New England Journal of Medicine (July 13, 2006) issues Safety Correction Re: Vioxx

Consumers International Report Accuses Industry of Unscrupulous Drug Marketing

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FYI

Once again, the New England Journal of Medicine (July 13, 2006) has had to eat crow after it published false and misleading clinical trial findings. The published correction issued by the NEJM to Merck's critical study of of its painkiller Vioxx, contradicts the company's position that the drug doesn't increase risk of heart attacks and strokes for people who took it for less than 18 months. The unsigned correction doesn't specify how soon after starting to take Vioxx the heightened risks begin but it advised that references to an 18-month safety threshold in the study "should be deleted." See:
http://content.nejm.org/cgi/reprint/NEJMx060029v1.pdf

As in the case of the SSRI antidepressants, the evidence contradicts pharmaceutical company claims about drug safety revealing instead, systemic patterns of deception.

According to The Wall Street Journal, Gregory Curfman, executive editor of the NEJM said that based on an analysis done by an independent bio statistician at the behest of the publication, "the risk could have begun at any point, including time points earlier than 18 months."

The correction comes about a month after Merck submitted its complete data and analysis from the study to the FDA stating it had incorrectly described a statistical method used to analyze the Approve data. In an interview, Gregory Curfman, executive editor of the journal, said that based on an analysis done by bio statistician Stephen W. Lagakos at the behest of the publication, "the risk could have begun at any point, including time points

earlier than 18 months." See:
http://content.nejm.org/cgi/reprint/NEJMp068137v1.pdf

Of note, the Wall Street Journal reports, there are roughly three months left before the statute of limitations in some states for filing a Vioxx lawsuit runs out.
Thus, plaintiff's attorney, Christopher Seeger, accused Merck of deliberately falsifying the claimed findings:
"This confirms that all along Merck knew the 18-month hypothesis was false. It was simply a litigation strategy."

Steven E. Nissen, M.D. Cleveland Clinic Foundation writes in part:
"The recent public disclosure of data from a 12-month extension study of the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial1 provides new insights into the effect of rofecoxib on cardiovascular events. These new data reveal the full results of both the original study and the extension phase, including data tables and KaplanMeier curves. In the original article, the APPROVe investigators reported event rates using an unusual censoring rule in which events were excluded if they occurred more than 14 days after the study drug was stopped.

All data in the new report are assessed by a conventional intention to-treat analysis. This new report also provides analysis that uses several different end points, including the widely used end point of the Antiplatelet Trialists' Collaboration (APTC) study.2

The original article included a post hoc hypothesis that curves for confirmed thrombotic events would not begin to diverge until after 18 months of exposure to rofecoxib.
However, all intention to-treat analyses in the newly released report show that the event curves begin to diverge much earlier, generally within four to six months."
[see, Figure 1 and 2]

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" It is now clear that the approach of censoring events that occurred more than 14 days after drug discontinuation had a significant effect on the results of the APPROVe trial.In a report of a serious drug-safety problem, even if the original study design pre specified censoring of late events, it is particularly important to provide alternative analyses if such analyses suggest a substantially different conclusion."

"Since patients who stopped the study drug early are likely to be people who had adverse reactions such as hypertension, heart failure, or renal dysfunction, they represent a particularly vulnerable group. It is now clear that the approach of censoring events that occurred more than 14 days after drug discontinuation had a significant effect on the results of the APPROVe trial.

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Curt D. Furberg, M.D., Ph.D. Wake Forest University School of Medicine writes:
"An update of the APPROVe trial data is now available. It contains additional information about events in the subgroup of participants whose data were censored if
they had an event more than 14 days after early discontinuation of the study medication. With the addition of 12 thrombotic events that occurred more than 14 days after the study drug
was stopped but within 36 months after randomization, it is now possible to analyze the three-year event data according to the intention-to-treat principle. Eight of the “new” events were in the
rofecoxib group, and these events had a clear effect on the published survival curve for rofecoxib (Fig. 2 of
the original article).

The curve is now more linear, and the narrowing of the distance between the rofecoxib and placebo curves at 18 months is almost gone. Statistical analysis shows no evidence of deviation from the proportional hazard over time.
The release of the new data raises questions. At the time the APPROVe trial was submitted and published, was the complete data set available to the authors for an intention-to-treat analysis?
Did they perform a proportionality test of the threeyear event data before publication?" cfurberg@wfubmc.edu

The unfolding revelations and false claims in published clinical trial reports confirm the accusations leveled at the drug industry by the European Consumers International.
The industry uses unscrupulous, systemic promotional practices to influence opinion and prescribing practices. "These include the sponsoring of patient lobby groups, funding disease awareness campaigns and use of hospitality packages for medical experts." Industry's claims about the cost of research and development are contradicted by industry's spending on marketing:
"The pharmaceutical industry spends nearly twice as much on marketing as it does on research and development, yet consumers know next to nothing about

where [$60 Billion] this money is going."

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Vioxx Study Correction May Add
Pressure to Merck's Defense
By HEATHER WON TESORIERO
June 27, 2006

The New England Journal of Medicine published a correction to a critical study of Merck & Co.'s painkiller Vioxx, contradicting the company's position that the drug doesn't increase risk of heart attacks and strokes to people who took it for less than 18 months.

The unsigned correction said key results in the New England Journal of Medicine's original publication of the study, called Approve, were reached by a different statistical method than was described in the article, and that when the data were subjected to the stated method, the contention that risk
increased only after 18 months didn't hold up. As a result, the correction said references to the 18-month threshold in the study "should be deleted." (See the correction1.)

The correction doesn't specify how soon after starting to take Vioxx the heightened risks begin. But in an interview, Gregory Curfman, executive editor of the journal, said that based on an analysis done by biostatistician Stephen W. Lagakos at the behest of the publication, "the risk could have
begun at any point, including time points earlier than 18 months." Dr.Lagakos's analysis also appeared on the journal's Web site.

Merck acknowledged it misidentified the statistical methodology that it used in its study, which it says it discovered last month and set in motion events that led to the published correction. But it disputes the contention of journal editors and other scientists that the new analysis changes the original conclusion. The company said it stands by its assertion that "the increased relative risk was observed beginning after 18 months." Theodore Mayer, co-lead outside counsel for Merck, said, "We believe our position is scientifically sound and we feel comfortable representing it."

Merck pulled its blockbuster painkiller off the market in September 2004, after the Approve study linked Vioxx to heart attacks and strokes in patients taking the drug for 18 months or longer. Since that time, several

scientists have challenged the 18-month premise, saying the drug could pose risks much earlier.

The correction could be a boon for plaintiffs' attorneys who have clashed with Merck on how quickly Vioxx's risks emerge in patients. The company faces 11,500 lawsuits from
people alleging Vioxx caused their heart attacks and strokes. A cornerstone of Merck's defense in the litigation has been that the drug couldn't have had a hand in injuries in people who took the drug for fewer than 18 months. So far, Merck has won three cases and lost three cases. Juries have found in favor of two plaintiffs who took the drug for fewer than 18 months. There is a trial under way in Atlantic City and another scheduled to start tomorrow in Los Angeles.

"This confirms that all along Merck knew the 18-month hypothesis was false," Christopher Seeger, plaintiff's attorney and key player in the Vioxx litigation, said. "It was simply a litigation strategy."

The New England Journal of Medicine also published letters from two physicians who have been outspoken critics of the 18-month hypothesis and who reiterated what they say is the validity of the
updated analysis. In an interview, Curt D. Furberg, whose letter appears in the journal, said, "The whole thing about an 18-month delay is gone. There is no support whatsoever for it."

In a response to the letters, Approve authors Robert S. Bresalier and John A. Baron wrote that an "indepth analysis of the extended patients in the Approve trial" is under way and will include an
independent analysis of the cardiovascular data. The two authors couldn't be reached for comment.

This is the second time Merck and the journal have differed in Vioxx study results. In December 2005, the journal issued an "Expression of Concern" over Merck's reporting of cardiovascular risks in a 2000 study known as Vigor. In that study, Merck used different cutoff points for stomach and cardiovascular results, which affected the number of reported heart attacks and sparked some criticism from outside scientists.

The Approve correction comes about a month after Merck submitted its complete data and analysis from the study to the Food and Drug Administration. At the time, MercMerck issued a statement saying it incorrectly described a statistical method used to analyze the Approve data. It said that didn't change the results of the study, and that Vioxx only appeared to pose risks after 18 months.
There are roughly three months left before the statute of limitations in some states for filing a Vioxx lawsuit runs out. It isn't unusual for there

to be an in increase in cases filed shortly before the statute deadline. Mr. Seeger says he estimates there will be 30,000 Vioxx suits.

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URL for this article:
http://online.wsj.com/article/SB115133539472190796.html

Hyperlinks in this Article:
(1) NEJM Correction: http://content.nejm.org/cgi/reprint/NEJMx060029v1.pdf
(2) Stephen W. Lagakos, Ph.D., Time-to-Event Analyses for Long-Term Treatments —
The APPROVe Trial http://content.nejm.org/cgi/reprint/NEJMp068137v1.pdf
(3) Letters to the Editor:
http://content.nejm.org/cgi/reprint/NEJMc066260v1.pdf
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http://news.bbc.co.uk/go/pr/fr/-/2/hi/europe/5116312.stm

BBC NEWS
June 26, 2006
Drug firms attacked on marketing. Top European pharmaceutical firms are using unscrupulous marketing practices to promote their products, a consumer report says.

The Consumers International lobby group accused drugmakers of using the methods to get doctors to prescribe products and persuade consumers they need them.

It said there was a "shocking" lack of publicity about where the $60bn (£33bn) annual marketing spend went.

Drug firms say that they act within strict guidelines.

The Association of the British Pharmaceutical Industry (ABPI) told the BBC News website that for UK-based firms there was "a stringent and transparent code of practice that goes beyond the requirements of UK law and the industry regulator".

Sponsorships
Consumers International said it had analysed the selling techniques of many leading companies, including Bayer, GlaxoSmithKline and Johnson & Johnson.

The current regulatory framework is clearly insufficient to prevent
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systemic violations of marketing regulations
Consumers International

Richard Lloyd, the group's director general, said: "The pharmaceutical industry spends nearly twice as much on marketing as it does on research and development, yet consumers know next to nothing about where this money is going."

He called for a revision of marketing regulations to achieve "more transparency from drug companies".

In most Western markets direct advertising to consumers is banned. But Mr Lloyd said there were other methods drug companies were using to influence opinion.

These include the sponsoring of patient lobby groups, funding disease awareness campaigns and use of hospitality packages for medical experts.

As producers of life-saving medicines it is important that we ensure doctors know full details ABPI

The report cites sponsorships by such firms as Eli Lilly and Pfizer. The latter, the maker of Viagra, sponsored a campaign by the Impotence Association which sported the Pfizer logo.

The report said only one of the firms studied, Orion Pharma, provided specific marketing budget information.

It also pointed to the "large numbers of serious, recent and repeated breaches of marketing codes".

This showed the "current regulatory framework is clearly insufficient to prevent systemic violations of marketing regulations".

However, the ABPI said the number of complaints raised showed the system, which had been strengthened this year, was working.

It said complaints from drug companies about fellow firms' activities showed the self-regulation was effective.

But it also said it was vital for doctors to know about products.

"There is no point having innovative new medicines if they remain unused," an association spokesman said.

Story from BBC NEWS:

http://news.bbc.co.uk/go/pr/fr/-/2/hi/europe/5116312.stm

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