Vioxx Redux: FDA on the Sidelines as Marketing Subsumes Evidence: Surviving Sepsis-NEJM

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Lilly's aggressive marketing of Xigris does indeed epitomize the worst ofthis industry's mission.

In 2001, Eli Lilly's chairman, president and CEO, Sidney Taurel, told shareholders: "No medicine better symbolizes our mission than Xigris," calling it "one of our industry's genuine breakthroughs." [1]

Lilly's aggressive marketing of Xigris does indeed epitomize the worst of this industry's mission. Since its controversial restricted approval in 2001, reports by independent scientists (not financially tied to Lilly) who have examined the completed data analysis from the first and subsequent controlled clinical trials of Xigris (recombinant human activated protein C (APC), reveal that the drug has failed to demonstrate a benefit even for patients for whom it was approved. [2] They also report that the risk from severe bleeding "associated with APC might actually be greater than originally estimated."

Sepsis is a life-threatening illness caused by overwhelming infection of the bloodstream by toxin-producing bacteria. If the benefit / risk ratio is negative, patients treated with Xigris are at increased risk preventable death.

In light of mounting concerns raised by expert scientists in critical care medicine-the latest in the New England Journal of Medicine-about the increased risk of hemorrhage and lack of proven efficacy of this controversial treatment for severe sepsis, AHRP calls upon the FDA to convene an advisory committee hearing to assess the cumulative safety and efficacy data as soon as feasible.

Dr. Peter Eichacker, Dr.Charles Natanson, and Dr. Robert Danner, senior investigators in Critical Care Medicine at the National Institutes of Health, whose article, "Surviving Sepsis-Practice Guidelines, Marketing Campaigns, and Eli Lilly" in this week's NEJM, lay out an insidious medical marketing controversy that has festered for five years within the community of critical care specialists.
http://content.nejm.org/cgi/content/extract/355/16/1640 The particular concern of these authors is Lilly's undue influence on the practice guidelines for sepsis care to include an expensive treatment for which the risks appear to outweigh the benefits. It is a concern shared by numerous other investigators [3]

In 2001, Lilly gained controversial approval to market Xigris (an activated protein C (APC) from the European Medicines Authority and the FDA on the basis of a single trial, PROWESS [4]. FDA approved the drug despite the advisory committee's split vote (10 to 10) due to concerns about the validity of the claimed efficacy and safety findings [5] [6].
http://www.fda.gov/ohrms/dockets/ac/01/minutes/3797m1.pdf

Dr. Eichacker and colleagues state that the "Surviving Sepsis Practice Guidelines" fail to disclose "the possible magnitude" of harm reported in a subsequent study published in October 2005 (ADDRESS): "the risk of bleeding associated with rhAPC might actually be greater than originally estimated..the possible magnitude of this increased risk (a 28-day incidence of serious bleeding of 6.5% as compared with 3.5% in the PROWESS study.)" They also note that the ADDRESS trial was suspended for lack of benefit, Thus, "the efficacy of APC has not been prospectively demonstrated in the patient population for which the drug is currently recommended." Given the magnitude of the increased risk and lack of benefit, why then, is Xigris being used?

The FDA claims it does not regulate the practice of medicine. In fact, when the FDA approves a drug, the manufacturer will utilize aggressive marketing

campaigns, influencing physicians with misleading claims of benefits to persuade them to prescribe the product. Limitations regarding safety and efficacy findings are-at most-buried in the scientific literature and fine print of the "label". Such sources rarely influence medical practice.

The FDA bears major responsibility for approving drugs for marketing that have not demonstrated safety and effectiveness "with substantial evidence through the conduct of well controlled trials"-as is required under the Food Drug and Cosmetics Act since 1962. FDA's approval of Xigris before it had demonstrated both safety and efficacy in two randomized controlled trials, by cutting corners and accepting Lilly's single flawed trial, validates the failing grades the agency has received, most recently by a blue ribbon committee of the Institute of Medicine. [7]
www.iom.edu/cms/3793/26341/37329.aspx

Of note, after the advisory committee's split vote [8] [9] business publications, such as The Street [10] and Bioportfolio [11] fully expected the FDA to reject approval of Xigris. Instead, the FDA gave the drug a glowing endorsement: "Xigris is a new treatment that helps to save the lives of patients with the most severe forms of sepsis" said FDA's Acting Deputy Commissioner Bernard A. Schwetz, D.V.M., Ph.D.
http://www.fda.gov/bbs/topics/NEWS/2001/NEW00780.html

Xigris is but one of many drugs and devices that the FDA licensed without adequate safety and efficacy evidence to justify that license. The list includes: Vioxx, Celebrex, Neurontin, Fen-Phen, vagus nerve stimulator (VNS) the entire class of antipsychotics and SSRI antidepressants. In each case the manufacturers embarked on a marketing strategy that submerged evidence of lethal risks with a barrage of unsubstantiated claims of efficacy. [12]
How many other harmful drugs are currently marketed?

To offset Xigris disappointing sales, Lilly hired Belsito, a PR firm, to orchestrate a well financed marketing campaign with generous unrestricted "educational" grants. Close to a million dollars was awarded to a group of influential physicians with prior financial ties to Lilly who founded the "Surviving Sepsis Campaign." Its message: "Look beneath the symptoms..Xigris offers safe and effective treatment so more survive."
http://www.xigris.com/index.jsp

Another $1.8 million grant created a bioethics task force-Values, Ethics and Rationing in Critical Care (VERICC). This panel of professional rubber stampers declared that physicians who do not prescribe Xigris are guilty of "unethical rationing." Bioethicists' duplicity in disparaging physicians' concerns about benefit / risk was noted by Christian Wiedermann, MD, [13] a Professor of internal medicine in Bolzano, Italy: "now, it seems as though bioethicists can be persuaded to speak power to truth." http://www.ahrp.org/COI/APC/xigrisWeidermanBioethics05.pdf

Not only did Lilly's Xigris marketing campaign to physicians misrepresent the body of evidence showing no benefit and increased risk from severe bleeding, but it provided another "educational" grant of close to a million dollars to a selected panel for new clinical practice guidelines. The guidelines recommend the use of Xigris as standard care when the evidence does not support that recommendation. Are patients and families infomed about the negative benefit / risk ratio? Are they afforded the right to refuse this treatment?

Five Years after its controversial approval, all scientific data from subsequent trials confirm advisory committee concerns:
Xigris failed to demonstrate a benefit in all trials:
ADDRESS-RESOLVE-ENHANCE. Instead, the drug caused a clinically significant increased risk of death from hemorrhage. An insightful re-examination of FDA documents four years after FDA approved the drug, Dr. Alasdair Mackenzie reported: [6] "Activated protein C: Do More Survive?" was published four years after the controversial approval in Intensive Care Medicine (2005). Dr. Mackenzie found numerous inconsistencies in the original trial (PROWESS)

not previously reported in the literature-including serious concerns about the study blind, changes in the APC solution, and an unexplained change in the "do not resuscitate rate" that might have skewed the results to favor the drug:

"In the second phase of PROWESS, when the difference in 28-day mortality developed, there was an unexplained reduction in "do not resuscitate" (DNR) rates in the APC arm: 74 patients (16%) before protocol amendment, 32 (9%) thereafter. The DNR rate in the placebo arm remained steady at around 18% in both halves [6]. Additionally, there were changes to enrolment sites across the two halves of the study: 20 sites were dropped and 45 added. The FDA felt it "worrisome" that there was a negative APC effect at the dropped sites whereas those added later tended to show a strong drug effect."
**http://www.ahrp.org/COI/APC/xigrisMackenzieICM05.pdf
Complete three-month survival analysis of PROWESS study (2004) revealed that Xigris offered no benefit over placebo. [2] [14]

In 2005, the ADDRESS study conclusions were published in the NEJM: [15] "The absence of a beneficial treatment effect, coupled with an increased incidence of serious bleeding complications, indicates that DrotAA should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score less than 25."
http://content.nejm.org/cgi/content/abstract/353/13/1332

The same year Lilly [16] notified healthcare professionals and the FDA that it was halting RESOLVE, a clinical trial in children because of "an unfavorable benefit / risk profile": "an interim analysis showed that the drug was largely ineffective in treating sepsis. over a placebo." In addition, "a higher rate of bleeding of the central nervous system was observed in patients taking Xigris over a placebo." The incidence of intracranial hemorrhage (ICH) in children treated with Xigris increased to a rate of 2% compared to 0.5% in children on placebo (during an infusion period, 0-6 days); and during the entire study period (28 days) ICH increased to 4% compared to 2% in children on placebo.
http://www.fda.gov/medwatch/SAFETY/2005/xigris_dearHCP_4-21-05.htm
Of note, the mortality rate in children with sepsis is very low (8% to 10%), thus any increase in Cerebral hemorrhage rate is alarming.

Post approval warnings:
http://www.fda.gov/medwaTCH/SAFETY/2005/xigris_DHCP.htm

Given the disturbing confirmatory findings about the serious risks posed by this treatment, knowledgeable physicians, such as Dr. Mackenzie have concluded: "Unfortunately, what is clear is the increased rate of serious bleeding events associated with APC administration. In conclusion, it is extremely difficult to justify ongoing use of APC in severe sepsis." [6]
Unfortunately, public perception has been molded by a clever, though dishonest, marketing campaign [17]
http://news.bbc.co.uk/2/hi/health/3091781.stm

Xigris is a case encapsulating a failed regulatory environment under the current FDA administration that has led to the perversion of "evidence-based medicine." The FDA does little to ensure drug safety by failing to implement federal law requiring manufacturers to prove safety and effectiveness "with substantial evidence through the conduct of well controlled trials" before marketing licensure is granted. Instead, FDA rationalizes and bends over backwards to approve drugs whose manufacturers have not proven safety and effectiveness "with substantial evidence through the conduct of well controlled trials." And many of those drugs later proved ineffective and unsafe. When the FDA approved drugs such as Xigris, it failed to follow the federally mandated science-based standard for approval. Even worse, FDA fails to take action when the post-approval evidence collected after its controversial approval of the drug, shows lack of efficacy for the population for whom it was approved. Worse still, the scientific data shows a significant increased risk of death.

How do FDA officials explain their failure to convene an advisory panel to re-examine the scientific evidence showing that Xigris has an unfavorable benefit / risk ratio-which means it kills more patients than it saves?

FDA's hands-off policy ("FDA does not regulate medicine") allows medical practice to be dictated by manufacturers' business interests-even if they undermine public health. FDA is responsible for: "protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices.and helping the public get the accurate, science-based information they need to . improve their health." FDA's current hands-off policy has led companies to disseminate dubious marketing claims under the mantle of "science-based" authority in practice guidelines: "Xigris offers safe and effective treatment so more survive." FDA officials know that the scientific evidence shows the opposite to be true.

The PR Campaign Overshadows Science and Safety:
Below is how the Council of Public Relations Firms describes this Case Study:
http://www.prfirms.org/resources/case_studies/Marketing_Communications/2004/SurvivingSepsis1.asp

Eli Lilly with Belsito & Company
A strategy was implemented to first raise awareness about rationing and then the disease state as a means of enhancing prospects of utilization of Xigris in the ICU. To implement this strategy, a three-pronged approach was developed:
1. Continue to support Xigris but only through highly-specific marketing initiatives to physicians and the medical trade media;
2. Work through an unrestricted $1.8 million educational grant from Lilly to form a task force, The Values, Ethics and Rationing in Critical Care (VERICC) Task Force, to study the issue of healthcare rationing in the ICU;
3. Raise awareness of severe sepsis and generate momentum towards development of treatment guidelines for the infection through establishment of the Surviving Sepsis Campaign

The key to media outreach was to provide journalists with a comprehensive press kit that could illustrate both the systemic problems that lead to healthcare rationing, and to outline the specific impact on patients. The kit included:
* An extensive background document on critical care costs
* A thorough backgrounder on healthcare rationing
* A seventy-page review of ongoing debates about the ethics of rationing
* A summary of survey results documenting the withholding of valuable healthcare
* A question-and-answer document to "connect the dots"
* Comprehensive information about the Task Force and its members

"Most importantly, sales of Xigris have begun to trend upwards. Through the first quarter of 2004, Xigris sales were up 36%."

Whether or not laws have been broken, the public health is further eroded by a broken regulatory system that cannot contain a powerful industry run amok.

"No medicine better symbolizes our mission than Xigris." [1]

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3. See annotated bibliography: http://www.cc.nih.gov/ccmd/htmlpg/surviving_sepsis.html

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5. Consultants to the advisory committee clarified what the serious concerns with PROWESS: "First, there were changes in the study protocol and in the drug preparation that appeared to divide the trial into two discernible phases in which the efficacy of activated protein C was different. Second, there was new information about the efficacy of the drug in various subgroups of patients. Third, there were new data on the toxicity of the drug." See: Warren HS, Suffredini AF, Eichacker PQ, Munford RS. Risks and benefits of activated protein C treatment for severe sepsis. N Engl J Med 2002;347:1027-1030. Commentary (Sounding Board) written by members of the FDA Anti-Infective Drugs Advisory Committee that describes issues related to the PROWESS trial and rhAPC

6. Mackenzie A. Activated Protein C: Do More Survive? Intensive Care Medicine, 2005, 31:1624-1626: **http://www.ahrp.org/COI/APC/xigrisMackenzieICM05.pdf

7. Institute of Medicine Report. The Future of Drug Safety, September, 2006. See also: www.ahrp.org/cms/content/view/344/27

8. FDA Advisory Committee Concerns are posted at: http://www.fda.gov/cder/biologics/review/droteli112101r1p2.pdf

9. The Advisory Committee vote: http://www.fda.gov/ohrms/dockets/ac/01/minutes/3797m1.pdf

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11. Bioportfolio reported: "Lilly suffered its first setback in October 2001 when an FDA advisory panel was unable to recommend approval for Xigris following a split vote. The panel were concerned that the Prowess study, on which the drug's application was based, had the patient entry criteria changed halfway through the trial, which may have exaggerated Xigris's efficacy results." See: Eli Lilly's Xigris: struggling to overcome its problems in the sepsis market, Bioportfolio: http://www.bioportfolio.com/news/datamonitor_29.htm

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Publication of the ADDRESS trial reporting that rhAPC was not effective in patients with either a low or high risk of death. Risk of hemorrhage in the trial was increased with rhAPC and mortality in surgical patients with one organ injury was increased in a trend similar to the PROWESS trial.

16. Lilly (2005) Association of Xigris with intracranial hemorrhage in pediatric patients and discontinuation of study F1KMC-EVBP (investigation of the efficacy and safety of drotrecogin alfa (activated) in pediatric severe sepsis) based on failure to reach desired clinical endpoints and an unfavorable benefit/risk profile, 6 May 2005. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/xigris_hpc-cps_e.html

17.BBC. Ban on use of life-saving drug, July 23, 2003: http://news.bbc.co.uk/2/hi/health/3091781.stm

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THE NEW ENGLAND JOURNAL OF MEDICINE
Surviving Sepsis - Practice Guidelines, Marketing Campaigns, and Eli Lilly
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Practice guidelines approved by expert panels are intended to standardize care in such a way as to improve health outcomes. In recent years, the developers of such standards have started grouping evidence-based interventions into "bundles," on the theory that inducing physicians to follow multiple recommendations written into a single protocol has a measurable effect on patients' outcomes. As a side effect, bundled performance measures are readymade for use in pay-for-performance initiatives, which can base reimbursement on compliance with all the components.

Unfortunately, the development of such clusters is vulnerable to manipulation for inappropriate- and possibly harmful - ends. Seeing in these bundles a potentially powerful vehicle for promoting their products, pharmaceutical and medical-device companies have begun to invest in influencing the adoption of guidelines that serve their own financial goals.

A case in point is the development of guidelines for the treatment of sepsis, which was orchestrated as an extension of a pharmaceutical marketing campaign. 1,2 Although its advocates viewed this effort as an important approach to reducing sepsis-related mortality, the campaign appears to have usurped guideline development for commercial purposes, possibly compromising highly regarded, third-party arbiters of medical quality in the process. Such intrusion into an initiative to benefit public health is of particular concern in this instance, since the drug incorporated into the performance measures was endorsed on the basis of a single controversial phase 3 trial that was still being called into question by additional studies even as the committee did its work.

In 2001, the Food and Drug Administration (FDA) approved Eli Lilly's Xigris (recombinant human activated protein C, or rhAPC, also known as drotrecogin alfa [activated]) for the treatment of sepsis. This approval was based primarily on a single phase 3 randomized, controlled trial - the Recombinant Activated Human Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study, published the same year - which showed a significant overall survival benefit at 28 days. The FDA acknowledged that there was controversy surrounding this decision, and half the members of the agency's advisory panel, pointing to methodologic and other important problems with the PROWESS study, voted to require that a confirmatory trial be performed before approval was granted. In its approval statement, the FDA recommended using rhAPC in patients deemed, on the basis of an Acute Physiology and Chronic Health Evaluation II score of 25 or more, to have a particularly high risk of death; since this criterion had not been prospectively validated, the agency asked Lilly to perform additional testing in selected subgroups. In the face of such uncertainty, initial sales of rhAPC fell short of market expectations (see timeline).3

To improve sales of rhAPC, in 2002, Lilly hired Belsito and Company, a public relations firm, to develop and help implement a three-pronged marketing strategy.1 First, the product's sales were to be supported by marketing initiatives targeted to physicians and the medical trade media.1 Second, because rhAPC was relatively expensive, word would be spread that the drug was being rationed and physicians were being "systematically forced" to decide who would live and who would die.1,3 As part of this effort, Lilly provided a group of physicians and bioethicists with a $1.8 million grant to form the Values, Ethics, and Rationing in Critical Care (VERICC) Task Force, purportedly to address ethical issues raised by rationing in the intensive care unit.3 Finally, the Surviving Sepsis Campaign was established, in theory to raise awareness of severe sepsis and generate momentum toward the development of treatment guidelines.

The first phase of the Surviving Sepsis Campaign was introduced at an October 2002 meeting of the European Society of Intensive Care Medicine (ESICM). In the second phase, launched in June 2003, international experts in critical care and infectious diseases were convened to create guidelines

for sepsis management, which were published in Critical Care Medicine in March 2004.4 Lilly provided more than 90% of the funding for these two phases, and many participants had financial or other relationships with the company.1,4 According to the Council of Public Relations Firms, Belsito helped to assemble the VERICC Task Force and launch the campaign, and initiated a media-outreach program to "raise awareness" of alleged rationing in severe sepsis with the intent of generating demand for rhAPC.1

Campaign participants might argue that, regardless of Lilly's concerted efforts, the guidelines were not influenced by the company and represent best practice based on the evidence that was available - largely from randomized, controlled trials.4 Although such trials represent the gold standard of medical evidence, overreliance on them in the construction of guidelines has a tendency to favor new drugs and devices, which typically undergo at least one such trial in order to obtain government approval. In this instance, that reliance meant that rhAPC was given a highly favorable rating (grade B), whereas established therapies for sepsis (such as antibiotics, fluids, and vasopressors), though included in the recommendations, received lower ratings (grade D or E), because most had not undergone randomized, controlled trials owing to a lack of equipoise.

This imbalance is made more troubling by the campaign's failure to discuss persisting concern about rhAPC, which has been reinforced by recent trials. After the PROWESS study, which had demonstrated an increased risk of serious bleeding, two other controlled trials - the aministration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) study and the Resolution of Organ Failure in Pediatric Patients with Severe Sepsis (RESOLVE) study - both of which were terminated early because they were deemed unlikely to show a significant difference in their primary end points, confirmed that increase in risk and resulted in warnings submitted by Lilly to the FDA regarding the use of rhAPC. Although the results of the ADDRESS study were reported at the October 2004 ESICM meeting, no mention of the study was included in a supplement to the Surviving Sepsis Campaign Guidelines published the following month in Critical Care Medicine.

Results from one open-label trial, the Extended Evaluation of Recombinant Human Activated Protein C (ENHANCE) study, published in October 2005, indicated that the risk of bleeding associated with rhAPC might actually be greater than originally estimated. Although data from the ENHANCE trial were available and are included in the guideline supplement, the possible magnitude of this increased risk (a 28-day incidence of serious bleeding of 6.5%, as compared with 3.5% in the PROWESS study) is not noted. Moreover, the efficacy of rhAPC has not been prospectively demonstrated in the patient population for which the drug is currently recommended.

Eleven professional societies are cited as sponsors of the Surviving Sepsis Campaign Guidelines. The Infectious Diseases Society of America (IDSA), however, declined to endorse them. According to Naomi O'Grady, the physician who chaired the IDSA's Standards and Practice Guidelines Committee from 2002 to 2005, the organization found fault with the manner in which the guidelines were developed, the use of a suboptimal rating system, and their sponsorship by a drug company. The peer-review process conducted by the IDSA might provide a model for an objective system of rating proposed guidelines in the future. But in this case, even the fact that the society decided not to endorse the ecommendations is not widely known. According to Dante L. Landucci, an intensivist at East Carolina University, Critical Care Medicine,which published the guidelines, removed mention of the IDSA's rejection from his invited editorial on the subject that appeared in print 3 months after the guidelines did.

As part of the third phase of the campaign, Lilly awarded unrestricted grants for an "Implementing the Surviving Sepsis Campaign" program.5 The main goal of this phase, launched in mid-2004, is the creation of performance bundles based on selected recommendations from the campaign guidelines. Again, many participants have self-reported financial or other

relationships with Lilly.4,5 Despite the persisting scientific controversy surrounding its safety and efficacy, rhAPC is included in one of these performance bundles. Neither the campaign's manual on bundle implementation nor a cover letter from the president of the Society of Critical Care Medicine mentions the ADDRESS and RESOLVE trials or the warnings they precipitated.5

In formulating and promoting the bundles, the campaign sought to collaborate with public, not-forprofit arbiters of the quality of health care, including the Voluntary Hospital Association, the Institute for Healthcare Improvement, and the Joint Commission on Accreditation of Healthcare Organizations.2,5 Implementation of the bundles is being advocated nationally in workshops organized under the auspices of the Society of Critical Care Medicine and funded by Lilly. Furthermore, the campaign has lobbied state governments to adopt the bundles. Efforts to institute these measures internationally are being promoted in a program called the "Surviving Sepsis Campaign Roadshow," also subsidized by Lilly. In addition, the company funds Advances in Sepsis, a widely distributed periodical that publicizes the campaign. These activities continue unabated amid increasing calls for a new, prospective study of rhAPC.

When properly formulated and applied, practice guidelines and performance standards hold the promise of improving patients' outcomes. Professional societies and other stakeholders must work together to promote a consistent guideline-development process, a robust rating system for guidelines that is applicable to all subspecialties, and a policy that prohibits the pharmaceutical and medical-device industries from directly or indirectly funding or influencing practice standards. The challenges involved in producing firstrate guidelines and performance standards are only exacerbated by the intrusion of marketing strategies masquerading as evidence based medicine.

Drs. Eichacker, Natanson, and Danner are senior investigators in the Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, MD. The opinions expressed are those of the authors and do not reflect the policies of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

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