EDITORIAL

Drug Research: Marketing Before Evidence, Sales Before Safety

David Klemperer

An Editorial to accompany the article "The Financing of Drug Trials by Pharmaceutical Companies and Its Consequences: Part 1. A Qualitative, Systematic Review of the Literature on Possible Influences on the Findings, Protocols, and Quality of Drug Trials" by Schott et al. in this issue of *Deutsches Ärzteblatt International*

What would your reaction be if the results of a football match were reported as 5:0 by one of the teams and as 3:1 by the other team? Exactly this is the result of one (1) of 57 studies that Schott et al. analyzed for their systematic review (2) on the following pages, when they evaluated the question of possible associations between the financial funding of drug trials and their results: pharmaceuticals manufacturer Lilly compared its substance olanzapine with risperidone in five studies (reported result: 5:0 for olanzapine); competitor company Janssen compared its own product risperidone with olanzapine in 4 studies and reported a score of 3:1 for risperidone.

This example is as irritating as it is typical. Schott et al., in the first part of their review—published in this issue and the next of *Deutsches Ärzteblatt International*—show that studies that are funded by industry are more likely to report positive results than independently funded studies. The authors methodologically and chronologically build on the work of Bekelman et al. (3) and show comparable, consistent results for the time period from 1980 to the end of 2009. The bias in generating knowledge about pharmaceutical drugs—relating to a wide range of substances and involving all the major pharmaceutical companies that conduct their own research—seems abundantly obvious.

Manipulation techniques

There is no secret to how the desired results are fabricated. It is possible to give a study a spin into the desired direction at any stage of the research process. The results will differ according to what the research question is, which of the possible end points are included, which patients are included or excluded, what is being compared, and which study period is selected. In the evaluation, it is common practice to change primary and secondary endpoints without disclosure (4). Suppressing results that might constitute an obstacle to marketing a substance, as well as the re-interpretation of negative and unclear results as positive results, are further methods of manipulation. Pharmaceutical companies often leave both doctors and patients in the dark about the real effects of their products. The knowledge base on which we as doctors reach decisions with our patients is often distorted, and doctors thus often unwittingly put their patients at risk. According to

calculations reported by Topol (5), rofecoxib triggered 160 000 additional myocardial infarctions and strokes per 10 million exposed patients. By means of manipulative and selective reporting of data to the licensing authorities, the manufacturer kept the public in the dark about the harms (6). A recently published investigative report from the US Senate about GlaxoSmithKline and the diabetes drug rosiglitazone concluded that the company was aware at an early stage that rosiglitazone caused an increased risk of myocardial infarction, but the company did not seek to report this information—instead, it tried to obfuscate it (7, 8).

Drug research is in a state of imbalance. The majority of studies are financed by the drug industry. Large pharmaceutical companies have distorted the evidence from numerous cases—clearly documented in their internal documentation and records—so as to render it suitable for marketing purposes (9).

Transparency as an antidote to manipulation

How can we, as doctors, contribute to finding a solution to the problem? Firstly, the situation has to be declared as unacceptable. The purpose of drug research needs to become the key element again: to treat diseases with medical substances that have a favorable ratio of benefits and harms. Consequently, a number of steps will follow automatically.

Since stakeholders tend to act according to incentives, these incentives have to be changed. If, for example, medical drugs are licensed only if additional benefits have been proved for patient relevant end points in a given indication, as the German Medical Association demanded in its annual general meeting (*Deutscher Ärztetag*) as early as 1990 (<http://davidklemperer.de/1990aet.pdf>), the pharmaceutical industry will define the end points of its studies accordingly. The key points for the implementation of the coalition contract for the supply of medicines (*Eckpunkte zur Umsetzung des Koalitionsvertrags für die Arzneimittelversorgung*) constitute a step in the right direction, provided the duty of information sharing on the part of the manufacturers is demanded stringently and made obligatory.

Transparency is the way forward as far as counteracting the manipulation of studies is concerned. From a scientific point of view, study protocols should be made available to a wide specialist audience even before

Fakultät Sozialwesen,
Hochschule Regensburg:
Prof. Dr. med.
Klemperer

patients are recruited, in order to be able to identify weaknesses before it is too late. For Cochrane Reviews, this has long been common practice and has proved successful. The raw data should not be kept as a trade secret either. The collection and evaluation of the data should be open to scrutiny, and the same goes for their interpretation. Study registries constitute an important step towards progress, especially in counteracting publication bias. The data required by the World Health Organization and other organizations for registries of clinical studies (10) are, however, not sufficient to guarantee the necessary transparency.

If we are serious about our patients' welfare, things cannot be allowed to remain as they are. Finding solutions is, however, likely to be less difficult than implementing them. The legislators will not solve the problems in isolation and under their own steam. However, the health ministry's key points may point in the right direction. But their concrete implementation will yield the desired results only if the insights provided by Schott et al. in their review, as well as the knowledge of the manipulation techniques, meet with the recognition they deserve and are valued accordingly. To this end, the government should be supported by means of a broad alliance that includes doctors, other health professionals, and consumer associations. The German Medical Association has nailed its flag to the mast by funding the study reported by Schott et al. As a next step, the lessons from the study should be put into practice and concrete demands made on our politicians in order to facilitate the victory of evidence over marketing and to put safety above profits, all in the interest of the safety of our patients. To "do no harm" should become the supreme law for the pharmaceutical industry too.

Conflict of interest statement

The author declares that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Translated from the original German by Dr Birte Twisselmann.

REFERENCES

1. Heres S, Davis J, et al.: Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an

exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry* 2006; 163(2): 185–94.

2. Schott G, Pachi H, Limbach U, Gundert-Remy U, Ludwig W-D, Lieb K: The financing of drug trials by pharmaceutical companies and its consequences: part 1. A qualitative, systematic review of the literature on possible influences on the findings, protocols, and quality of drug trials [Finanzierung von Arzneimittelstudien durch pharmazeutische Unternehmen und die Folgen – Teil 1: Qualitative systematische Literaturübersicht zum Einfluss auf Studienergebnisse, -protokoll und -qualität.] *Dtsch Arztebl Int* 2010; 107(16): 279–85.
3. Bekelman J E, Li Y, et al.: Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003; 289(4): 454–65.
4. Ewart R, Lausen H, et al.: Undisclosed changes in outcomes in randomized controlled trials: an observational study. *Ann Fam Med* 2009; 7(6): 542–6.
5. Topol EJ: Failing the public health—Rofecoxib, Merck, and the FDA. *N Engl J Med* 2004; 351(17): 1707–9.
6. Psaty BM, Kronmal RA: Reporting mortality findings in trials of rofecoxib for alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. *JAMA* 2008; 299(15): 1813–7.
7. Staff Report on GlaxoSmithKline and the Diabetes Drug Avandia. Prepared by the staff of the Committee on Finance, United States Senate, Max Baucus, Chairman, Chuck Grassley, Ranking Member. <http://finance.senate.gov/press/Gpress/2010/prg022010a.pdf>. Accessed March 3, 2010.
8. Nissen SE: Setting the RECORD straight. *JAMA* 2010; 303(12): 1194–5.
9. Spielmanns G, Parry P: From evidence-based medicine to marketing-based medicine: evidence from internal industry documents. *Journal of Bioethical Inquiry* 2010; 7: 13–29.
10. Dreier G, Hasselblatt H, Antes G, Schumacher M: Das Deutsche Register Klinischer Studien: Begründung, technische und inhaltliche Aspekte, internationale Einbindung. *Bundesgesundheitsblatt – Gesundheitsforschung – Gesundheitsschutz* 2009; 52(4): 463–8.

Corresponding author

Prof. Dr. med. David Klemperer
Fakultät Sozialwissenschaften
Hochschule Regensburg
Seybothstr. 2
93053 Regensburg, Germany
david.klemperer@hs-regensburg.de

Cite this as: Dtsch Arztebl Int 2010; 107(16): 277–8
DOI: 10.3238/arztebl.2010.0277