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Drug Safety: Academic Perspective

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Disclosure

- Alnylam Pharmaceuticals,
- Amylin Pharmaceuticals,
- Arthritis Foundation,
- Inspire Pharmaceuticals,
- Medtronic,
- Merck & Co,
- NovaCardia,
- Novartis,
- OSI Eyetech,
- Scios,
- Theravance;
- Blue Cross and Blue Shield of North Carolina,
- EnablEd,
- Forest Laboratories,
- GlaxoSmithKline,
- Novo Nordisk,
- Orexigen Therapeutics,
- General Electric,
- PepsiCo,
- Procter & Gamble;
- Cancer Consultants, Inc,
- Tellus, LLC.

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Use of Large vs. Smaller Drug-Safety Databases

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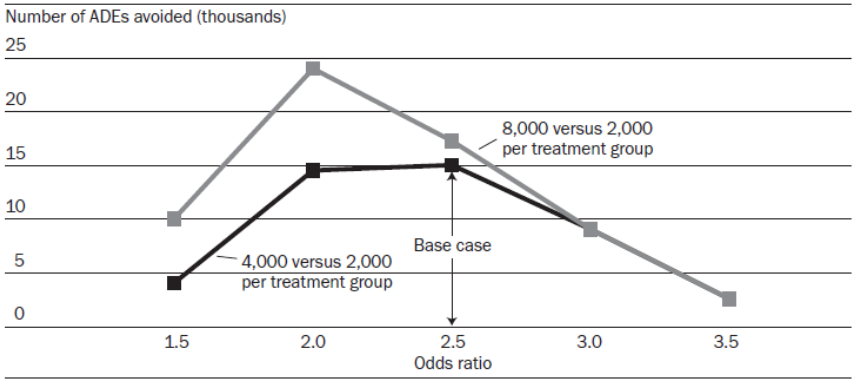
Use Of Larger Versus Smaller Drug-Safety Databases Before Regulatory Approval: The Trade-Offs

This complex undertaking must go beyond considerations of safety and efficacy to include legal, ethical, political, and economic factors.

by Shelby D. Reed, Kevin J. Anstrom, Damon M. Seils, Robert M. Califf, and Kevin A. Schulman

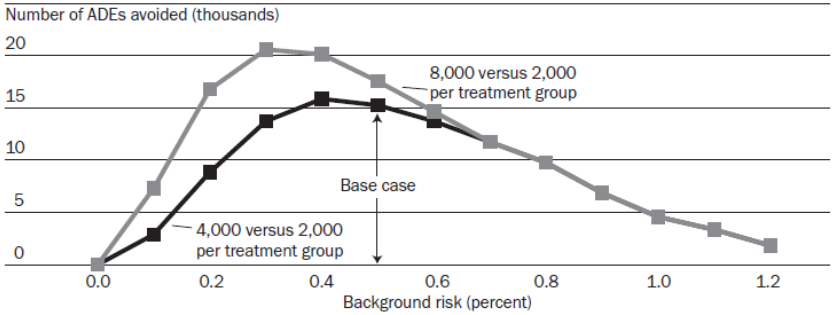
ABSTRACT: Although efforts to revamp the drug-safety system have been directed at strengthening postmarketing surveillance, strategies for the preapproval stage may be useful. One strategy would be to require larger sample sizes in preapproval safety databases. To evaluate the potential benefits and costs of this approach, we developed a hypothetical model to estimate the expected incremental number of adverse drug events that could be avoided in a postapproval population. We found that the potential to limit adverse events can be an important consideration in sample-size determinations for preapproval trials. Requiring larger preapproval databases could be a cost-effective means of reducing adverse events in postapproval populations. [*Health Affairs* 27, no. 5 (2008): w360–w370 (published online 5 August 2008; 10.1377/hlthaff.27.5.w360)]

EXHIBIT 1
Incremental Number Of Adverse Drug Events (ADEs) Avoided With Larger Versus Smaller Drug-Safety Databases When Varying The Odds Ratio



SOURCE: Authors' calculations.
NOTE: The exhibit shows the incremental number of ADEs avoided in a postapproval population of ten million patients when varying the odds ratio between drug safety databases consisting of 4,000 or 8,000 patients per treatment group versus 2,000

EXHIBIT 2
Incremental Number Of Adverse Drug Events (ADEs) Avoided With Larger Versus Smaller Drug-Safety Databases When Varying The Background Risk



SOURCE: Authors' calculations.
NOTE: The exhibit shows the incremental number of ADEs avoided in a postapproval population of ten million patients when varying the background risk between drug safety databases consisting of 4,000 or 8,000 patients per treatment group versus 2,000 patients per treatment group (odds ratio, 2.5).

Reed S, Anstrom KJ, Seils DM, et al. Aug. 5, 2008 Health Affairs Vol 27, No. 5

How Changes in Drug-Safety Can Affect Innovation

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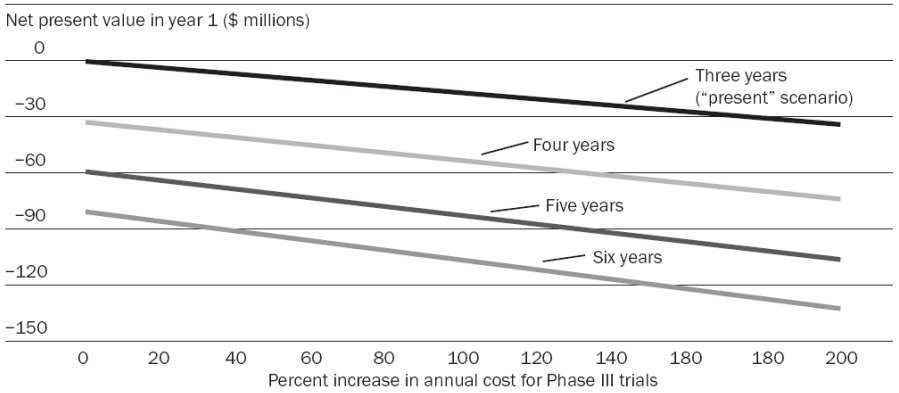
How Changes In Drug-Safety Regulations Affect The Way Drug And Biotech Companies Invest In Innovation

Expanded Phase III clinical testing will affect these decisions more than increased postmarketing safety efforts will.

by Shelby D. Reed, Robert M. Califf, and Kevin A. Schulman

ABSTRACT: Changes in the economics of product development resulting from heightened safety regulations could have a sizable negative impact on drug and biotechnology companies' decisions about investing in innovation. We developed a model to compare the potential economic effects of pre- and postmarketing strategies to identify safety problems with new drugs. Although expanding Phase III clinical testing and postmarketing safety surveillance are not perfect substitutes, our findings suggest that even a large increase in funding for the latter will have a relatively small adverse impact on investment decisions by drug companies and venture capital firms, compared with the former. [*Health Affairs* 25, no. 5 (2006): 1309–1317; 10.1377/hlthaff.25.5.1309]

EXHIBIT 1
Net Present Value In Year 1 When Varying Both The Cost And The Duration Of Phase III Clinical Trials In The "Expand Phase III" Scenario



SOURCE: Authors' analysis.
NOTE: For explanation of scenarios, see text.

Source: Reed S, Califf R, Schulman K. Health Affairs Sept/Oct. 2006. Vol, 25. No. 5

Designing Diabetes Trials for Safety

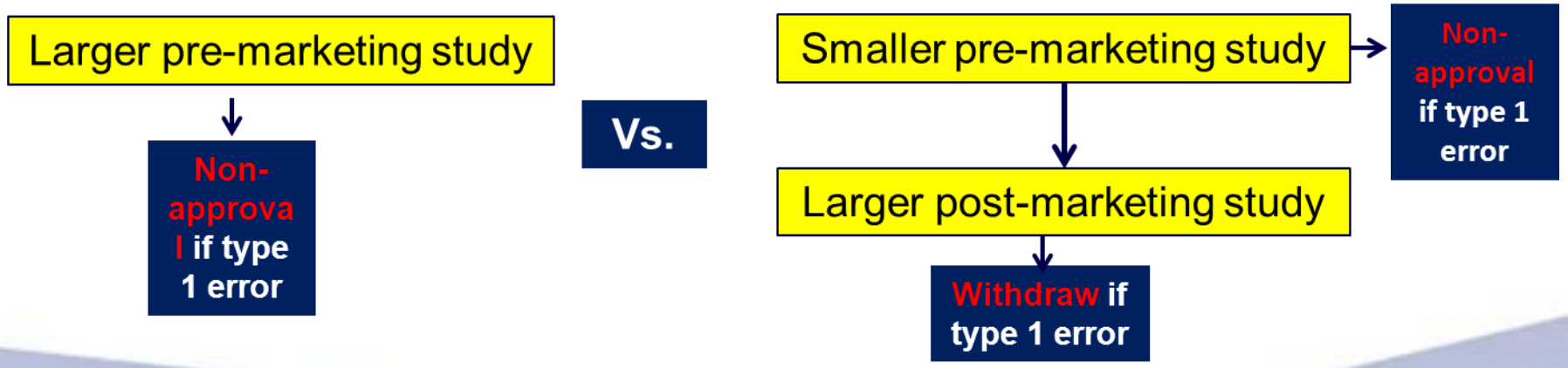
Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (December 2008)

- FDA Guidance in 2008 provided insights into trial design for NDA/BLA submissions regarding cardiovascular risk for diabetes therapies
  - If data in the premarketing application shows an upper bound of RR for the two-sided, 95% CI to be < 1.3, guidance stated that a post-marketing cardiovascular trial "generally may not be necessary"
  - If the data shows an upper bound between 1.3 and 1.8 and the risk-benefit analysis supports approval, a post-marketing trial designed to achieve a RR of < 1.3 may be allowed

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Designing Diabetes Trials for Safety

- It is unclear if it is in the financial interest of a sponsor to conduct a large phase III to demonstrate a RR of < 1.3 or first conduct a smaller trial to target a RR of < 1.8 in order to get the drug on the market more quickly
  - In either case, sponsors run the risk of a type I error which would find an increased RR, even if one does not exist



Reference Reed/Hirsch Forthcoming

Designing Diabetes Trials for Safety

- Our initial analysis compared the costs and benefits of a 5,000 person phase III trial, designed to show a RR of < 1.3, to a smaller phase III of 1,000 patients to achieve a RR < 1.8
  - Accounting for the probability of type I errors, the baseline economic analysis favored the larger phase III with an increase in expected value of ~ $615 million
  - A larger phase III remained favorable unless the drug could achieve more than 50% market share immediately after approval despite less robust data from a small phase III or the blockbuster is expected to generate over $15 million in yearly sales
  - The strategy of starting with a smaller phase III trial appears to have a lower expected value for sponsors, but might entail less financial risk
- Further economic analysis of this guidance is ongoing

Reference Reed/Hirsch Forthcoming