Challenges in identifying published registration studies for FDA-approved pharmaceuticals

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ABSTRACT

Objective: Identifying published registration studies for use as primary references presents a challenge. Product approvals are based on results of registration studies. We tested an approach to identify registration studies using clinical trial data in prescribing information (PI).

Research design and methods: PIs were reviewed for a sampling of products granted FDA approval during 2011-2013. Registration study data were assessed in the clinical trial sections of PIs, and PubMed was searched using the generic drug name and "phase 3," the latter as a surrogate for registration.

Results: 29 products were identified.* Some discrete trial or aggregate-only information was provided in 32% of PIs; 68% provided details by trial, the latter mostly with single registration trials. No PI included ClinicalTrials.gov identifiers or published data citations. Results of cross-matching a random sampling (n=9) of PIs showed no correlation between numbers of studies included in PIs, number of PubMed hits from the above search, and number of papers with phase 3 in the title. More detailed searching, eg, with patient numbers and drug regimens, yielded better yet still inconsistent results and caused a large increase in time spent to identify publications.

Conclusions: Identifying published registration studies appears to be an exercise in back guessing based on various parameters. A standardized system is needed whereby registration study data can be easily tied to published studies.

**Abstract revised based on reanalysis of data: redundant information (1); confirmation of FDA approval prior to January 1, 2011 (2)*

INTRODUCTION

Medical publication professionals are responsible for multiple aspects of publications that disseminate data on a variety of topics. A key responsibility is to ensure that source materials used to support claims within manuscripts are accurately and appropriately referenced. Among the most important sources are the pivotal trial publications associated with registration studies. However, identifying these pivotal trial publications is not straightforward, and often leads the publication professional to a new 'side job'—that of detective—which includes spending significant time and following breadcrumbs left by individual sources. This process is unwieldy, especially given our current cost-sensitive environment and drive across the industry to do more with less. In this research project, we tested an approach to try to identify registration studies using clinical trial data in the prescribing information (PI). Here, we present our results, which include not only our findings expanded to cover all 29 of the products identified (Table 1), but also some associated practical implications, and recommendations for change to help ameliorate this problem.

METHODS

Step-wise approach to identifying pivotal trials' publications

Step 1: Identification of approved products

- Searched Drug Approval Reports (drugs@FDA.com) for branded drugs approved 1/1/2011-12/31/2013 and indicated for treatment of solid tumors, COPD, MS, and RA
- PIs downloaded from either FDA or manufacturers' websites

Step 2: PubMed and PI search

- Searched PubMed for generic names of shortlisted drugs, applying the built-in clinical trials filter. Display settings modified to show ≤200 abstracts per page, sorted by publication date
- Searched PIs for reference citation and/or ClinicalTrials.gov identifier

Step 3: Approaches to identifying pivotal trials—each subsequent approach tried after failure of the prior approach

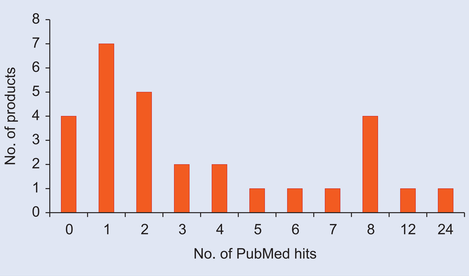
- Attempted identification of pivotal trial publications by comparison of study details in abstracts with "phase 3" or "phase III" mention in the title or body, with details of confirmatory trials in the clinical studies section of the PIs
- When this failed, we searched the abstracts for patient numbers and/or drug doses mentioned in the confirmatory trials in the PIs
- When this failed, we removed the clinical trial filter to display more abstracts and repeated the above process
- Multiple registration trials for a drug were accorded a single data point, and pivotal study publication was considered as identified based on the finding of at least one pivotal trial publication
- We also searched the heath care professional sections of the product websites for pivotal trial publications
- Finally, we searched ClinicalTrials.gov to check for mention of registration or pivotal trial status

RESULTS

Table 1. Overview of products and pivotal study publications

No. of drugs by disease category (N=29)	n (%) abstracts including CT identifier	n (%) abstracts or title including "phase 3"	n (%) websites with pivotal study citation
COPD: 6 (21%)	6 (100)	1 (17)	3 (50)
MS: 2 (7%)	2 (100)	1 (50)	2 (100)
Oncology: 20 (69%)	18 (90)	17 (85)	12 (60)
RA: 1 (3%)	1 (100)	1 (100)	1 (100)

Figure 1. Filtered PubMed results with "phase 3" or "phase III" mentioned in title or abstract



Use of PubMed

- Filtered results from PubMed ranged from 0-24 hits per product (Figure 1)
- Fewer COPD vs oncology trials identified phase 3 in title/abstract
- Pivotal or registration studies were not designated as such in the title or abstract
- ClinicalTrials.gov ID number was included in a majority of abstracts, albeit not consistently; however, it was included for all oncology-trial publications
- Overall PubMed findings
  - Most pivotal trial publications found in PubMed were identified when the clinical trial filter was applied
  - In some instances, applying the clinical trial filter excluded the pivotal trial publication, likely due to some inaccuracies in PubMed's indexing of studies
  - When this occurred, manual abstract searching was required, which led to a considerable increase in time and effort spent

Review of PIs

- Similar to the findings of our pilot, no PIs linked trials included in the clinical studies section to pivotal study publications for the additional 20 products assessed
- Trial data were presented sometimes as discrete study data (83%) or as aggregate data (17%); this difference from the initial random pilot sample is likely due to small sample size
- Discrete study data were seen more frequently with oncology products

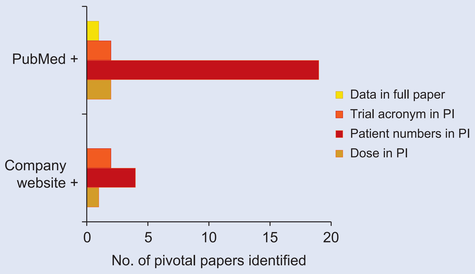
Review of Company Websites

- All company websites provided some clinical trial results information
- The information source was not consistent, and appeared to be divided equally between citing pivotal trial papers and "data on file" or PI

Use of ClinicalTrials.gov

- Despite requirements for trials to be registered in ClinicalTrials.gov, there is no field to denote registration/pivotal trial status

Figure 2. Approaches beyond PubMed alone for identifying pivotal study publications



- Ultimately, all pivotal trial publications were identified
- Using the combined search approaches in Figure 2, it took approximately 10-15 minutes to identify the pivotal trial publication for each product
- Of the approaches tried, matching patient numbers to either the PubMed abstract or publications cited on the company website was the most fruitful
  - Further review of the publication was required, however, as in some cases there were discrepancies in number of patients in the PI and shortlisted publications, probably due to reporting of different populations (randomized, ITT, safety)
  - This added time to the average of 10-15 minutes per product to ensure that the correct publication was identified
- Characteristics that can help identify pivotal trial publications are
  - Descriptive titles that include comparators, indication, and study design or study acronym
  - Multiple authors from different national or international institutions or a research group
  - Publication in leading clinical or therapy area journals
  - Accompanying errata and comments appearing with the abstract
- Pivotal publications with short, less-informative titles can be easily missed when screening abstracts by titles

CONCLUSIONS

- Lack of standardized identifier makes identification of pivotal or registration studies difficult and time consuming
- The process we tested was unwieldy, and evolved from failures of more routine approaches (ie, either a PubMed search or PI review) that one would assume to provide the necessary information
- Recommendations for change include
  - ClinicalTrials.gov to include a field for designation as registration study
  - FDA to require PI to include ClinicalTrials.gov identifier(s)
  - Journals to require inclusion of registration study designation in abstract and body of manuscript
  - Medical writers to routinely include registration study designation in abstract and body of manuscript

DISCLAIMER

The authors were fully responsible for the design of the research, analysis of the results, and writing of the poster.

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