ORIGINAL ARTICLE

Does the Pharmaceutical Industry Influence Guidelines?

Two Examples From Germany

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SUMMARY

Background: The recommendations in clinical guidelines are based on clinical trial findings and expert opinion. The influence of drug companies on these two factors is illustrated with two examples.

Methods: A judicially ordered expert review revealed that the market authorization holder (MAH) of gabapentin manipulated study data. Gabapentin was, therefore, chosen as an example for this article to analyze whether manipulated data serve as a basis for recommendations in German clinical guidelines. A search was carried out for manipulated publications on gabapentin that found their way into guidelines published by the Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften,* AWMF). To analyze the possible effects of financial ties between guideline authors and drug companies, the S3 guideline on the treatment of psoriasis vulgaris with efalizumab was compared with guidelines whose authors had no conflicts of interest. One of the authors of this article had noted variable prescribing practices for psoriasis among dermatologists while carrying out an economic assessment for a German state Association of Statutory Health Insurance Physicians.

Results: The data that had been manipulated by the MAH of gabapentin served as a basis for recommendations to prescribe gabapentin in guidelines that were published by the AWMF. Efalizumab was judged more favorably in the S3 guideline than in a guideline issued by the National Institute of Health and Care Excellence: for example, the evidence for it was judged as good, the use of efalizumab for induction and combination therapy in psoriasis vulgaris was recommended, and efalizumab was said to improve patients' health-related quality of life.

Conclusion: Public access to all trial data must be ensured so that independent evaluations are possible. We take the view that the responsibility for creating guidelines should be borne by authors and organizations that do not have any conflicts of interest.

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Clinical guidelines are systematically developed decision aids for the appropriate medical management of specific disease conditions. They can serve as a basis for physicians and patients to make well-informed joint decisions (1, 2). Guidelines are also consulted by payors in the health-care system in matters concerning reimbursement, and by lawyers in medical malpractice cases (e1).

Guidelines are usually issued by medical societies or government bodies. The Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften,* AWMF) coordinates the development of guidelines by the individual medical societies (3). The guidelines whose methods are of the highest quality are called S3 guidelines: These are created after a systematic review of the literature by a representative group of guideline developers in a transparent consensus process (4). These guidelines' recommendations on drug treatment are based on the findings of clinical trials and on the opinions of the participating experts (5).

The recommendations contained in guidelines are often not based on good evidence from clinical trials, but rather on expert opinion or "standards of care" (6). Especially when adequate trial data are unavailable, the personal opinions of members of the expert committee can influence the recommendations that appear in the guideline. It is entirely possible for identical data to be interpreted in opposite ways by different experts with or without conflicts of interest (7).

Conflicts of interest are defined as situations that create a risk of inappropriate influence by secondary interests on professional judgment or behavior that is supposed to serve a primary interest (8, 9). A conflict of interest is thus an extant condition, rather than an act on the part of an individual (10). Conflicts of interest arise when potential material or social advantages are at odds with the primary goals specified by medical ethics (9, 11).

Clinical trials that are paid for by drug companies are more likely to yield favorable results for the sponsor than independently performed trials. This fact has been demonstrated repeatedly in recent years (e2–e4, 12, 13).

TABLE 1

Guidelines published by the AWMF with recommendations about gabapentin based on publications that were manipulated by drug companies

Guideline	Recommendation about gabapentin	Publication cited	Evaluation of publication, according to Dickersin (19)	
			Bias	Example
Migraine treatment, 2008 (23)	Classified as a substance for migraine prophylaxis with little evidence and as a drug of second choice. "The antiepileptic drug gabapentin had a mild prophylactic effect in one trial (Mathew et al. 2001). Further trials are needed." (23)	Mathew et al. 2001 (e27)	– selective analyses	Publication of analyses from which patients were excluded
			– primary outcome redefined in publication	Highlighting of statistically significant positive results that are at variance with the results of the research report by selective evaluation of a subgroup of patients
			– multiple publication	Publication of two nearly identical abstracts without reference to each other
			– time lag bias	Full-text publication three years after end of study
			–citation bias	No mention of other negative findings
			– spin	Conclusions do not match actual study findings per research report
Treatment of neuropathic pain, 2008 (24)	Recommended for the treatment of post-herpetic neuralgia, polyneuropathy, phantom pain, HIV neuropathy, and pain after spinal cord injury. "In a group of patients with various types of neuropathy, improvement of burning pain and hyperalgesia was demonstrated, and a trend was found toward improvement of allodynia and lancinating pain (Serpell et al. 2002). Further controlled trials on patients with spinal cord injury, painful Guillain-Barré syndrome, and phantom pain also revealed positive effects. (…) Recommendation: Gabapentin can be recommended as an effective and usually well-tolerated drug for the treatment of neuropathic pain (A)." (24)	Serpell et al. 2002 (e28)	– selective analyses	The analyzed trial population does not correspond to the trial population described in the protocol. The times of data evaluation were changed to create statistically significant results.
			– citation bias	In a meeting poster, only positive trials were mentioned.
			– ghost authorship	Publication written by professional medical writers
			– spin	Negative findings reported to sound positive
			– design bias	Excluded patients who were „nonresponders" to gabapentin in the past resulting in a selective study population
Treatment of perioperative and post-traumatic pain, 2007 (25)	"Among the anticonvulsants that have been tested for the treatment of perioperative pain, gabapentin lowered the amount of opioid medication that was needed perioperatively." (25)	Among other sources, a Cochrane review by Wiffen et al. 2005b (26)*, which cites:		
		Backonja et al. 1998 (e29)	–selective analyses	Analyses to examine possible association of side effects and primary outcome, requested by those outside and inside company, were not produced
			–design bias	Patients were unblinded by CNS side effects. This may have biased the results in favor of the intervention.
		Caraceni et al. 2004 (e30)	– misrepresentation of facts	Inconsistent statements in the research report and the publication regarding the duration of the trial period, randomization, and intention-to-treat population
		Dallochio et al. 2000 (e31)	– citation bias	Failed to cite a relevant trial that did not show any superiority of gabapentin
			– design bias	According to internal documents, this open trial was specifically designed to refute the unpublished trial (see above).

		Gorson et al. 1999 (e32)	– location bias	Negative findings were published only as a letter to the editor and as an abstract.
			– time lag bias	Internal memos indicate company delayed publication.
			– spin	Inappropriately positive conclusions
		Serpell et al. 2002 (e28)	see under "Treatment of neuropathic pain, 2008" (above)	

*The Cochrane review is currently undergoing revision (e33)

There have been few publications to date analyzing the influence of drug companies on clinical guidelines, and very few in Germany (e5). There have been several studies reporting of the frequency with which guideline authors declare conflicts of interest: 80% to 100% of the guidelines studied contained no such information (e6–e9, 14), yet, when such information is given, as many as 90% of the authors turn out to have financial links to drug companies (e8–e15). The effect of conflicts of interest on the content of guidelines has only rarely been studied (e5).

In this article, we present two aspects of the influence of drug companies on guidelines, giving a concrete illustration of each. We investigate whether data that have been manipulated by drug companies find their way into guidelines published by the AWMF, and we also investigate whether potential effects of conflicts of interest among guideline authors are detectable in the guidelines' recommendations.

Manipulated data

The example of gabapentin vividly shows that drug companies sometimes provide manipulated and misleading information. In keeping with the practice of *Deutsches Ärzteblatt International*, no trade names will be given in this article.

Gabapentin was approved in 1995 as an antiepileptic drug (e16, e17). Since 2001, it has also been approved in many European countries, including Germany, for the treatment of peripheral neuropathic pain in adults, e.g., painful diabetic neuropathy and post-herpetic neuralgia. The United States Food and Drug Administration has not approved gabapentin as a medication to treat pain for any indication other than post-herpetic neuralgia (e16, e18).

The drug company that manufactures gabapentin was forced by an American court to make more than 8000 pages of internal documents publicly available. It acknowledged having used illegal marketing methods and paid a fine of $430 million (15, 16).

Publications regarding the efficacy of gabapentin were also found to have been manipulated (17, 18, e19). For example, primary endpoints were changed and unfavorable data were not reported in order to give the impression that gabapentin is effective for non-approved indications.

Kay Dickersin, the director of the US Cochrane Center and of the Center of Clinical Studies in Baltimore (Maryland, USA), gained access to internal company documents relating to gabapentin while serving as an expert for the judicial proceeding (19). Her report was highly critical of publications of trials conducted with drug-company support that concerned the use of gabapentin for the following indications (not approved in the USA): migraine, psychiatric/bipolar diseases, nociceptive pain, and neuropathic pain.

Dickersin found that these publications contained the following types of manipulation, among others:

- selective evaluation of patient data
- retrospective changes of primary endpoints
- inappropriately positive conclusions in relation to actual findings
- authorship of ghostwriters (19).

Because the judicial expert report demonstrated the manipulation of data on gabapentin by the market authorization holder (MAH), we have chosen gabapentin as an example to see whether publications that have been manipulated by drug companies find their way into guidelines published by the AWMF.

Guideline authors' conflicts of interest

To study the potential effects of guideline authors' financial links to drug companies, we compared the recommendations of the German S3 guideline on the treatment of psoriasis vulgaris (issued in 2006; see *eBox 1*) with those of contemporaneous guidelines written by authors without any such links. Moreover, the guideline authors' declarations of conflicts of interest were analyzed and studied for completeness.

This particular guideline was selected because one of the authors of the present study had noted variable prescribing practices among dermatologists for efalizumab in the treatment of psoriasis while carrying out an economic assessment for a German state Association of Statutory Health Insurance Physicians. The dermatologists who prescribed efalizumab cited the S3 guideline as indicating that this was appropriate.

The S3 guideline on the treatment of psoriasis vulgaris was published in 2006 by the Division of Evidence Based Medicine of the Department of Dermatology, Venerology, and Allergology of the Charité – Universitätsmedizin Berlin, which had been

commissioned to create the guideline by the German Dermatological Society (*Deutsche Dermatologische Gesellschaft,* DDG) and the Association of German Dermatologists (*Berufsverband der Deutschen Dermatologen,* BVDD) (20). The project was paid for by the DDG sponsors' group; a number of drug companies were "content partners" of the DDG at that time. Active financial support was provided by the MAH of efalizumab (Serono GmbH), among others (21).

The creation of this S3 guideline was supported and moderated by the Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften,* AWMF). It was carried out by a group of experts composed of five practice based and five hospital based dermatologists, who had been named by the BVDD and the DGG, respectively.

The guideline was revised after the European Medicines Agency recommended that the approval of efalizumab be suspended.

Methods

Manipulated data

In Dickersin's expert report, the manipulation of certain publications on the use of gabapentin for migraine, psychiatric/bipolar diseases, and nociceptive and neuropathic pain is described in detail (19). Two of the authors of the present review (Claudia Dünnweber and Gisela Schott) searched for these publications in pertinent guidelines downloaded from the AWMF website. They then examined the recommendations contained in the guidelines in the light of the underlying publications that had the defects described by Dickersin.

Guideline authors' conflicts of interest

Guidelines that were roughly contemporaneous with the German S3 guideline (November 2006 ± 12 months), and that were written by persons who had no conflict of interest because of ties with drug companies, were sought in the database of the Guidelines International Network (www.g-i-n.net) and in the websites of the medical societies from various countries that can be accessed via www.leitlinien.de.

We looked for conflicts of interest among the S3 guideline authors by applying the multimodal screening technique described by Cosgrove et al. (22, e10) to the guideline homepage, with the aid of the Google search engine and the Medline database, in publications from the years 2004–2008.

Results

Manipulated data

The guidelines published by the AWMF on the treatment of migraine (23) and the treatment of neuropathic pain (24) contained recommendations based on publications that, according to Dickersin (19), were manipulated by the MAH *(Table 1)*. Manipulated publications were also included in the Cochrane review that was cited as the basis for a recommendation in the guideline on the treatment of perioperative and post-traumatic pain (25, 26).

Moreover, data from trials that were not published by the MAH of gabapentin were not available for consideration by the authors of the guidelines on the treatment of neuropathic (24) and post-traumatic pain (25). For example, the drug company carried out five trials in which gabapentin was given together with other drugs to treat nociceptive pain after orthopedic surgery (and in other situations). None of these trials revealed any statistically significant benefit of the additional administration of gabapentin (19). None were published, and thus none were available for consideration in either the Cochrane review or the guideline on the treatment of perioperative and post-traumatic pain (25, 26).

Guideline authors' conflicts of interest

Comparison of statements about efalizumab—The search for independently created guidelines on the treatment of psoriasis vulgaris with efalizumab, published within 12 months of November 2006, yielded two hits, one of which was used in the present study: a guideline by the National Institute for Health and Clinical Excellence (NICE) entitled "Etanercept and efalizumab for the treatment of adults with psoriasis" (27), which was published in July 2006 and is partly based on a Health Technology Assessment (HTA) report (28) financed by the National Health Service (NHS) of the United Kingdom. The authors of the HTA report and those of the guideline had no conflicts of interest (27, 28).

The second hit was excluded for a number of reasons, most importantly because it contained no explicit recommendations about pharmacotherapy (e20).

Various statements made in the NICE guideline and the German S3 guideline on the use of efalizumab in the treatment of psoriasis vulgaris are displayed and compared in *Table 2* and *eTable 1*.

Clearly, multiple aspects of efalizumab and its use are judged more favorably in the S3 guideline than in the NICE guideline. For example, the S3 guideline states that there is good evidence for, and thus recommends, the use of efalizumab as induction and combination therapy for psoriasis vulgaris. The putative improvement of health-related quality of life under treatment with efalizumab is also emphasized in the S3 guideline but is not mentioned in the NICE guideline.

Information about conflicts of interest in the S3 guideline—Information about the guideline authors' conflicts of interest were not given in the guideline itself but were available on the webpage of the guideline-writing group (21). Of the 15 voting participants in the consensus process by which the S3 guideline was generated, 10 had financial links (sometimes extensive ones) to as many as 11 different drug companies *(eTable 2a, b)*.

TABLE 2

A comparison of statements about efalizumab in the NICE guideline and the S3 guideline

	NICE guideline* (27)	S3 guideline* (20)	Comparison and commentary
Recommendation about therapeutic use	Efalizumab, within its licensed indications, is recommended for the treatment of adults with plaque psoriasis under the circumstances detailed in section 1.1 only if their psoriasis has failed to respond to etanercept or they are shown to be intolerant of, or have contraindications to, treatment with etanercept.	Efalizumab is recommended for induction therapy in moderate or severe psoriasis vulgaris, particularly if other treatments are contraindicated or have been tried with inadequate therapeutic benefit or intolerable side effects.	In the NICE guidleines, efalizumab is recommended if the conditions of drug approval are met and under the further condition that etanercept cannot be used or has been ineffective. In contrast, in the S3 guideline, efalizumab is also explicitly recommended for induction therapy in certain situations. This recommendation is inconsistent with the drug's approval status.
Evidence adduced to support the recommendation	A total of five randomised controlled trials (RCTs) that studied efalizumab at a dose of 1 mg/kg once a week were included in the Assessment Report. (…) Inadequacies in the reporting of the trials meant that the quality of four of the trials could not be properly assessed by the Assessment Group.	A total of six trials meet the inclusion criteria of this guideline, five of which provide level A_2 evidence and one of which provides level B evidence concerning monotherapy with efalizumab. The overall level of evidence is therefore level 1.	The quality of the evidence is rated more highly in the S3 guideline than in the NICE guideline (see also *eTable 1*). In the HTA report that served as a basis for the NICE guideline, five trials were cited whose quality was related as poor (3 trials), satisfactory (1 trial) and good (1 trial). In the S3 guideline, six publications are cited, whose quality was rated as evidence level A_2 (5 trials) and level B (1 trial [e34]; level B indicates a low-quality comparative trial). The last-named trial was, however, not a comparative trial and should have been given a lower evidence level. Data from a further trial are represented in two different publications (e35; e36). The overall level of evidence is unjustifiably rated as 1, where 2 would have been appropriate.
Recommendation and evidence about combination therapy	The SPC states that efalizumab has not been studied in combination with immunosuppressive systemic anti-psoriasis medicinal products and therefore combination therapy with these products is not recommended. The SPC also states that 'combination therapy with topical corticosteroids is not associated either with any untoward effects or with any observable significant benefit above monotherapy.'	No controlled trials of combination therapy are available. Combination with topical antipsoriatic drugs (topical corticosteroids, vitamin D3 derivatives, tazaroten, dithranol) seems possible and appropriate.	The NICE guideline refers to the product information, in which it is stated that combination therapy with topical corticosteroids yields no additional benefit compared to monotherapy with efalizumab. In the S3 guideline, it is stated that no controlled trials of combination therapy are available. The authors write that combination with topical antipsoriatic drugs seems possible and reasonable.
Efficacy in previously treated patients	–	Efalizumab has been found effective in patients for whom other systemic treatments were unsuitable.	With respect to efficacy in previously treated patients, the S3 guideline explicitly states that the drug has been found effective in patients for whom other systemic treatments were unsuitable. This assertion is not supported by a reference to the literature. The NICE guideline contains no statement concerning the efficacy of efalizumab in previously treated patients.
Depiction of effect on quality of life	–	Along with improved skin condition, as reflected by the above PASI values, patients treated with efalizumab also reported a marked improvement in their health-related quality of life (e37).	The S3 guideline indicates that patients treated with efalizumab have marked improvement in their health-related quality of life. A publication is cited in support of this assertion (e37), but the quality of this publication is not assessed, nor is it indicated what instrument was used to measure quality of life. No statement is made in the NICE guideline about any effect of efalizumab on quality of life.

Assessment of safety	Overall, the publicly available information for efalizumab indicates that the drug is well tolerated over a 12 week period and in the long-term, however, few data for long-term treatment are available for detailed information. (…) Consequently the Committee agreed with the experts' advice that a register should be established in order to collect information on long-term outcomes (including adverse events) in patients with psoriasis treated with cytokine inhibitors.	The available data point to a favorable safety profile for efalizumab. A definitive assessment of its efficacy and safety, for long-term as well as short-term treatment, must await further studies in larger groups of patients with longer follow-up.	The safety of efalizumab is similarly judged in the two guidelines: The drug seems to be well tolerated, but data on long-term safety are not yet available. Therefore, the NICE guideline contains a call for the establishment of a register to collect data on long-term safety, with the further remark that efalizumab might conceivably increase the risk of cancer. No such suggestion is made in the S3 guideline.

*This table contains direct quotations from the NICE guideline (in the original English) and the S3 guideline (translated from the original German).
SPC: Summary of product characteristics;
PASI: Psoriasis Area and Severity Index

All 10 participants declaring financial links to drug companies had received money from Serono GmbH, the drug company that obtained approval for efalizumab. These 10 included both of the authors of the section entitled "Biologics" in the S3 guideline, in which efalizumab was discussed. One of the two is a member of the advisory board of Serono GmbH.

For the five voting participants who declared no conflict of interest, further searching did not yield any evidence of financial links to pharmaceutical companies. It would thus appear that all conflicts of interest were appropriately declared.

Discussion

The recommendations on drug treatment that are found in guidelines are based in large measure on the findings of clinical drug trials, but they also depend to some extent on the opinions of the experts who participate in the writing of the guideline.

This study shows that published data on gabapentin that were known to have been manipulated by the MAH of the drug found their way into the recommendations of guidelines that were published by the AWMF. Moreover, efalizumab for the treatment of psoriasis vulgaris was judged more favorably in the German S3 guideline than in the NICE guideline. Most of the authors of the S3 guideline had extensive conflicts of interest, particularly through financial links to the manufacturer of efalizumab; in contrast, authors with conflicts of interest were excluded from participation in the creation of the NICE guideline.

Manipulated evidence

The case of gabapentin clearly illustrates that data manipulated by the drug companies serve as the basis of recommendations in German guidelines, and that biased publications are cited to support these recommendations. Manipulated evidence was also used as the basis for statements made about gabapentin in a certified CME publication (29, 30).

We do not direct our criticism at the authors of the guideline in question (or those of the CME publication just mentioned), but rather at the MAH of gabapentin. Internal company documents reveal that trial results were deliberately withheld. For example, the British director of a clinical trial comparing three different dosages of gabapentin for the treatment of neuropathic pain complained that his trial was not published. Employees of the drug company thereupon wrote each other multiple e-mails in which it was stated, for example, that "I don't think we should be too hasty with this request" and that "...made it very clear that we should take care not to publish anything that damages neurontin's marketing success" (19). [Neurontin is the manufacturer's trade name for gabapentin—Ed.]

Guideline authors' conflicts of interest

The potential effects of guideline authors' conflicts of interest are illustrated by the present comparison of statements about efalizumab made in the S3 guideline, whose authors declared numerous conflicts of interest (20), and in the NICE guideline, none of whose authors had a conflict of interest (27). The lack of editorial independence of the S3 guideline was also criticized recently in an article on the quality of guidelines for the treatment of psoriasis vulgaris (31).

The assessment of efalizumab in the S3 and NICE guidelines is based on somewhat different groups of clinical trials, possibly because some trials were not published by their sponsors (e21–e23). The trials that were considered in both of the guidelines yielded similar findings *(eTable1)*. Nonetheless, multiple aspects of efalizumab and its use are judged more favorably in the S3 guideline than in the NICE guideline. Without venturing to judge the correctness of the S3 guideline's recommendations on the use of efalizumab, but simply note that they serve the interests of the manufacturer to a greater extent than the recommendations of the NICE guideline.

Possible effects of the favorable depiction of efalizumab in the S3 guideline may be seen in a doctoral dissertation about the prescribing behavior of practice-based dermatologists in the German federal states *(Länder)* of Berlin and Brandenburg (e24). An

evaluation of 8500 patient visits to 49 dermatologists revealed that efalizumab was prescribed more often after publication of the S3 guideline, and that the study participants tended to overrate its effectiveness. For example, efalizumab was prescribed to patients with psoriasis and joint involvement, even though the drug has been found to be ineffective against psoriatic arthritis (e24). This pattern of prescribing behavior may have been caused by other factors aside from the S3 guideline, e.g., marketing by the manufacturer.

The comparative findings discussed in the present article merely document an association; they do not constitute proof that the authors' conflicts of interest led to the more positive assessment of efalizumab in the S3 guideline. In the hierarchy of evidence grades, the present article reaches the low level of a case report. Case reports do, however, have a role to play in evidence-based medicine, as they can provide important clues (32).

Conclusions and recommendations

Intensive efforts are now underway in multiple countries to reform the process of guideline development. A call has been issued for guideline authors to declare transparently their conflicts of interest that arise from financial links to drug companies (33–35). A separate, and contrasting, call has been issued for the acceptance as guideline authors only of persons with no links to industry whatsoever (36, 37).

The Institute of Medicine (IOM), an advisory body that counsels the United States government, has recommended that

- persons with conflicts of interest should, in general, be excluded from the development of guidelines, and that
- the direct sponsoring of guideline creation by drug companies should be forbidden.

The procedure for determining what conflicts of interest are present should be just as transparent as the financing of the guideline (8). Detailed recommendations are given for the exceptional situations in which the participation of experts with conflicts of interest is unavoidable (8, 38). For example, the chairman of the guideline group should be an expert without any conflict of interest, and persons with conflicts of interest should never constitute a majority of the guideline-creating group. Furthermore, experts with conflicts of interest should not participate in decision-making processes.

In Germany, in April 2010, the presidium of the AWMF issued recommendations, based on those of the IOM, for handling conflicts of interest in medical societies, and particularly in the creation of guidelines (39). These rules should now be consistently followed by the participating medical societies and guideline authors, and violations of the rules should be dealt with appropriately.

The proof that drug companies manipulate drug trials for their own benefit has led to demands that drug trials should more often be carried out independently of the financial interests of drug companies. This will only be possible, however, if more money from public sources is made available for this purpose (12, 13). The creation of guidelines should also be in the hands of independent individuals and organizations.

This article is based on the findings of an expert assessment belonging to Part 2 of a project entitled "The Influence of Trial Sponsors on the Scientific Findings of Drug Trials" *(„Einflüsse der Auftraggeber auf die wissenschaftlichen Ergebnisse von Arzneimittelstudien")*, which was sponsored by the German Medical Assembly *(Deutscher Ärztetag)* in the framework of an initiative to promote health services research *(Förderinitiative Versorgungsforschung)* of the German Medical Association *(Bundesärztekammer)*. The full versions of the expert reports can be seen on the homepage of the German Medical Association at the following Internet address: www.baek.de/versorgungsforschung/expertisen

Some of the findings of this study were presented at the evidence-based medicine congress in 2011 and at the annual meeting of the DGPPN in 2012.

Conflict of interest statement

Dr. Schott is employed by Arzneimittelinformationsdienst AID e.V.

Ms. Dünnweber, M.P.H., has an employment relationship with the German Private Health Insurance Association (*Verband der privaten Krankenversicherung*).

Mr. Pachl, Dipl.-Biol., is employed by Arzneimittelinformationsdienst AID e.V.

Prof. Mühlbauer, Prof. Niebling, and Prof. Ludwig state that they have no conflicts of interest.

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KEY MESSAGES

- The case of gabapentin shows that data manipulated by drug companies can find their way into the recommendations contained in guidelines.
- Most authors of guidelines issued by medical societies have conflicts of interest.
- The case of the German guideline on the treatment of psoriasis vulgaris shows that, when experts with conflicts of interest participate in the writing of guidelines, new drugs tend to be judged more positively. Such guidelines serve the interests of drug companies more than guidelines by authors without conflicts of interest.
- The rules for the participation of experts with conflicts of interest in the writing of guidelines need to be more rigorously observed.
- Comprehensive legal regulations are needed to establish public access to study protocols, raw data, and all other relevant documents from clinical trials in order to enable independent assessment of drug efficacy and safety.

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For eReferences please refer to:
www.aerzteblatt-international.de/ref3513

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ORIGINAL ARTICLE

Does the Pharmaceutical Industry Influence Guidelines?

Two Examples From Germany

Gisela Schott, Claudia Dünnweber, Bernd Mühlbauer, Wilhelm Niebling, Henry Pachl, Wolf-Dieter Ludwig

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eBOX 1

Efalizumab

- **Mechanism of action**

Efalizumab is a recombinant humanized monoclonal antibody that binds specifically to the CD11a subunit of LFA-1 (lymphocyte function–associated antigen 1), a protein located on the surface of leukocytes. This inhibits the binding of T-lymphocytes to cells of other types. Efalizumab presumably alleviates the clinical manifestations of psoriasis by inhibiting multiple steps in the immunological cascade (e25).

- **Areas of application**

Efalizumab* was approved in September 2004 for the treatment of moderate to severe plaque psoriasis in adults, on the condition that other systemic treatments, including cyclosporine, methotrexate, and UVA photochemotherapy were insufficiently effective, contraindicated, or poorly tolerated (e25).
In 2009, the European Medicines Agency suspended the approval of efalizumab. The reasons given were the "modest" benefit of the drug and its serious adverse effects (e26).

- **Adverse effects**

The main adverse effects of efalizumab are infections of various types. During the time in which efalizumab was available, three cases of progressive multifocal leukoencephalopathy (PML) were reported under treatment with the drug, two of which were fatal (e26).

*In accordance with the practice of *Deutsches Ärzteblatt* and *Deutsches Ärzteblatt International*, no trade names of drugs are given

eTABLE 1

Literature cited in the HTA report and in the S3 guideline concerning the efficacy of efalizumab

Reference	Quality*1		Findings
	HTA report (28)	S3 guideline (20)	Percentage of patients with an improvement of PASI*2 by ≥ 75% at 12 weeks (efalizumab*3 vs. placebo)
Gordon et al. 2003 (e36)	good	A_2	27% vs. 4%
Lebwohl et al. 2003 (e38)	satisfactory	A_2	22% vs. 5%
Leonardi et al. 2005 (e35)*4	–	A_2	39% vs. 2%
Menter et al. 2005 (e39)	–	A_2	same as Gordon et al. 2003 (e36): identical clinical trial
Gottlieb et al. 2004 (e34)	–	B	41% (no control group)
Papp et al. 2001 (e40)	–	A_2	25% vs. 2%
ACD2058g. (industry submission) Feltham: Serono Ltd., 2004 (e23, e25)	poor	–	39% vs. 2%
ACD2600g. (industry submission) Feltham: Serono Ltd., 2004 (e22, e25)	poor	–	24% vs. 3%
IMP24011. (industry submission) Feltham: Serono Ltd., 2004 (e21, e25)	poor	–	31% vs. 4%

– : not assessed

*1In the HTA report on efalizumab, on which the NICE guideline is partly based, the quality of clinical trials with respect to efficacy was assessed with a standardized checklist containing questions about whether the inclusion criteria were specified, whether the trial was double-blinded, and whether an intention-to-treat analysis was carried out (among other topics). The overall quality of each trial was then rated as excellent, good, satisfactory, or poor.

In the S3 guideline, each trial was assigned an evidence level reflecting the quality of its methods:
A_1: meta-analysis containing at least one randomized trial of level A_2 and in which findings are consistent across trials.
A_2: randomized, double-blind comparative clinical trial of high quality (e.g., sample size calculation, flow diagram, intention-to-treat analysis, adequate size)
B: randomized clinical trial of lesser quality, or other type of comparative trial (non-randomized: cohort or case-control study)
C: non-comparative trial
D: expert opinion

The overall state of the evidence concerning the efficacy of an intervention as monotherapy is also assigned a level of evidence:
1: evidence level A_1 trials or multiple evidence level A_2 trials with largely consistent findings
2: evidence level A_2 trials or multiple evidence level B trials with largely consistent findings
3: evidence level B trials or multiple evidence level C trials with largely consistent findings
4: little or no systematic evidence

*2PASI: Psoriasis Area and Severity Index
*3The results shown are with efalizumab at a dose of 1 mg/kg body weight/week except in the trial of Gottlieb et al. (efalizumab 2 mg/kg body weight/week, [e34]) and Papp et al. (efalizumab 0.3 mg/kg body weight/week [e40]).
*4The data reported by Leonardi et al. (e35) partly correspond to those of the ACD2058g trial as documented in the HTA report

eTABLE 2a

Statements on conflicts of interest by authors of the S3 guideline on drugs for psoriasis vulgaris*

Project cordination / responsibilities			
Project director	Prof. A	**Activity as a consultant for:** Serono GmbH Essex Pharma GmbH Wyeth Pharma GmbH **Endowment of professorship:** Fumedica GmbH	efalizumab infliximab etanercept
Project coordination/ methods	Dr. B	none	
	Dr. C	HTA report, biologics: Wyeth Pharma GmbH	etanercept
	Dr. D (until 1/2005)	none	
Med. documentation	E	HTA report, biologics: Wyeth Pharma GmbH	etanercept

* In accordance with the practice of *Deutsches Ärzteblatt* and *Deutsches Ärzteblatt International*, no trade names of drugs are given

eTABLE 2b

Statements on conflicts of interest by authors of the S3 guideline on drugs for psoriasis vulgaris*[1]

Expert group / "5 + 5 group"		
Hospital-based dermatologists (named by the DDG)		
Prof. F*[2]	Advisory boards Biogen Idec GmbH Wyeth Pharma GmbH Lectures Essex Pharma GmbH Schering Plough **Serono GmbH** Wyeth Pharma GmbH Clinical trials Leo Pharma GmbH Wyeth Pharma GmbH Abbott GmbH & Co. KG Biogen Idec GmbH **Serono GmbH**	 fumaric acid ester etanercept, methotrexate Infliximab – **efalizumab** etanercept, methotrexate calcipotriol, calcipotriol + betamethasone etanercept, methotrexate adalimumab fumaric acid ester **efalizumab**
Dr. G (substitute for Prof. F)	Clinical trials Leo Pharma GmbH Wyeth Pharma GmbH Abbott GmbH & Co. KG Biogen Idec GmbH **Serono GmbH**	 calcipotriol, calcipotriol + betamethasone etanercept, methotrexate adalimumab fumaric acid ester **efalizumab**
Dr. H*[2]	Lectures **Serono GmbH** Essex Pharma GmbH Biogen Idec GmbH Clinical trials Biogen Idec GmbH Essex Pharma GmbH Wyeth Pharma GmbH **Serono GmbH** Employee of Intendis GmbH since 2006	 **efalizumab** infliximab fumaric acid ester fumaric acid ester infliximab etanercept, methotrexate **efalizumab** diflucortolone valerate, calcipotriol, calcipotriol + betamethasone
Prof. I*[2]	Lectures / advisory boards Abbott GmbH & Co. KG Biogen Idec GmbH (formerly Fumapharm AG) Essex Pharma GmbH Hermal GmbH & Co. Intendis Dermatologie GmbH Leo Pharma GmbH Novartis Pharma GmbH **Serono GmbH** Wyeth Pharma GmbH Clinical trials Abbott GmbH & Co. KG Biogen Idec GmbH (formerly Fumapharm AG) Boehringer Ingelheim Pharma GmbH & Co. KG Essex Pharma GmbH Leo Pharma GmbH **Serono GmbH** UCB GmbH Wyeth Pharma GmbH	 adalimumab fumaric acid ester infliximab dithranol, dithranol + salicylic acid diflucortolone valerate, calcipotriol, calcipotriol + betamethasone calcipotriol, calcipotriol + betamethasone pimecrolimus, cyclosporine **efalizumab** etanercept, methotrexate adalimumab fumaric acid ester – infliximab calcipotriol, calcipotriol + betamethasone **efalizumab** – etanercept, methotrexate

Dr. J (substitute for Dr. I)	Lectures—Self-Help for Psoriasis Patients	
Prof. K*[2]	Financial support Biogen GmbH **Serono GmbH** Wyeth Pharma GmbH Essex Pharma GmbH	 fumaric acid ester **efalizumab** etanercept, methotrexate infliximab
Prof. L*[2]	Consulting activity / lectures / clinical trials Abbott GmbH & Co. KG Biogen Idec GmbH (formerly Fumapharm AG) Centocor B.V. Essex Pharma GmbH Intendis Dermatologie GmbH Leo Pharma GmbH Novartis Pharma GmbH **Serono GmbH** Wyeth Pharma GmbH	 adalimumab fumaric acid ester ustekinumab, golimumab infliximab diflucortolone valerate, calcipotriol, calcipotriol + betamethasone calcipotriol, calcipotriol + betamethasone pimecrolimus, cyclosporine **efalizumab** etanercept, methotrexate
Dr. M (substitute for L)	Clinical trials Biogen Idec GmbH (formerly Fumapharm AG) **Serono GmbH** Medimmune Inc. Centocor B.V.	 fumaric acid ester **efalizumab** biologics ustekinumab, golimumab
Practice-based dermatologists (named by the BVDD)		
PD Dr. N*[2]	none	
PD Dr. O*[2]	Advisory boards **Serono GmbH** Wyeth Pharma GmbH Lectures **Serono GmbH** Leo Pharma GmbH Clinical trials **Serono GmbH** Essex Pharma GmbH Wyeth Pharma GmbH	 **efalizumab** etanercept, methotrexate **efalizumab** calcipotriol, calcipotriol + betamethasone **efalizumab** infliximab etanercept, methotrexate
Dr. P*[2]	Served as an expert for the HTA report (DIMDI) on the treatment of psoriasis	
Dr. Q*[2]	Advisory boards **Serono GmbH** Essex Pharma GmbH Wyeth Pharma GmbH Clinical trials **Serono GmbH** Essex Pharma GmbH Wyeth Pharma GmbH Leo Pharma GmbH Intendis Dermatologie GmbH	 **efalizumab** infliximab etanercept, methotrexate **efalizumab** infliximab etanercept, methotrexate calcipotriol, calcipotriol + betamethasone diflucortolone valerate, calcipotriol, calcipotriol+betamethasone
Dr. R*[2]	Advisory board **Serono GmbH**	 **efalizumab**

Extended multidisciplinary group		
Pharma-economics: Prof. S*[2]	<u>Lectures / advisory boards</u> Abbott GmbH & Co. KG Biogen Idec GmbH (formerly Fumapharm AG), Essex Pharma GmbH Hermal GmbH & Co. Intendis Dermatologie GmbH Leo Pharma GmbH Novartis Pharma GmbH **Serono GmbH** Wyeth Pharma GmbH <u>Clinical trials</u> Abbott GmbH & Co. KG Biogen Idec GmbH (formerly Fumapharm AG) Essex Pharma GmbH Leo Pharma GmbH **Serono GmbH** UCB GmbH Wyeth Pharma GmbH	 adalimumab fumaric acid ester infliximab dithranol, dithranol + salicylic acid diflucortolone valerate, calcipotriol, calcipotriol + betamethasone calcipotriol, calcipotriol + betamethasone pimecrolimus, cyclosporine **efalizumab** etanercept, methotrexate adalimumab fumaric acid ester infliximab calcipotriol, calcipotriol + betamethasone **efalizumab** – etanercept, methotrexate
Dr. T (substitute for S)	no information	
Pharmacology: PD Dr. U*[2]	none	
Dr. V (substitute for U)	none	
Nursing: W*[2]	none	
Patient rep.: X*[2]	none	
Y (substitute for X)	none	
Psychosomatic medicine: Prof. Z*[2]	<u>Financial support</u> **Serono GmbH** Leo Pharma GmbH Intendis Dermatologie GmbH Biogen Idec GmbH	 **efalizumab** calcipotriol, calcipotriol + betamethasone diflucortolone valerate, calcipotriol, calcipotriol + betamethasone fumaric acid ester
Moderation of the consensus process: PD Dr. Ä	none	

*[1] In accordance with the practice of *Deutsches Ärzteblatt* and *Deutsches Ärzteblatt International,* no trade names of drugs are given
*[2] Voting participants in the consensus process