KEI Research Note 2014:3 (draft 2)

Size of Clinical Trials, data from the FDA 2010 NME and BLA approvals, preliminary results

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Introduction

The most significant cost for the development of new drugs is associated with the human use clinical trials performed to establish the safety and efficacy of products. Those costs are driven by the number of patients in trials, and the per patient costs of the trials. Several published estimates of drug development costs are based upon samples that have very large averages for the number of patients in trials.[1] KEI is examining the existing evidence regarding the size of trials used to support the FDA approval of new drugs.

In looking at the size of the trials, KEI also considers this advice from the Office of Health Economics:

> "Mean estimates of R&D costs per successful drug are useful in providing an overall picture, but should be treated with caution. Important cost differences exist across therapeutic areas, firm sizes and compound origins."[2]

In 2010, the US FDA approved six new biologic drugs, and 15 new drugs classified as new molecular entities (NME). We examine the data from the 2010 approvals, as preliminary results that are part of a larger project to examine the number of patients in all FDA BLA and NME approvals from 2010 to 2014.

For the 2010 approvals, we report on data on the size of trials that were cited in the FDA medical review associated with the approval of the drug, as well as the information about trials published on the drug label. The data from the FDA Medical Reviews are more inclusive and include Phase I, II and III trials, while the data from Section 14 of the FDA label for the drug typically reports only the key trials used to evaluate safety and efficacy.

The data suggests policy makers should not use averages that are skewed by a handful of products with large trials to make inferences about the costs associated with particular drugs.

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[1] See, for example: DiMasi, J. et al. (2003) The price of innovation: New estimates of drug development costs. Journal of Health Economics. 22(2), 151-185. Adams, C. and Brantner, V. (2006) Estimating the cost of new drug development: Is it really $802 million? Health Affairs. 25(2), 420-428. Mestre-Ferrandiz, J., Sussex, J. and Towse, A. The R&D Cost of a New Medicine, Office of Health Economics, Monograph December 2012.

[2] https://www.ohe.org/publications/rd-cost-new-medicine

For 18 of the 21 drugs approved in 2010, the FDA medical reviews provided data for all patients in the trials cited in the reviews. In two cases, the medical reviews provided incomplete data on the number of patients in trials, however, we were able to find the missing data from the NIH clincialtrials.gov database. In one case, we are still missing data on Phase I trials. For all 21 drugs, we have written to the companies that registered the drugs to review our calculations.

We have examined this data to calculate statistics relating to the entire year of drug approvals, and for subsets of data, such as drugs for cancer, or drugs first approved as orphan products. We have also examined, in some detail, the distribution of the data. A major finding was that the average number of patients enrolled was significantly larger than the statistical median, and that just two drugs (denosumab and dabigatran) accounted for more than half of all patients enrolled in the clinical trials.

The Skew and Kurtosis statistics for the data from the medical review are 2.8 and 7.3 respectively, illustrating the problematic nature of relying on the average to make inferences about individual values.

Data

The data collected on the 2010 approvals are summarized in Table 1.

Table 1, Basic statistics on the size of trials

	Patients in trials cited in Medical Review	Patients listed in Section 14 of the 2010 FDA label
Average	5,224	2,657
Median	2,655	909
Standard deviation	8,254	4,597
Below average	16	19
Total patients	109,698	55,798
Top two drugs	57,727	31,644
	52.6%	56.7%
Average top 7	12,441	6,714
Avg middle 7	2,589	1,046
Avg bottom 7	642	211
Avg bottom 16	1,964	841
Bottom 16 / all	37.6%	31.6%
Median top 7	6,650	3,992
Median middle 7	2,655	909
Median bottom 7	459	212
The two drugs for cancer		
Average	1,504	426
Cancer avg / all	28.8%	16.0%
Orphan at designation		
Average	976	223
Median	406	156
Orphan avg / all avg	18.7%	8.4%

The complete data are availble here: http://goo.gl/P7EfHA.

Commentary

Note that for 16 of the 21 drugs in 2010, the size of the trials were below average, and often significantly so.

For the data on the number of patients cited in the FDA medical review, the average number of patients for the 16 drugs with the least numbers of patients enrolled was 1,964, or 38 percent of the average for all drugs (5,224). For the bottom third of drugs with the least numbers of patients enrolled (7 drugs), the average was just 642 patients, or 12.3 percent of the average for all drugs.

The 2010 approvals included two cancer drugs that had an average of 1,504 patients (listed in the medical review), a number that was just 29 percent of the average for drugs as a whole. The numbers for the two cancer drugs are consistent with data on all oncology products approved from 2005 to 2014, which KEI will publish separately.

Six of the 21 new drugs for the year 2010 were approved as Orphan Drugs. For these six drugs, the average number of patients in trials cited in the medical review was 976, just 19 percent of the average for all drugs.

Many of the current disputes over drug pricing involve drugs for cancer, or drugs that qualify as orphans. The new drug for Hepatitis C, Sovaldi, was based upon evidence from trials with an enrollment of 2,467 patients, a number that was 47 percent of the average for the 2010 approvals.

As noted above, this data suggests policy makers should not use averages that are skewed by a handful of products with large trials to make inferences about the costs associated with particular drugs.