Comparison of content of FDA letters not approving applications for new drugs and associated public announcements from sponsors: cross sectional study

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- Analysis: Presumed safe no more: lessons from the Wingspan saga on regulation of devices (*BMJ* 2014;348:g93)
- Analysis: Assessment of US pathway for approving medical devices for rare conditions (*BMJ* 2014;348:g217)
- Feature: Quality of evidence behind FDA approvals varies widely (*BMJ* 2014;348:g1075)

STUDY QUESTION

What reasons does the FDA give for non-approval of marketing applications for new drugs and certain biologicals and how does the content of their non-approval letters for drugs ("complete response letters") compare with associated subsequent public statements issued by drug sponsors (drug companies)?

SUMMARY ANSWER

Many (87%) FDA complete response letters identify safety and/or efficacy concerns. In many cases, sponsors did not issue a press release in response and, when they did, they omitted most (86%) of the FDA's reasons for not approving applications. Filings with the US Securities and Exchange Commission provided few additional statements matching those in the letters.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Because the FDA's reasons for not approving drug applications are rarely made public, press releases issued by sponsors are often the only publicly available source of information regarding these decisions. Press releases and other public statements issued by sponsors as a result of FDA complete response letters omit most of the statements in the letter. Sponsors' public statements are incomplete substitutes for the detailed information contained in complete response letters.

Participants and setting

All applications for licensing of new drugs and biologicals for which the Center for Drug Evaluation and Research of the US Food and Drug Administration (FDA) initially issued a complete response letter (n=61) from 11 August 2008 to 27 June 2013.

Design

Complete response letters and press releases were divided into discrete statements related to seven domains (general; efficacy; safety; clinical pharmacology; non-clinical studies; chemistry, manufacturing, and controls; labelling) and assessed to determine whether statements matched. Filings with the US Securities and Exchange Commission were also searched to identify additional matches.

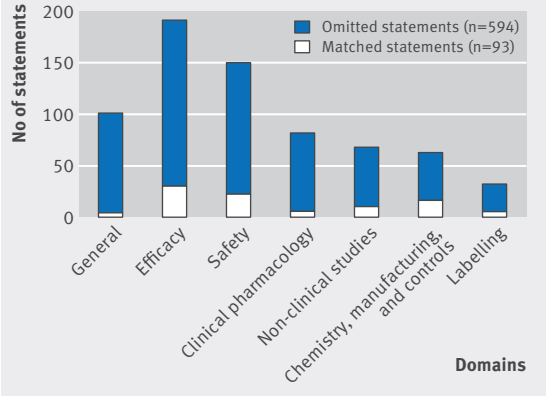
Primary outcome

The number and percentage of complete response letters with deficiencies in each of the domains and the number and percentage of such statements that appeared in the associated press releases.

Main results

A total of 687 statements were identified in all 61 complete response letters (median 8 statements per letter; range 1-38). Half of all statements were in the efficacy domain (191 statements; median 4 and maximum 17 per complete response letter) or the safety domain (150 statements; median 3 and maximum 11). For 18% of letters, no press release was issued and for an additional 21%, there were no matching statements. Ninety three (14%) of the 687 statements in the 61 complete response letters were matched in press releases. Inclusion of the Securities and Exchange Commission filings increased the matching rate to 15%. The matching rates for efficacy and safety were 16% and 15%, respectively. Seven letters reported higher mortality rates in treated participants; only one associated press release mentioned this fact. Twenty two press releases (36%) had one or more statements that could not be matched to a statement in the complete response letter, including seven statements (12% of 59 such statements) that raised questions about the regulatory process or standard or expressed disagreement with the FDA's interpretation of clinical data, and 5% (three) referred to data that the FDA neither reviewed nor cited in the letter.

Matched and omitted complete response letter statements by domain



Bias, confounding, and other reasons for caution

Firstly, we did not seek to characterise the accuracy of particular press release statements, only whether they contained a statement generally covering the same topic discussed in the complete response letter. Secondly, our reported matching rates could overstate the correspondence between letters and press releases. Thirdly, the practice of assigning letters and press release statements to domains and potentially limits the reproducibility of this research.

Generalisability to other populations

We included only complete response letters issued by the Center for Drug Evaluation and Research, and our results cannot be extrapolated to other FDA centres involved in product approvals.

Study funding/potential competing interests

This study received no funding, and there are no competing interests.

Selective reporting in trials of high risk cardiovascular devices: cross sectional comparison between premarket approval summaries and published reports

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STUDY QUESTION

How are characteristics of clinical trials and primary results for high risk cardiovascular devices reported in US Food and Drug Administration (FDA) documents compared with peer reviewed publications?

SUMMARY ANSWER

Many clinical trials for FDA approved high risk cardiovascular devices remain unpublished. Even when they are published, the study population, primary endpoints, and results can differ substantially from data submitted to the FDA.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

It is known that there is reporting bias of clinical data in new drug applications when they are published. This study adds data for new high risk cardiovascular device applications and shows that most clinical studies reviewed by the FDA are either not published or have clinically relevant discrepancies between FDA summaries and corresponding publications.

Participants and setting

All cardiovascular devices receiving FDA premarket approval from 1 January 2000 to 31 December 2010 had their FDA summary data and corresponding publications reviewed.

Design

A cross sectional comparison of FDA summary data and corresponding publications.

Primary outcomes

Clinical trial characteristics, primary endpoints, and safety and efficacy results were compared between the FDA documents and their corresponding publications.

Main results and the role of chance

There were 106 cardiovascular devices that received premarket approval from 1 January 2000 to 31 December 2010. FDA premarket approval documents for these devices contained a total of 177 studies, of which 86 (49%) were published as of 1 January 2013. These 86 publications corresponded to 60 distinct devices. The mean time from FDA device approval to publication was 6.5 months (range −4.8-7.5 years). The reported number of patients enrolled differed for 22 (26%) of the studies compared. Of 152 primary endpoints identified in the FDA documents, three (2%) were labelled as secondary, 43 (28%) were unlabelled, and 15 (10%) were not found in the corresponding publications. Among the primary results, 69 (45%) were identical, 35 (23%) were similar, 17 (11%) were substantially different, and 31 (20%) could not be compared.

Comparison between primary endpoints and results (n=152): FDA summaries and associated publications

	No (%)
Primary endpoints	
Labelled as secondary in corresponding publication	3 (2)
Not labelled in corresponding publication	43 (28)
Not found in corresponding publication	15 (10)
Primary results	
Identical between summary and corresponding publication	69 (45)
Differ by <5% between summary and corresponding publication	35 (23)
Differ by >5% between summary and corresponding publication	17 (11)

Bias, confounding, and other reasons for caution

There is no systematic listing in the FDA's publicly available documents of the trial principal investigators and clinical trial registries and so some publications might have been missed. In addition, we performed the Medline search on 15 January 2013, for publications up to 1 January 2013, and delays in indexing publications on Medline can exceed two weeks. To ensure that we did not inadvertently overlook a publication, we directly contacted the research divisions of device manufacturers and asked about any publications not found through our search algorithm. In many cases, we received no response from device manufacturers and therefore were unable to locate some studies that might have been published

Generalisability to other populations

These results are consistent with the previously identified selective reporting in drug trials, but how they compare with trials of other classes of devices is unknown. Our findings might be generalisable beyond the United States. In the European Union, independent organisations called notified bodies authorise device marketing. The evidence reviewed by notified bodies is not mandated to be publicly available, which makes it challenging to directly compare published data with data reviewed by notified bodies. As devices generally receive CE mark before FDA approval, however, it is less likely that clinical studies have been published in the medical literature at the time of CE mark, but it is unknown how this compares with data reviewed by the notified bodies. Increased transparency of clinical trial data reviewed by regulatory bodies before device approval and increased dissemination of such data through peer reviewed publications are consistent with the principles and goals of clinical research and would better serve patients and clinicians by better informing clinical decisions.

Study funding/potential competing interests

There was no funding for this study. RFR is a member of the FDA Circulatory System Devices Panel.

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- Feature: FDA official: "clinical trial system is broken" (*BMJ* 2013;347:f6980)
- News: US Congress considers new tracking system for medical devices after excessive recalls (*BMJ* 2012;344:e29150)
- News: Cardiologists call for a single European system to oversee medical devices (*BMJ* 2011;342:d3144)

Use and risks of surgical mesh for pelvic organ prolapse surgery in women in New York state: population based cohort study

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- Use and risks of surgical mesh for pelvic organ prolapse surgery
- For more on pelvic organ prolapse see our urological surgery specialty page at bmj.com/specialties/urological-surgery

STUDY QUESTION

How often is mesh used during repair surgery for pelvic organ prolapse, and is its use associated with complications and repeat surgery (reinterventions)?

SUMMARY ANSWER

Despite warnings released by the US Food and Drug Administration (FDA) since 2008, mesh based procedures for prolapse repair surgery in New York state have continued to grow and could be associated with an increased risk of urinary retention within 90 days and reinterventions within one year.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Mesh is thought to reduce recurrence rates after pelvic organ prolapse surgery and provide better anatomical results.
In this statewide study, risks of mesh based surgery were age specific, with a higher risk of reintervention in patients younger than 65 years and higher risk of urinary retention in patients aged 65 years and older.

Participants and setting

The study included 27 991 women undergoing pelvic prolapse repair surgery in New York state, from 2008 to 2011. A propensity score was used to match patients with or without mesh by patient characteristics (age, race, and insurance status), procedure year, concurrent hysterectomy or sling procedure, comorbidities, service type, facility academic status, ownership, and procedure volume.

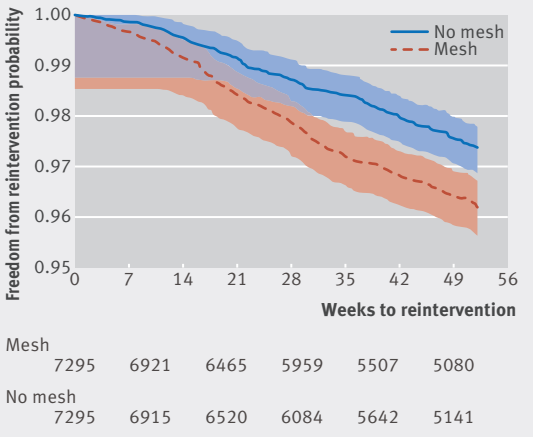
Design, size, and duration

A total of 7338 and 20 653 patients underwent prolapse repair procedures with and without mesh, respectively. After propensity score matching, there were 7295 patients in each group. One year follow-up was studied for reintervention following index surgery and mean follow-up time of the cohort was 45.1 weeks.

Main results and the role of chance

Mesh use increased by 44.7%, from 1461 procedures in 2008 to 2114 procedures in 2011. Complications following surgery were not common, irrespective of the use of mesh. In a propensity matched cohort, patients who underwent surgery with mesh had a higher chance of having a reintervention (mesh 3.3% *v* no mesh 2.2%, hazard ratio 1.47 (95% confidence interval 1.21 to 1.79)) within one year, and were more likely to have urinary retention (mesh 7.5% *v* no mesh 5.6%, risk ratio 1.33 (1.18 to 1.51)) within 90 days. In subgroup analyses, mesh use was associated with a higher risk of reintervention within one year in patients younger than 65 years, and a higher risk of urinary retention in those aged 65 years and older.

Time to reintervention within one year following pelvic organ prolapse surgery with or without mesh placed between 2008 and 2011 in New York state, after propensity score matching



Bias, confounding, and other reasons for caution

Although transabdominal procedures were reported to account for less than 25% of pelvic organ prolapse surgery, we were unable to distinguish between vaginal and abdominal mesh completely with current procedural or terminology codes. Information regarding the severity of pelvic organ prolapse cannot be captured through administrative data, but there has not been standard instruction on the use of mesh regarding the severity of pelvic organ prolapse. Our main outcome measure was the occurrence of reintervention, which was a patient centered endpoint.

Generalisability to other populations

Patients of all age groups and all insurance payers in New York state were included, and therefore can be generalized to a patient population who underwent surgery in the United States.

Study funding/potential competing interests

This study was funded in part by the US National Institutes of Health and FDA. AS received funding from the FDA for establishing the MDEpiNet Science and Infrastructure Centre, and is director of the FDA's Medical Device Epidemiology Network's (MDEpiNet) Science and Infrastructure Centre; BC is a senior investigator and JM is an analyst within the Weill Cornell Medical College's Patient Centered Comparative Effectiveness Program.

Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study

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- Editor's Choice: Slowing the opioid analgesic overdose epidemic (*BMJ* 2013;346:f730)
- News: Opioid overdose deaths rose fivefold among US women in 10 years (*BMJ* 2013;347:f4415)
- Research: Risk of death during and after opiate substitution treatment in primary care (*BMJ* 2010;341:c5475)

STUDY QUESTION

What is the relation between the receipt of concurrent benzodiazepines and opioid analgesics and death from drug overdose in patients receiving prescription opioids for the treatment of acute and chronic pain and pain from cancer?

SUMMARY ANSWER

Among veterans receiving opioid analgesics, receipt of benzodiazepines was associated with an increased risk of death from drug overdose.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Benzodiazepines are commonly involved in deaths from overdose related to opioid analgesics, a major cause of injury and mortality in the United States. This study showed that receipt of benzodiazepines was associated with an increased risk of death from drug overdose among veterans receiving opioid analgesics in a dose-response fashion.

Participants and setting

Participants were US veterans and patients in the Veterans Health Administration (VHA) who received opioid analgesics in 2004-09.

Design, size, and duration

This was a case-cohort study involving veterans who died from a drug overdose (n=2400) while receiving opioid analgesics and a random sample of veterans (n=420 386) who received VHA medical services and opioid analgesics over a six year period. We examined the association between history of benzodiazepine prescription, dose, type, and schedule and our main outcome measure, death from drug overdose, defined as any intentional, unintentional, or indeterminate death from poisoning caused by any drug, determined by information on cause of death from the National Death Index.

Adjusted hazard ratios for deaths from drug overdose while veterans were receiving opioid analgesics by history of benzodiazepine prescription and daily benzodiazepine dose

Model 1	
Benzodiazepine prescription history:	
None	1.00 (reference)
Former	2.33 (2.05 to 2.64)
Current	3.86 (3.49 to 4.26)
Model 2*	
Daily benzodiazepine dose (mg/day):	
>0-10	1.00 (reference)
>10-20	1.69 (1.42 to 2.01)
>20-30	2.34 (1.91 to 2.86)
>30-40	2.65 (2.10 to 3.33)
>40	3.06 (2.38 to 3.92

*Included only periods when veterans were currently receiving benzodiazepines.

Main results and the role of chance

Of the veterans who received opioid analgesics, 27% (12 069) also received benzodiazepines during the study period. About half of the deaths from drug overdose (n=1185) occurred when veterans were concurrently prescribed benzodiazepines and opioids. Risk of death from drug overdose increased based on history of benzodiazepine prescription: the adjusted hazard ratios were 2.33 (95% confidence interval 2.05 to 2.64) for former prescriptions versus no prescription and 3.86 (3.49 to 4.26) for current prescriptions versus no prescription. Risk of death from drug overdose increased as daily benzodiazepine dose increased. When compared with clonazepam, temazepam was associated with a decreased risk of death from drug overdose (0.63, 0.48 to 0.82). Benzodiazepine dosing schedule was not associated with risk of death from drug overdose.

Bias, confounding, and other reasons for caution

Because benzodiazepines were more likely to be prescribed to those with substance use and other psychiatric disorders, conditions that carry their own risk for death from overdose, the association with receipt of benzodiazepines could be partially explained by these underlying conditions or the severity of those conditions. We attempted to deal with this possibility by adjusting for characteristics of patients at baseline, including demographic information, medical and mental health diagnoses, and the daily opioid dose, in a multivariable model and by distinguishing between periods of current and former receipt of benzodiazepines. Nonetheless, because those with current receipt of benzodiazepines might have had more severe conditions for which benzodiazepines were prescribed than those with former receipt, some residual confounding could exist. Thus it is important to note that within the present study, benzodiazepines might be better thought of as a marker of risk with unknown direct causal links to death from overdose.

Generalisability to other populations

This study involved only US veterans, mostly men, who received care in the VHA. Whether results are generalisable to other populations with different risk factors for death from drug overdose is unclear.

Study funding/potential competing interests

This work was supported by funding from the Veterans Affairs Health Services Research and Development Service and the National Institutes of Health. The sponsors had no role in the study design, data analysis, or writing of the manuscript.