How do priority and orphan status designations affect review times for new oncology indications approved through a supplemental application? A retrospective analysis

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Background

The Food and Drug Administration (FDA) requires a New Drug Application (NDA) or Biologics License Application (BLA) in order to review and approve a new molecular entity (NME) in the United States. The Prescription Drug User Fee Act (PDUFA) outlines goal review times for the FDA in an effort to facilitate timely review of new medications. Under PDUFA IV, the FDA and Congress had agreed upon goal review times of six months for priority applications and ten months for standard applications.[1] Many oncology products are labeled to treat multiple tumor types, with each indication subject to review and approval by the FDA. Sponsor companies initiate this review by submitting a supplement (type SE1) to the existing NDA or BLA application.

Objective

- The primary purpose is to assess the review time and proportion of submissions granted priority review status for SE1 applications that were approved for oncology products from 1998 to 2011.
- Our secondary objective is to compare the review times between the initial indication and additional indications for oncology new molecular entities (NMEs) approved during the same time period and to evaluate the lag time between NME approvals and new indication submissions.

Methods

- We conducted a retrospective analysis of FDA data concerning oncology SE1 applications (for solid and liquid tumors) approved between 1998 and 2011; including both New Drug Applications (NDAs) and Biologic License Applications (BLAs).
- This study includes a cohort analysis involving the products that were approved as new molecular entities (NME) and had at least one SE1 application approved during the study period.
- Using FDA data the following information was gathered for original NDAs, BLAs and SE1 applications approved during 1998-2011:
  - Indication
  - Review classification
  - Submission date
  - Approval date
  - Review time
  - Orphan drug status
- We calculated some descriptive statistics for the data set and conducted t-tests to determine if there was a statistically significant difference in review times. We also calculated lag times between original NDA/BLA approval and SE1 application submission for the cohort compounds. Unfortunately, data was not available on orphan status for all SE1 applications; therefore this variable was not analyzed.

Results

- 80% of the oncology original NDAs/BLAs approved between 1998 and 2011 received priority review.
- Similarly, oncology SE1 applications received a priority review 72% of the time. There was no statistically significant difference between these two proportions (p>0.5).
- SE1 applications for oncology products are granted priority review at the same rate as their original NDA/BLA counterparts; which is the majority of oncology applications.

Results (continued)

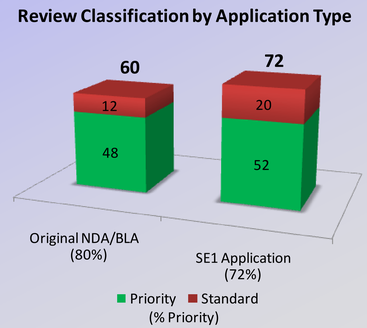

Figure 1: Proportion of original NDA/BLA and SE1 applications approved 1998-2011 receiving priority review designation. There is no statistically significant difference in the proportion of priority designations between original NDA/BLA and SE1 applications (p>0.5).

- Original NDA/BLA applications had slightly longer mean review times than SE1 applications. This difference was most pronounced for standard applications; with a mean review time for standard original applications of 18.6 months compared to 11.6 months for standard supplements. This analysis shows no statistically significant difference in review times between all original NDAs/BLAs and all SE1 applications approved for oncology products between 1998 and 2011.
- In the cohort analysis, we found that mean review times were higher for SE1 applications than the original NDA/BLA; but this difference was not statistically significant. The means were skewed by a few outliers, especially in the second and third SE1 application subsets, which had small sample sizes.

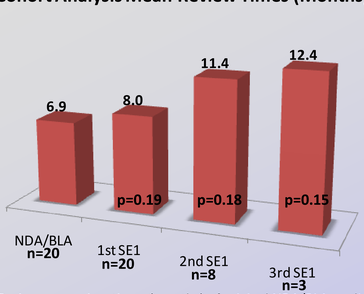

Figure 3. Average review times (months) of original NDA/BLA applications compared to first, second and third SE1 applications for cohort compounds. P-values represent one-tailed t-tests between each SE1 and the original application.

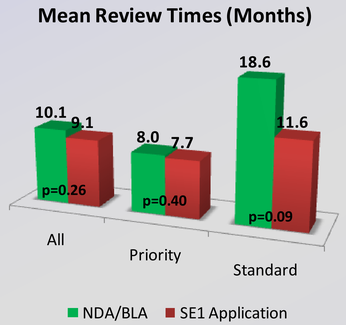

Figure 2: Mean review time (in months) for original NDA/BLA applications and additional indication (SE1) supplements for oncology products approved between 1998 and 2011; broken out by priority and standard review classification.

- Second and third SE1 applications had progressively longer review times than the first. This may be due to the fact that some oncology indications require more evidence to support the new labeling; as a first line treatment, for instance. These more complex SE1 applications may have required additional clinical trials and were therefore not approved in a single action; resulting in significantly longer review times. There were no statistically significant differences in review times between first, second, or third SE1 applications and the original NDA/BLA.

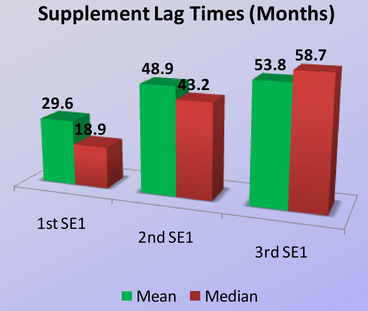

Figure 4. Average lag times (in months) of additional indication (SE1) applications as measured from time of NME approval to time of SE1 submission.

Discussion

- Our analysis did not reveal any discernable patterns or trends in the lag times of SE1 applications. There is a wide range of lag times, ranging from a couple of days to several years. One would expect the timing of an SE1 application filing to vary depending on several factors including the individual product's characteristics as well as the strategy and available resources of the sponsor company.

Limitations

- Our study did not account for SE1 applications that were terminated while in regulatory review.
- This study does not consider the effect that the number of FDA or sponsor actions has on review times.
- There was a small sample size for the cohort analysis, only 20 compounds met the inclusion criteria.
- This analysis only looks at oncology products, which are likely not representative of regulatory review trends in other therapeutic areas.

Conclusions

The comparable rates of priority review among these two groups indicates that SE1 supplements for oncology products are considered by the FDA to be just as important as original NDAs/BLAs. One would expect that SE1 applications would take less time to review than original NDA/BLA submissions given that the FDA does not need to re-evaluate certain sections of the applications; however, we found that this is not necessarily the case for oncology products. According to the Tufts Center for the Study of Drug Discovery (CSDD), oncology applications are reviewed more quickly by the FDA than non-oncology ones;[2] therefore it is unlikely that these results are applicable to other therapeutic areas. PDUFA V will extend review time goals for original NDAs and BLAs by two months, resulting in a 12 month review for standard applications and 8 months for priority.[3] However, review time goals for efficacy supplements—including SE1 applications—will not be extended;[3] a decision which is supported, at least for oncology products, by this analysis. It remains to be seen how review times for oncology NDAs/BLAs will be affected by PDUFA V, as this division has a history of reviewing drugs quickly.

References, Disclosures and Acknowledgements

1. PDUFA Reauthorization performance goals and procedures fiscal years 2008 through 2012
2. Milne CP, Kaitin K, Feldman L. Impact Report: Analysis and insight into critical drug development issues. Tufts CSDD Impact Report. 2012;14(5): 1-4
3. PDUFA Reauthorization performance goals and procedures fiscal years 2013 through 2017

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation: Noah Greenberg, Sanchali Kasbekar and Vishal Patel are paid employees of Rutgers University participating in post-doctoral fellowships in the Research and Development, Global Regulatory Sciences, and Promotion Integrity departments, respectively, of Bristol-Myers Squibb. Contact information of the authors: noahgreenberg22@gmail.com, skasbekar220@gmail.com, and vpatel641@gmail.com.

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