Commentary

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Bioethics, the Surviving Sepsis Campaign, and the industry

More than three decades ago, bioethicists entered the world of medicine and life sciences. Not surprisingly, their work has sometimes been used as a cover to serve corporate interests. For example, in 1996 the Wall Street Journal reported that Eli Lilly was routinely using homeless alcoholics as "healthy volunteers" for Phase I trials of new drugs. The company then assembled a team of bioethicists and got what it paid for: bioethicists agreeing that testing drugs on the homeless was ethically acceptable [1]. It was only to be expected that there would be disagreement among bioethicists on this point, because the harsh conditions under which these subjects live, and their desperation, make it all but impossible for them to give bona fide consent, an ethical logic routinely applied to prisoners, who are excluded from most research [2].

Another reason to worry about bioethicists being paid by corporations to render ethical judgments could come from recent intensive care medicine discussions on cost and efficacy, in which labeling the unwillingness of doctors to use a drug is branded as unethical. One such case is that of Eli Lilly and its product Xigris – a drug to treat severe sepsis. Physicians have been slow to prescribe the expensive drug after the European Agency for the Evaluation of Medicinal Products (EMEA) and the US American Food and Drug Association (FDA) restricted approval in late 2001 and early 2002, respectively, because of questions about its mechanism of action, efficacy, and safety [3]. By the spring of 2002, it was clear sales were falling far short of expectations. Therefore, Lilly put its external public relation contract for Xigris out for bid. The winning proposal came from Belsito & Co., Manhattan, NY [4]. Under the premise that it was unethical not to use the drug, its pitch for the Lilly contract was titled, "The Ethics, The Urgency and The Potential." In October 2002, Eli Lilly created the "Values, Ethics and Rationing in Critical Care Task Force" (VERICC) with a $ 1.8 million grant. VERICC was officially founded in October 2003 and, according to its Web site, is "an independent, multidisciplinary research initiative dedicated to the study of Intensive Care Unit rationing practices, attitudes and behaviors among U.S. critical care physicians, nurses and hospital administrators." It not so subtly promotes Lilly's interests by referring to Xigris, among others, as a "lifesaving medication ranking high on the 'to-be-rationed' list [5]. In her book entitled "The Truth About the Drug Companies: How They Deceive Us and What to Do About It", former Editor-in-Chief of the New England Journal of Medicine, Marcia Angell, confirms the roles of the New York WPP agency [6] and elsewhere she states: "there is no question in my mind that medical researchers, educators, and clinicians have been corrupted by their close and lucrative ties to industry" [7].

A review of the risks and benefits of drotrecogin alfa (activated), the generic name for Xigris, in the New England Journal of Medicine concluded in September 2002 that "… there is not sufficient evidence at present for it to become the standard of care" [6]. This estimation significantly interfered with Eli Lilly's marketing strategy and the investment in VERICC, as the unwillingness of doctors to use the drug can only be labeled unethical with a drug clearly considered beneficial and its use recommended as standard of care.

During the conduct of Phase III clinical development of Xigris, novel guidelines had been prepared by the "International Sepsis Forum" (ISF) and were published in 2001 in "Intensive Care Medicine", the official journal of the European Society of Intensive Care Medicine (ESICM), "to assist decisions in health care for sepsis" [7]. The ISF was created by medical opinion leaders in the field of sepsis and, according to the Forum's Web site, "funding of the ISF is provided by sponsors as an unrestricted educational grant to the ISF" [8]. Eli Lilly is listed among seven companies that financed the ISF. With regard to funding, it is stated in the ISF Web site: "Corporate support is recognized on all ISF published and informational materials. Each corporate partner is updated regularly on ISF educational programs and has the opportunity to send a company representative to observe ISF Steering Committee meetings and Management Strategy Groups/Management Guidelines Workshops." The hidden and grave implication is that ISF Sepsis Guidelines were likely to have been elaborated under the direct supervision of representatives of the sponsoring pharmaceutical industry. This, of course, is against any of the current recommendations on how to develop treatment guidelines [9, 10].

The ISF then went on to co-operate more closely with the major critical care medicine professional societies in Europe and the US with the goal to improve management, diagnosis and treatment of sepsis. The Surviving Sepsis Campaign (SSC) was formed in 2002 as a collaboration of the ISF with the ESICM, and the american Society of Critical Care Medicine (SCCM). Of course, also the SSC is open to funding from industry, and again Eli Lilly served as major sponsor among an ever smaller list of pharmaceutical companies (Baxter Healthcare Corporation, Edwards Lifesciences, and Eli Lilly and Company). The stated goal of the collaborative effort is "to change

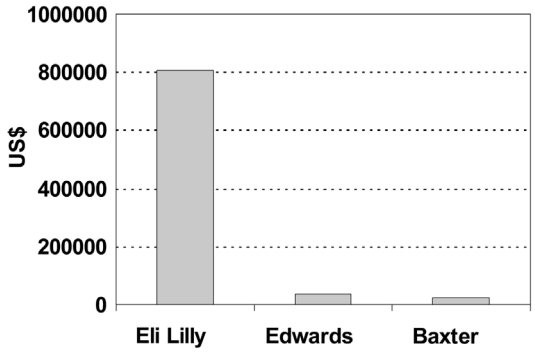

Fig. 1. Funding of Surviving Sepsis Campaign costs (US Dollars) as acknowledged in the guideline's original publication [11, 12]

physician behavior". As to their mission statement, the SSC offers to provide leadership, support, and guidance to governments and agencies toward the development of coherent global and national strategies for the diagnosis and treatment of sepsis [11].

The first phase of the cooperation between the ISF and the two big medical societies, ESICM and SCCM, was built around the Barcelona meeting of the ESICM in 2002 and included an initial medical campaign that should identify sepsis as a killer, underline the need to make progress in public awareness and help reduce mortality. The cost of phase I including the conduct of two surveys was approximately US$ 702.600, and was met by grants from Eli Lilly (94%), Edwards (3%), and Baxter (3%) [12, 13].

The SSC then released new guidelines called "Surviving Sepsis Campaign Guidelines for the Management of Severe Sepsis and Septic Shock". They appeared in the March 2004 issue of "Critical Care Medicine" [12] and the April 2004 issue of "Intensive Care Medicine" [13]. In the summary publication it is stated that "ISF Guidelines on Sepsis served as starting point" [12, 13]. This time, however, under 'acknowledgments' subsection, sponsor companies were mentioned entirely separately from the process by which the guidelines were developed by the many contributors. Doubts were voiced as to whether the authors, despite the size of the committee, would have been able to conduct an exhaustive review of all the evidence available, in accordance with standards, in a so short a time period between June and December 2003 [14]. Costs for this phase of SSC activities mainly included the meeting, teleconferences, and website update and amounted to approximately $158,750, and were borne by grants from Eli Lilly (90%) and Edwards (10%) [12, 13]. "Most of the expense for this effort has been time by the committee who received no reimbursement." This means that committee members must have received payments for their participation. The conflict of interest statements collected in accordance with SCCM and ESICM guidance [12, 13] discloses that of the 43 committee members 12 (about one 1 of 4) had received speakers bureau payments, consultant fees, or research Grants from Eli Lilly, the major sponsor in the SSC Guideline development (Fig. 1). Finally, these guidelines were published in the name of 11 medical societies and organizations (Table 1). This now serves as basis for Eli Lilly and Company to reframe its marketing problem as an ethical problem.

EMEA and FDA considered the evidence from PROWESS [15], the only trial available for the registration of Xigris, to be problematic, and license to market the drug was restricted to a subgroup of high risk patients [3]. No mention of the trial's problems [6] has been made in the guideline summaries, thus suggesting that Xigris is accepted as standard of care. The guidelines have been heavily criticized for this and several other reasons such as internal inconsistency, and selective evidence presentation namely, omission of existing unfavorable evidence, on the one hand and overemphasis of evidence that can be interpreted as favorable, on the other [16–24].

Because of the results of post-approval study obligations for the FDA, Eli Lilly recently had to add a warning to the label of Xigris [25]: "Among the small number of patients enrolled in PROWESS with single organ dysfunction and recent surgery (surgery within 30 days prior to study treatment), all-cause mortality was numerically higher in the Xigris group (28-day: 10/49; in-hospital: 14/48) compared to the placebo group (28-day: 8/49; in-hospital: 8/47). In a preliminary analysis of the subset of patients with single organ dysfunction and recent surgery from a separate, randomized, placebo-controlled study (ADDRESS) of septic patients at lower risk of death (APACHE II score < 25 or single sepsis-induced organ failure at any APACHE II score), all-cause mortality was also higher in the Xigris group (28-day: 67/323; in-hospital: 76/325) compared to the placebo group (28-day: 44/313; in-hospital: 62/314). Patients with single organ dysfunction and recent surgery may not be at high risk of death irrespective of APACHE II score and therefore may not be among the indicated population. Xigris should be used in these patients only after careful consideration of the risks and benefits." EMEA also tightened the Xigris label for the European Union including the recommendation that the product only be used in high-risk patients, mainly in situations when therapy can be started within 24 hours of the onset of organ failure and that it should only be used by experienced doctors in institutions skilled in the care of patients with severe sepsis [26]. Most recently,

Table 1. Medical societies and organizations officially supporting the Surviving Sepsis Campaign Guidelines

American Association of Critical-Care Nurses
American College of Chest Physicians
American College of Emergency Physicians
American Thoracic Society
Australian and New Zealand Intensive Care Society
European Society of Clinical Microbiology and Infectious Diseases
European Society of Intensive Care Medicine
European Respiratory Society
International Sepsis Forum
Society of Critical Care Medicine
Surgical Infection Society

Lilly has had to stop early a pediatric clinical study of Xigris after interim results showed that it was ineffective and might pose a safety risk in this population [27].

In her book entitled "The Truth About the Drug Companies: How They Deceive Us and What to Do About It", former Editor-in-Chief of the New England Journal of Medicine, Marcia Angell, describes the role of the marketing agency [4] and elsewhere she states: "There is no question in my mind that medical researchers, educators, and clinicians have been corrupted by their close and lucrative ties to industry" [28]. If bioethicists want to return to their original mission, they must understand the ways in which their field and their ideas are being used and whose interests are in fact being protected by their ethical judgments. When the ethics label is wielded in the service of economic interests, bioethics is increasing the distance between caregivers and the wisdom needed to heal. Pursuing the commendable objective of protecting the vulnerable from the power of the medical industrial complex, pioneers of bioethics noted that several features of modern life – including new ways of paying for medical care, increasing mobility (which separated caregivers from their original communities) and new technologies – were reducing the art of healing to little more than medical technique. They attempted to speak truth to power. That was then. Now alas, it seems as though bioethicists can be persuaded to speak power to truth.

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