# CORRESPONDENCE

## 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

### Part 2. A Qualitative, Systematic Review of the Literature on Possible Influences on Authorship, Access to Trial Data, and Trial Registration and Publication

by Dr. med. Gisela Schott MPH, Dipl.-Biol. Henry Pachl, Ulrich Limbach, Prof. Dr. med. Ursula Gundert-Remy, Prof. Dr. med. Wolf-Dieter Ludwig, Prof. Dr. med. Klaus Lieb in issues 16/2010 and 17/2010

### Wholesale Accusations?

This literature review raises serious accusations against the pharmaceutical industry with regard to conducting, evaluating, and (non-) publication of clinical studies and asks for greater transparency. However, the analysis includes almost exclusively clinical studies from before 2005; since that year, pharmaceutical companies that conduct research have been registering their trials publicly and after licensing approval have also been publishing their results. Each year, several 10 000s of studies are running worldwide (currently about 90 000). Extrapolating from a small number of studies, whose results were allegedly manipulated, to all of them is not honorable.

Why is the pharmaceutical industry accused of running certain placebo controlled studies if that is what the licensing authorities are explicitly demanding? Why has attention not been paid to the fact that specialist journals usually want to publish positive results only, and negative or inconclusive ones only in exceptional circumstances? Clinical studies are designed by doctors; they are examined and approved by various licensing authorities and ethics committees; and they are conducted by doctors in hospitals and practices. What exactly is it that Schott and colleagues are accusing their colleagues of? The pharmaceutical industry has submitted its findings to the licensing authorities, which does scrutinize these in detail. Since 1995, the clinical study results for all medicinal products authorized by the EU have been publicly accessible via the European Public Assessment Reports (EPARs). Public trial registration and publication have been a statutory requirement in Europe since 2005 and in the United States since 2008. We therefore cannot quite follow these wholesale accusations.

The EU has been planning for many years to make its study database EudraCT publicly available. We sincerely hope that 2010 is the year when this will eventually happen.

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### Opinion Leaders

Manipulation of drug trials is possible only if there is a not insubstantial number of doctors who volunteer to act as authors, representatives, or opinion leaders generally. This raises the question of why such opinion leaders are obviously easy to find. The main reason for this easy availability is the habilitation procedures at universities. A habilitation procedure to gain a university professorship is hardly possible today without third-party funding. Further, medical faculties nowadays often use the amount of third-party funding they have received as a means of advertising themselves. However, it is not difficult to understand that such funding does come at a price, particularly in the non-surgical disciplines. Many colleagues have such third-party funding to thank for their subsequent careers. In this way, the foundations are laid for lifelong closeness to the pharmaceutical industry, which knows full well how to cultivate and exploit this closeness.

This is not primarily an oversight or mistake committed by doctors; rather, it is a systematic error inherent in an understanding of medical excellence that is based on publications and third-party funding. In the case of manipulated drug studies, universities' habilitation and research procedures have just as much to answer for as statutory initiatives to achieve excellence that provide counterproductive stimuli.

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## Notorious Weaknesses

That any publication is driven not only by scientific innovation but also but secondary motives is an undisputed truth. Such motives can include financial interests but also vanity, which can go so far that the authors even resort to explaining the order in which their names appear in additional footnotes.

Personally, I do not understand the chosen method—of a systematic literature search—for this article. Maybe the authors referred to their work as a qualitative review because of a lack of specificity, among other reasons. In my experience, each and every one of the observed phenomena can be observed in studies that are conducted by the pharmaceutical industry as well as in so-called independent studies. It therefore would have been useful to conduct a quantitative analysis. The authors would have had to limit themselves to one therapeutic subject or one therapeutic question, but it would have enabled them to analyze the publications in detail, to compare the descriptions with those of industry independent studies, and to comment. Maybe there is a scientific or regulatory reason for why certain industry-funded studies used placebo or lower dosages more often than industry-independent studies?

The notorious weaknesses of industry-independent studies were unfortunately not discussed. In this context, the pharmaceutical industry—and thus the quality of its studies—benefits from a continuing dialogue with the licensing authorities about further developments of the methodology. And consistent implementation of quality standards (GCP, "good clinical practice") when conducting studies is still a greater challenge for industry-independent funders.

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## Trend Gives Cause for Concern

The authors in their conclusion unfortunately do not mention some further important aspects of clinical drug research. The 12th revision of the German Drug Registration and Administration Act has resulted in extreme amounts of bureaucracy. Further, the financial costs of drug studies have vastly increased. For investigator-initiated trials, the full legal responsibility lies with the investigator or study center. A study in which we wanted to investigate polyneuropathies as adverse effects after administration of cytotoxic drugs failed, for example; legally this would have been research under the drug law, with all consequences in reporting much more than the intended study of drug safety. The intended improvement to all patients' safety has resulted in obstacles to and ultimately discrimination against independent drug research. Among the last 67 drug studies in our ethics committee, not a single one had as main outcome parameter adverse effects or safety concerns. Since the 12th revision of Germany's drug law, drug research has changed its course towards primarily industry studies and efficacy studies and away from long-term safety studies. In the face of these

worrying trends, the demands made by Schott et al are unsatisfactory. A paradigm shift in clinical drug research is what is needed. The costs would have to be shared among everyone—for example, through a joint fund: the pharmaceutical industry, the funding bodies—even if only to reduce the costs of treating adverse drug reactions. The authors from the Drug Commission of the German Medical Association should have deduced the necessary suggestions from their analysis in order to avoid future drug scandals effectively. This entails not only a full disclosure of competing interests and substantial support from industry-independent research funds, but also the acceptance and publication of negative findings (1). However, more than all that it requires a de-bureaucratization of safety studies for medical drugs.

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## National Foundation

The authors asked for medical drugs to be licensed only in the context of proven additional benefit for patient-relevant end points relating to the indication. That may be honorable but it does not get us anywhere. The difficulty lies in particular in defining the additional benefit and the patient relevant end points. And that is where the pharmaceutical industry with its licensing studies dominates.

The 12th revision of Germany's drug law has resulted in dramatically more difficult conditions and greater costs for scientifically driven studies. As a result, even the large scientific studies are now strongly dependent on industry funding and lose independence in terms of their research questions.

We suggested establishing a national foundation for cancer research in order to fund studies. In Germany, more than Euro250bn are spent on health, and of that, more than Euro41bn on medical drugs. At the same time, there is practically no public funding for studies. Activities of this kind can be supported by a small percentage of the total healthcare costs. Why are we not spending this money? The dividends would be ample.

If there is no will to provide public funding for clinical studies, then the results should surprise nobody.

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## Search Bias

Clinical studies are intended to confirm characteristics of medical drugs. For this purpose, a study design is defined, which always means immediate sponsor bias. This is independent of whether the sponsor comes from pharmaceutical, academic, or independent institutions.

There is no legal requirement to publish. In spite of this, many pharmaceutical companies—additionally to Good Clinical Practice (GCP) and the Declaration of Helsinki—have subscribed to an ethical code according to which collected data have to be published.

Publication, however, presents a central problem. Positive studies are often published, and with enthusiasm; negative studies are rarely published or merely in review articles (publication bias). This is only very partly the pharmaceutical industry's responsibility,