [via FOIA] is about 24 months." As such, we assessed the clinical efficacy evidence supporting supplemental approvals by accessing the earliest available FDA drug labels containing mention of the new indication. These drug labels contain information about the characteristics of interest - comparator(s) and study outcomes of the pivotal efficacy trials – and the characteristics reported in these drug labels matched those reported in the small number of FDA medical reviews for supplemental indications that we were able to access. We therefore are confident in using drug labels as our source of analysis for the data needed for this study. We also used drug labels as our source of analysis for original indications, with findings consistent with prior research.
1.3: We assume that to evaluate the quality of the studies the authors used the data from the Drugs@FDA database in addition to the drug label. What type of data is available? Does it include a description of all trials used for the approval? Did you have to look at the publications for the trials included in	**R.1.3:** We utilized the Drugs@FDA database to identify the approval date, chemical type, and orphan drug status (in conjunction with the FDA Orphan Drug Product database) for each supplemental

the database? A box that lists the information in Drugs@FDA database and the drug labels may help readers understand the process better. Did you consider looking at published studies if the information was not provided in the drug label? Did you look at changes in black box warnings?	approval. A description of all trials used for approval can be found in the FDA medical review documents, which, if available, is accessible through the Drugs@FDA database. However, as mentioned above (R.1.2), this document was not available for 80% of supplemental approvals included in our study, thus requiring us to utilize FDA drug labels to identify key information about the pivotal trials leading to approval. The pivotal efficacy studies described in the drug labels were often not easily located via Medline/PubMed, and we therefore did not seek to identify the full publication for each supplemental approval's efficacy trials. It is worth noting that the two trial design characteristics we assessed in our paper – comparator and outcome for the pivotal efficacy studies of each supplemental approval – were adequately described in the drug labels that we reviewed, and thus we do not believe that looking at published studies was necessary. We did not seek to evaluate evidence of safety supporting the supplemental approvals, since information on early-phase trials would have been necessary to evaluate safety. Information about such studies are often not published and are inconsistently described in the drug labels, so the lack of accessibility of the FDA review packets is a hindrance to full and accurate reporting on this topic. We did not look at changes in black box warnings since our study focused on efficacy.
1.4: The results narrative is somewhat monotonous and difficult to follow. The tables are helpful. Could you redraft the results section to make it clearer and more engaging?	**R.1.4:** We have redrafted the Results section to elucidate our findings in a clearer and more succinct manner, removing certain sub-sections and addressing the flow.
1.5: What are the legal implications of supplemental approvals? Is there less risk of sanctions for off-drug labeling if companies have a supplemental indication request in with the	**R.1.5:** Drug companies are generally prohibited from promoting unapproved ("off-label") uses of drugs in an

FDA? Does that incentivize companies to submit weak evidence just so they can point to the fact that they are trying to get approval?	unsolicited manner, regardless of whether they have submitted a supplemental application.[1] However, since drug companies are allowed to provide information on off-label uses upon unsolicited prescriber request, in such a situation, the company may indicate that it is seeking FDA approval for a certain off-label indication. However, there is no published literature to support or refute this, so we did not include it in the manuscript.
1.6: What will be the impact of the 21st Century Cures Act on the supplemental approval process?	**R.1.6:** We believe that the 21st Century Cures Act will be most impactful on the supplemental approval process through its encouragement of greater reliance on non-traditional study designs, including observational studies, as well as biomarkers and surrogate measures to establish a therapy's efficacy. The 21st Century Cures Act also explicitly instructs the Secretary of Health and Human Services to establish a streamlined data review process for supplemental applications. We have devoted a new paragraph in the discussion to the 21st Century Cures legislation, which was still under development when we originally submitted this study (pg 16).
Reviewer 1's Comments	**Authors' Responses**
2.1: My main concern with this study is that the authors did not compare the original indication(s) with the supplemental indication(s). Doesn't the type of study endpoint and comparator depend on the indication being studied? Therefore, if the supplemental indication differed significantly from the original indication wouldn't that affect the study design?	**R.2.1:** We are comparing study endpoints and comparators used in studies supporting supplemental vs. original indications at the aggregate level (including when stratifying by supplement category, therapeutic category, etc.) rather than at the level of individual drugs. As such, we do not believe that it is necessary to compare supplemental indications with original indications, because that approach would leave out numerous supplemental

[1] For a brief discussion of a time when the FDA tried—and failed—to make one type of off-label marketing dependent in part on a supplemental indication application, see Kesselheim and Mello, Prospects for regulation of off-label drug promotion in an era of expanding commercial speech protection. Univ North Carolina Law Review 2014;92: 1539-1604, pgs 1548-1549.

	indications for which a comparable original indication is not included in our study, and vice-versa.
2.2: Page 5, lines 14-21: If 50% of new drugs are approved with placebo controlled trials and 50% with uncontrolled trials does that mean that there are no new drugs approved with trials against an active comparator?	**R.2.2:** We thank the reviewer for bringing this to our attention. We intended to say that half of new drugs are approved after being tested against placebos or uncontrolled trials and have made the pertinent corrections in the revised manuscript: *"Recent studies of the pivotal clinical trials used to meet this standard indicate that approximately half of new drugs are approved after being tested against placebos or uncontrolled trials."*
2.3: Page 6, line 10: I would question the use of the word "rigor" here as it implies that more than the endpoints and comparators will be assessed.	**R.2.3:** We agree with the reviewer and have changed the phrase from "rigor of trials" to "characteristics of trials" in the revised manuscript: *"However, the characteristics of trials that support drugs' supplemental indications has not been analyzed."*
2.4: Page 8, lines 37-44: How was the study classified if both a placebo and active comparator were used? Would the classification differ depending on the indication being studied, i.e., is it more useful to use a placebo control for some types of indications and an active control for other types)?	**R.2.4:** The use of both placebo and active comparator in a study can occur in two different situations: 1. A 3-arm study comparing the study drug to the active comparator and to placebo. In these cases, the study was classified as an active comparator study. 2. A 2-arm study in which study drug + active comparator was compared to placebo + active comparator. For example, in a trial supporting the supplemental approval of bevacizumab (Avastin) for use in metastatic renal cell carcinoma, bevacizumab plus interferon alpha-2a was compared to placebo plus interferon alpha-2a. In these cases, the study was classified as a placebo study since the active comparator was included in both arms, thus making the main comparison between the study drug and placebo. We did not alter our classification criteria for different indications; rather, we

	established a uniform approach to analyzing our data.
2.5: Page 9, lines 8-10: What was the reason for separating clinical outcomes and clinical scales?	**R.2.5:** We believe that clinical outcomes and clinical scales measure different types of patient responses to therapy, with the former measuring endpoints such as mortality and incidence of myocardial infarction and the latter measuring patient responses based on pre-defined quantitative measurements. The classification of study endpoints as clinical outcomes, clinical scales, or surrogate endpoints was also utilized in the following studies: Downing NS, Aminawung JA, Shah ND et al. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. JAMA. 2014;311(4):368-377.; Clement FM, Harris A, Li JJ et al. Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada. JAMA. 2009;302(13):1437-1443.
2.6: Page 9, lines 30-34: If a drug was originally approved for multiple indications was it counted more than once?	**R.2.6:** Each supplemental and originally-approved indication was counted once for our analysis.
2.7: Page 15, lines 3-8: A new paper in Drug Safety questions how useful the Sentinel Initiative is at present.	**R.2.7:** We thank the reviewer for bringing this paper to our attention and have cited the paper and made mention of the Sentinel Initiative's limitations in our Discussion section: *"The FDA's Sentinel Initiative is a nationwide active surveillance program which draws upon multiple healthcare data sources and has the potential to shorten the time needed to identify safety issues related to drug and medical products, though major hurdles must still be surmounted before this system can reliably serve as the principal source for risk assessment and drug safety decisions."*
2.8: Page 15, lines 49-53: From the regulators point of view there might not be an imperative to approve supplemental indications but from a patient's point of view there might be if the off-label use is not covered by insurance.	**R.2.8:** We have removed this sentence from the revised manuscript.
2.9: Page 17, line 8: What kind of monitoring are the authors	**R.2.9:** We are referring to both safety

referring to?	and efficacy monitoring and have made mention of this in the last sentence of the text: *"However, the high degree of heterogeneity of supporting evidence for supplemental indications, in the setting of legislations promoting drug approvals based on decreasing evidentiary standards, underscores the need for a robust system of post-approval drug monitoring for efficacy and safety, timely confirmatory studies, and reexamination of existing legislative incentives to promote the optimal delivery of evidence-based medicine."*
Reviewer 2's Comment	**Authors' Response**
3.1: The authors initially intended to use the FDA medical reviews to assess the quality of the supporting data for supplemental indication approval, but found that it only existed for 20% of the supplemental agents (which seems like an important finding in and of itself). They then went to the drug labels as their source data. The important question to resolve is: how do these two data sources differ? For example, do the FDA reviews also contain unpublished data that might not be included on the drug label?	**R.3.1:** FDA medical reviews contain detailed descriptions and analyses of all relevant studies carried out by the sponsor to evaluate a drug's safety and efficacy, and necessarily contain more unpublished data than the FDA drug labels. However, our study aimed to examine the study comparators and study endpoints of the pivotal trial(s) (often Phase III trials although can be Phase II for rare diseases) supporting each drug's efficacy for the supplemental indication, and we found that this information was reliably described in the FDA drug labels. In addition, cross-checking with the 20% of supplemental approvals for which an FDA medical review was available confirmed the accuracy of these study characteristics as described in the drug labels.
3.2: And who generates the drug labels? Is there any chance of selection bias in terms of what information gets captured on the drug labels (if, perhaps, not all reviewed studies get included on the drug label)? The authors make a good point in their limitations section that their results should be valid since they were comparing drug labels to drug labels (p. 16, line 39), but clarifying what is known about how these two data sources differ and whether drug labels have been validated as being as accurate as FDA medical reviews would nonetheless provide important information to the reader.	**R.3.2:** Drug labels are generated by the manufacturers in conjunction with the FDA (the FDA has to approve the original drug label and any changes made). Not all studies are described in FDA drug labels, as they usually are in the FDA medical review documents. However, since drug labels are a central means through which manufacturers communicate information about their drug products to the medical community

	(and is a source referenced by other highly-cited sources such as UpToDate and Micromedex), we would expect that the labels would contain a description of all *pivotal* studies supporting a drug's efficacy for the supplemental indication (as described above, often Phase III trials although can be Phase II for rare diseases). We have included the following sentence in the Methods section to clarify this point to the readers: *"In contrast to most medical reviews, FDA drug labels do not contain a description of all pre-clinical studies and clinical trials supporting an approved indication. However, drug labels do describe the study design and results of the so-called pivotal trials that most clearly establish a drug's efficacy for that use."* We are not aware of any studies seeking to validate drug labels as being as accurate as FDA medical reviews, but do note in the Discussion section that our findings for the originally approved indications using drug labels is consistent with prior studies that used FDA medical reviews.
3.3: A great deal of information is presented on the original approvals and the subsequent supplemental approvals, by various subcategories. At times this information can be difficult to follow, in part because the denominators change frequently throughout the work and because single drugs could be approved for a multiple indications either initially or subsequently. In the text the authors provide more thorough information (eg, p. 12 line 42 describing the ten supplemental approvals for expanded populations that had no efficacy trials) but these data are not presented in tables 2 and 3, making these tables more difficult to follow. Furthermore, at times it is difficult to determine which proportions refer to which categories, such as "Compared to the original orphan approvals, these non-orphan supplemental approvals were supported by a similar proportion of active comparator trials (28% [11/40] vs. 24% [10/42])" (p. 13, lines 51-53) in which the 11/40 would appear to refer to the original orphan approvals, but other data elsewhere suggests that it should be the 10/42 that refer to these approvals.	**R.3.3:** Please refer to **R.3.4** for more thorough changes to the Tables per the reviewer's suggestions. Regarding the reviewer's point that "at times it is difficult to determine which proportions refer to which categories," we have made clearer indication in the text regarding the correct attributions. For example, the sentence that the reviewer refers to in the original manuscript (p. 13, lines 51-53) now reads: "Compared to the original orphan approvals…(28% [11/40] for non-orphan supplemental indications vs 24% [10/42] for original orphan indication, p=0.70)…"
3.4: To this end, consider re-formatting how the tables are laid	**R.3.4:** We thank the reviewer for these

out. Would including columns for "no comparator" (in Table 2 for example) or "no outcome trial" in Table 3 help? For example, reading across the first row of Table 2, one adds 41 supplemental approvals for new indications with active comparators to 77 with placebo comparators, getting only 118 out of the 136 total approvals. It would be more clear if the rows and columns summed to 100% each time. Likewise, I found it hard at first to understand the "modified" and "expanded" population rows in Table 2 under the Original approval column (because original approvals were not themselves modified or expanded). Those cells are describing that "of those original approvals that went on to have modified indications, 37 of the 83 had active comparators vs. 47 of the 93 new indications for these 83 drugs." Clearly that is cumbersome to spell out, but the current Tables 2 and 3 generate more confusion rather than clarifying the message. No clear solutions are evident to me, but consider taking the approach of following the drugs themselves (eg, make a table just for those drugs that went on to new indications, etc.) or expanding the tables so that one can track all the drugs in each table. The authors do have a footnote to this effect in both tables, but I did not find the footnotes informative. Expanding the tables may allow for removal of some of the text in the manuscript that repeats many of the same comparisons, allowing the reader to stay focused on the main take-home messages the authors would like to report in the discussion.	helpful suggestions. We have added columns for "no comparator" to Table 2 (Table 3 in revised manuscript) and have added a footnote indicating the 3 additional approvals (2 supplemental and 1 original) that were based on historical-controlled trials, which we distinguished from "no comparator" trials; this footnote also mentions the 10 supplemental indications that were approved with no clinical efficacy trials. We did not add columns for "no outcome trials" to Table 3 (Table 4 in revised manuscript) because we were able to classify the endpoints of trials supporting all supplemental and original approvals as clinical outcome, clinical scale, or surrogate; the only approvals unaccounted for in Table 3 then were the 10 supplemental approvals that did not have formal clinical efficacy trials, which were reiterated in the footnote. We also agree with the point the reviewer made that "original approvals were not themselves modified or expanded" and as such have moved all original approvals from the "modified indication" and "expanded population" supplement categories into the "new indication" category in both Tables 2 and 3, allowing for a comparison between all "new indication" supplemental approvals and all original approvals.
3.5: Is it possible that the excluded approvals related to "labeling revisions" (p. 6, line 38) also excluded approvals of drugs for new indications? Clarifying exactly what falls under a "labeling revision" beyond saying that these "focus mainly on administrative and/or logistical modifications" (p. 6 line 41) may help the reader understand whether bias was introduced into the sample of included approvals at this point.	**R.3.5:** Supplemental approvals that fall under the category of "labeling revisions" range from minor changes to the wording of sections of the labels to additions of new dosage strengths (e.g., inclusion of darunavir 150 mg to drug label) and adverse effects (e.g., inclusion of acute generalized exanthematous pustulosis as an adverse event for darunavir). New indications would generally not be classified in this category, and we were not able to identify any such approvals in the >100

	"labeling revision" supplemental approvals that we sampled while conducting this study (though we cannot exclude this possibility with complete certainty). We mentioned these examples in the revised manuscript to better clarify the nature of these supplemental approval categories to readers: *"…excluding supplements categorized by the FDA as relating to "Labeling Revisions" and "Manufacturing Change or Addition," which focus mainly on administrative and/or logistical modifications and ranges from minor wording changes in the label to addition of new dosage strengths and adverse events…"*
3.6: Consider describing the rationale for not including those drugs and biologics that were not originally approved as novel therapeutic agents (p. 6 line 53) and the relative frequency of supplemental indication approvals for non-novel agents; this will be especially relevant if the number of supplemental indications for non-novel agents dwarfs the number for novel agents (ie, if this is the case, the findings of the study may have limited generalizability to all supplemental indication approvals).	**R.3.6:** We chose not to include non-novel agents, including new formulations, since these therapeutics can be subject to different clinical evidence requirements, including approval based on bioequivalence studies alone. As such, inclusion of such agents would have complicated our efforts to make comparisons between the evidence supporting supplemental approvals and original approvals. Our focus on novel therapeutic agents is also consistent with previous studies that explored the clinical evidence supporting the original approval of therapeutics. This permitted us to compare our findings of study characteristics supporting original approvals using FDA drug labels with prior studies that utilized FDA medical reviews to achieve this purpose. The consistency between our study and prior research provides greater assurance of the validity of our methodology, which we were required to employ given the low accessibility of FDA medical reviews for supplemental approvals. Future studies should explore ways to capture and analyze the evidence supporting the supplemental approval of non-novel agents, which in our study constituted

	approximately 30% of supplemental indications (132/438, see Figure 1). We described our rationale in the Limitations section of the Discussion: *"First, we only included supplemental indication approvals for drugs originally approved as novel therapeutic agents, so our study findings are not representative of the evidence base supporting all supplemental indication approvals, including for new formulations and other non-novel therapeutics, which may be subject to different requirements for demonstration of clinical evidence, including approval on the basis of bioequivalence studies."*
3.7: Consider listing at the top of Appendix 1 how the drugs are arranged (chronologically, alphabetically, etc.).	**R.3.7:** We have re-arranged the drugs chronologically from 2005-2014 and have indicated as such at the top of Appendix Table 1.
3.8: Would it be useful to readers to know if there has been a trend in the annual number of approvals over time (p.10, line 20)?	**R.3.8:** Our study focused on a 10-year time frame, and we did not analyze the supplemental and original approvals by time period (other similar studies, referenced in endnotes 1-3, also did not conduct time trends). As such, we believe that formally evaluating a trend in the annual number of approvals over time, beyond what is shown in Figure 2 and Table 1, is not needed. However, we would be happy to conduct this analysis if the editors deem it worthwhile.
3.9: The information in Table 1 is repeated in the text (p. 10, lines 23-42) – could consider removing the information from one of these two places.	**R.3.9:** We have edited this portion of the text to highlight only the more important findings from Table 1, allowing the reader to refer to the table for more in-depth analysis.