Original Research

# Davids versus Goliaths: Pharma and academia threats to individual scientists and clinicians

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## Background

We previously described experiences of clinicians who published adverse drug reaction reports. We now report on threats and intimidations leveled against clinicians and scientists who received publicly documented threats after communicating safety, efficacy, or data integrity findings contrary to corporate interests.

## Methods

Data on threats and intimidations were obtained from transcripts of governmental hearings or agencies, university-affiliated reports, media interviews, and investigative journalism articles. Content and timing of threats and intimidation, subsequent harms, numbers of persons seriously injured or who died from individual toxicities, financial payments from sponsors related to safety, efficacy, or data integrity concerns, and civil settlements and criminal findings were evaluated.

## Findings

Twenty-six individuals who communicated safety, efficacy, or data integrity concerns were targets of threats and intimidation from corporate employees (twenty-three individuals) or regulatory personnel (three). Seventeen individuals identified instances where pharmaceutical sponsors submitted fraudulent data in support of regulatory approval of a drug or device. Scientist and clinician communications were followed by drug/device withdrawals (fourteen drugs/devices), black box warnings (six drugs), withdrawal of a sponsor's application for regulatory approval (one device), and delay of approval of a sponsor's application for regulatory approval (one drug). Actions mainly occurred after persons communicated with pharmaceutical employees (fourteen). Intimidation efforts by corporate personnel included threats of lawsuits (eighteen individuals), hiring private investigators (nine), and public disparagement at conferences (eleven). Related intimidation efforts carried out by academia or regulatory agency superiors included threats of: loss of positions (six), loss of grant funding (two), delays in decisions regarding tenure (two); or reassignment to a low-level position (one). Academic harms included lost: hospital or university appointments (nine and six, respectively), grant funding (two), chairperson title of an international clinical trial group (one), and journal editorial board position (one). Corporate harms included payment of $1 million to defense attorneys in three cases filed against clinicians.

## Interpretation

Threats and intimidation carried out by corporate employees and/or academic supervisors followed public communication of concerns regarding patient safety, drug efficacy, or data integrity, including instances where sponsors were identified as having submitted fraudulent data to regulatory or government agencies. Consideration should be given to filing criminal charges against pharmaceutical executives who are discovered by scientists or clinicians to have knowingly submitted fraudulent data to regulatory or governmental

agencies, rather than causing the scientists and clinicians who submit such reports to risk losing their reputations and occupations.

## INTRODUCTION

Reluctance to report research findings may arise from fear of retaliation from pharmaceutical or device corporations when findings are contrary to corporate interests.[1,2] Research is increasingly funded by pharmaceutical corporations, which introduces bias toward publication of favorable results.[3] We previously reported that actions taken by industry and academic leaders against clinicians who authored adverse drug reaction reports were mostly punitive.[1,2] Case studies describe threats from pharmaceutical executives to clinicians when findings contrary to corporate interests were communicated. Attacks on scientists' and clinicians' character or their methodologies are threats described in case narratives, although no systematic review of threats and intimidation has been reported. In our study of fourteen clinicians who authored oncology-related serious adverse drug reaction reports, 83% experienced professional harms.[1] In our study of eighteen clinicians who authored serious drug reaction reports for drugs with $1 billion or more in annual revenue, 61% experienced professional harms.[2] Our objective is to expand upon case report literature and these two case series on harms to report on threats and intimidations targeted against clinicians and scientists who communicated, or attempted to communicate, findings contrary to corporate interests.

## METHODS

The principal investigator of a National Institutes of Health (NIH)-funded pharmacovigilance initiative established at the University of South Carolina (2011–2020) and at Northwestern University Feinberg School of Medicine (1998–2010) queried by email all clinicians or scientists at over fifty universities in the United States, Europe, Canada, and Asia who had previously served as first or last author of SONAR or RADAR peer-reviewed publications identifying important but previously unrecognized serious adverse drug reactions (SH, DMA, BD, TBH, BS, BJW, PSR, PRY, MLF, WJH, JMR, HST, JMM, MWS, KK, STR). These individuals were asked to identify instances where they personally presented findings contrary to corporate interests and subsequently experienced publicly documented threats from pharmaceutical manufacturers. These clinicians or scientists were asked to identify colleagues (clinicians or scientists) who had experienced similar publicly documented threats. Overall, twenty clinicians and six scientists included in this analysis had been publicly threatened or intimidated after communicating, or attempting to communicate, findings related to safety, efficacy, or data integrity between January 1, 1980, and December 31, 2020, and quoted in publicly available documents specifics of threatening activities (Table 1). Individuals identified as potential candidates for this study by RADAR/SONAR collaborators were excluded if public documentation of threats was unavailable. Using publicly available documents, information about motivations for conducting research with findings contrary to corporate interests and timing of related threats and intimidation was abstracted. Weekly, three research assistants who had independently abstracted the study data and two study senior investigators (CLB, SH) reviewed the abstracted data. Individual researchers reported on assessments of researcher motivation and reporting of threats, intimidation, and harms against clinicians or scientists of interest. Additional analyses provided information on time in months between threats and intimidation, harms, and regulatory notifications and also the magnitude of the costs incurred by patients, academic institutions, and pharmaceutical corporations. Qualitative analyses characterized scientists' and clinicians' primary motives for communicating their findings based on statements included in publicly available documents into the following categories: concerns related to patient safety, drug efficacy, or data integrity. This framework was developed with consultant input in our 2019 and 2021 studies on harms of reporting serious adverse drug reactions.[1,2]

### DATA

Data sources for threats included publicly available reports from government agencies, Congressional hearings, and an investigation commissioned by the Canadian Association of University Teachers, documents produced for jury trials and settlement agreements, Department of Justice press releases, and news articles primarily from *The New York Times*, *The Wall Street Journal*, *The Guardian*, *The New Yorker*, and *Science*. Data focused on information about manufacturers; clinician and scientist authors' experiences of threats, intimidation, and harms; numbers of persons experiencing toxicities related to drugs or devices that were the focus of communications; payments for injuries/deaths associated with toxicities; and settlements or fines paid to government programs or affected patients. Interrater agreement was 98%, with one disagreement over whether the research had focused on patient safety or data integrity. The study's principal investigator resolved this disagreement, supporting the data integrity focus. Safety-related drug/device withdrawals were identified from FDA's public announcements. Additional information included publicly reported dates of FDA approval, communications of findings, details of publication, boxed warnings, and withdrawal of drugs or devices from marketing.

### ANALYSES

Threats and intimidation were characterized according to concepts described in case reports as being against the "messenger" and/or against the "message." For several individuals, threats and intimidations were followed by harms, including: loss of employment, job demotion, delayed academic tenure decisions, personal payments of legal fees for lawsuits filed against individual clinicians and scientists after public communication of clinical or basic science findings, loss of grant funding, and loss of academic positions.[2] Formal documentation of corporate efforts to harm careers

**Table 1. Overview of clinicians and scientists who received threats after publicly communicating findings contrary to corporate interests**

| Person and concern [data source] | Avenue through which concerns were first communicated | Concerns | First threat or intimidation tactic | Funder of source of concern |
|---|---|---|---|---|
| Clinical Trial Data (n=10) | | | | |
| 2001: Topol[4–8] | Manuscript galleys were forwarded by Topol to Merck for review and comment | Rofecoxib associated cardio-vascular toxicity | Merck sent letters to US physicians alleging that Topol's data analysis was wrong and attempted to "trash" Topol[5] | Merck |
| 2001: Singh[9] | Singh reported concerns to Merck | Rofecoxib associated cardio-vascular toxicity | Pharmaceutical executive called Singh's Chairman and requested that Singh be fired[9] | None |
| 1982: Wilmshurst[10–13] | 1982: Presented safety and efficacy findings to manufacturer of amrinone[12] | 1982: Clinical studies with amrinone identified severe toxicity and minimal benefit | 1982: Corporate executives initially offered Wilmshurst funds not to publish his findings. After this offer was refused, corporate executives threatened a lawsuit if the findings were submitted to a journal[12] | Grants from the St Thomas's Hospital Cardiac Research Fund; the St Thomas's Hospital Endowment Committee. |
| 2003: Henke[1,14] | 2003: Lancet | Epoetin - Mortality and tumor growth in the oncology setting | 2007: CEO of the manufacturer of an erythropoiesis stimulating agent (ESA) threatened Henke at a meeting at corporate headquarters | Roche |
| 1999: Buse[15,16] | 1999: Presented at medical society meeting | Rosiglitazone - Cardio-vascular toxicity | 1999: GlaxoSmith-Kline Research and Development Chair reported that Buse was "for sale" made other negative comments to Buse's department chair. | GSK |
| 2005: Wilmshurst[12,17–19] | Presented findings to NMT Inc on safety and efficacy of the STAR-Flex device that was evaluated in the MIST clinical trial. | Patent foramen ovale closure device - Clinical trial results: 33% of sixty-five patients with device implanted to close patent foramen ovale continued to have shunts | 2006: NMT Inc threatened libel suit in United Kingdom if Wilmshurst published his findings from the MIST trial. Four libel suits were filed beginning in 2007 | NMT Inc. |
| 1996: Olivieri[20] | Research Ethics Board sub-mission | Deferiprone - Lack of efficacy and severe toxicity | 1996: Law suits were threatened and then filed[20] | Medical Research Council of Canada; Apotex |
| 2005: Blumsohn[21–23] | 2004: wrote to editors of Journal of Bone and Mineral Research stating that abstracts had been submitted with his name but without his know-ledge | Risedronate - Omission of data on bone resorption findings for 40% of risedronate-treated clinical trial participants | The University of Sheffield threatened academic discipline and possible termination.[23] Blumsohn later received a severance agreement. | Proctor and Gamble |
| 2010: Jiang[24] | 2010: Draft of meeting abstract sent to company; presentation was blocked. | Risedronate - Irregularities in reporting of bone radiograph findings among clinical trial participants | Censure by the University of Sheffield for abstract submission, in alleged breach of prior contract with another pharma company.[24] | Procter and Gamble |

| Person and concern [data source] | Avenue through which concerns were first communicated | Concerns | First threat or intimidation tactic | Funder of source of concern |
|---|---|---|---|---|
| 1990: Dong[25,26] | 1990: Study report sent to manufacturer | Thyroxine - Similar efficacy of generic and brand-name drug. | 1995: Boots Pharma threatened litigation if Dong submitted her findings for publication, hired private investigators to follow her, and attacked her reputation | Boots Pharma |
| Meta-analysis (n=2) | | | | |
| 2007: Bennett[1,27–29] | Proceedings of ASCO | Epoetin and darbepoetin - Mortality and tumor growth | 2007: Vice President for Research of Amgen, an ESA manufacturing corporation threatened Bennett at a medical conference | National Cancer Institute |
| 2004: Mosholder; (Meta-analysis )[30] | FDA Advisory Board meeting presentation about anti-depressant associated suicide[30] | Anti-depressant - Association of suicidality in children and adolescents | 2004: FDA officials conducted internal investigation to identify who had "leaked" Mosholder's findings to the press | Employee of FDA |
| Case series (n=3) | | | | |
| 2007: Frachon [9,70,123] | L'Agence nationale de securement du médicamentent des produits de sante presentation in France | Cardiac valvular problems with benfluorex | Servier executives threatened and filed lawsuits against Franchon | INSERM |
| 1996: Kern[31–33] | 1996: Draft abstract presented to Micro-fibres Inc. for review and comment | Textile product - Described "flock worker's syndrome" among workers at Microfibres, Inc | Microfibres threatened to file suits if the abstract were presented at a medical conference. | None |
| 2006: Thomsen[30,34–37] | Presented findings at a medical conference | Gadodiamide - Nephrogenic systemic fibrosis developed among chronic kidney disease patients on dialysis after gadodiamide contrast injection for magnetic resonance angiogram | 2009: General Electric threatened libel suit. A lawsuit was filed in the United Kingdom. | None |
| Registry data (n=2) | | | | |
| 2003: Mangano[33] | Published manuscript with safety findings in the NEJM[33] | Valdecoxib-associated risks of heart attack and stroke | Pfizer threatened and filed a lawsuit; hired a person to steal data from Mangano's laboratory. | Pfizer |
| 2006: Graves [38,39] | Findings were presented at orthopedic surgery conference | DePuy Prosthetic Hips - Identified high failure rate of hip prostheses failure | 2007: DePuy sent out "white paper" claiming that Grave's results were due to poor operative skills of surgeons | Australian Orthopedic Association |
| Case-control study (n=3) | | | | |
| 2005: Graham[40–42] | Graham reported findings at a Senate committee meeting | Rofecoxib associated infarct and sudden death toxicity | FDA officials sought transfer of Graham to Commissioner's Office; threatened disciplinary action; told journal editors that Graham was "a dangerous demagogue and bully" | Employee of FDA |

| Person and concern [data source] | Avenue through which concerns were first communicated | Concerns | First threat or intimidation tactic | Funder of source of concern |
|---|---|---|---|---|
| 1996: Rich[43–46] | Rich presented at the American Thoracic Society Conference | Anorexin drugs - Primary pulmonary hypertension | After a television interview, Wyeth Vice President threatened harm if Rich participated in another interview | Institut de Recherches Servier and the Belgian Federal funds |
| 2000: Brass[47,48] | Findings presented to Roche | Phenyl -propanol-amine (PPA): Identified possible association of PPA products with hemorr-hagic stroke | 2000: Pharmaceutical employee threatened to sue Brass if he sent safety data to FDA; also disparaged Brass to others | Roche |
| Clinical observation (n=7) | | | | |
| 1988: Cliché[49,50] | Cliché reported clinical details of two patients[49,50] | Anorexin drugs - Each case developed severe cardiac disease | Corporate employees in drug safety department warned that bad things would happen if more adverse events were reported | None |
| 1991: Healy[51] | Presented suicide risk concerns at the U of Toronto | Anti-depressant - Identified anti-depressant associated suicide risk | 2000: Pharmaceutical corporation hired private investigators to tail Healy | None |
| 2007: Nargol[52] | Findings were presented to DePuy | DePuy Prosthetic Hips - Identified risks of prosthetic break-down | 2007: DePuy claimed that Nargol's procedures were faulty | None |
| 2003: Hampshire (FDA Adverse Event Reports review)[53,54] | Presented findings to FDA supervisor | Ivermectin and pyrantel was linked to deaths and toxicity of 522 and 5,000 dogs, respectively, in FDA safety database. | Wyeth hired private investigators, asked FDA commissioner to reassign Hampshire; FDA supervisor requested criminal charges be filed against her[53] | FDA Employee |
| 2000: Hayes (animal studies)[55,56] | Findings were submitted to EPA | Atrazine - Feminization of atrazine-exposed male frogs | 2000: Threatened by corporate vice president | Syngenta initially; then, National Science Foundation |
| 2002: Chapela (plant studies)[57,58] | 2002: Findings were submitted to Nature | Maize corn - Abnormalities in genetically modified product | 2002: Threatened by corporate executives that professional harms would occur | None |
| 2014: Narchasm[59–61] | 2014: Presented his findings to a Wall Street Journal Reporter | 2014: Uterine morcellator was linked to spread of uterine sarcoma to lungs | 2014: Device manufacturer threatened libel suit; hired private investigators; spread rumors about Narchasm to medical community[59,60] | None |

of clinicians or scientists were sought in materials obtained via discovery during court proceedings or as part of government- or university-commissioned investigations.

Clinicians' and scientists' stated summaries of personal experiences with the communication process were categorized according to whether the relevant employer was described as supportive, antagonistic, or neutral to communication efforts.

Median and ranges for time from FDA approval date to public reporting, receipt of perceived threats by clinicians or scientists, box warning addition, or drug/device withdrawal from marketing were calculated. Total criminal fines paid by corporations included in this study were also determined.

### ROLE OF THE FUNDING SOURCES

The study sponsors had no involvement in study design, data collection, analysis, data interpretation, report writing, and the decision to submit.

## RESULTS

Multiple sources document clinicians' and scientists' findings of harm or lack of efficacy of pharmaceuticals and medical devices.[10,14,21,24,43,47,55,62–71] These communications described toxicity or deaths,[11,14,43,47,55,62–68] failure to identify efficacy,[10,69–71] mechanism of action,[21] and radiographic findings (Tables 1 and 2).[24] A median of ten years separated dates of communications of findings and regulatory approval of relevant drugs or devices (range: zero years prior to fifty-eight years following FDA approval). A median of two years separated dates of initial communication to drug/device withdrawal or black box warning (Figures 1A and 1B).

### PATIENT IMPACT

Of the twenty-six drugs and one device included in this study, twelve drugs and two devices were withdrawn from marketing, black box warnings were added to labels of six drugs, one device's application for FDA approval was withdrawn, and one drug's initially proposed submission of an FDA application for approval was delayed by thirteen years (Figures 1A and 1B). These responses occurred at a median of two years following initial scientist or clinician public communication efforts.

An estimated one million persons developed serious toxicities or died from adverse drug reactions from drugs and devices discussed in this article (Table 4). Fenfluramine-phentermine was implicated in serious injury or death in three hundred thousand persons.[104] A related drug, benfluorex, was implicated in two thousand deaths.[78] Ivermectin/pyrantel was associated with 552 reports of deaths occurring among dogs.[105] Between 88,000 and 140,000 serious coronary heart disease events in Americans were estimated to have been caused by rofecoxib.[42]

### PAYMENTS

Payments to patients and/or government agencies following investigations of sixteen adverse drug or device reactions exceeded $25 billion (Table 4). Median corporate settlements for civil, criminal, and shareholder lawsuits were $761 million (range: $3.6 million for benfluorex to $22 billion for fenfluramine-phentermine).[50,106] Sales of four drugs decreased markedly following FDA meetings on toxicities of four drugs (epoetin and darbepoetin dropped from $7.1 billion collectively in 2007 down to $3 billion collectively in 2008),[107] gadodiamide (dropped from $1 billion in 2006 down to < $100,000 by 2009),[36] and rosiglitazone (dropped from $3 billion in 1999 down to $680 million in 2008).[108] For fourteen additional drugs and one device (Figure 1B), sales decreased to zero following of removal of the product from the market.

### DATA SOURCES

Nine communications were based on reviews of clinical trial data (Table 1). Five instances involved clinicians and scientists who were initially prevented from presenting their findings. One bone physician reported being unsuccessful in obtaining original phase III clinical trial data for an industry-sponsored trial in which he had conducted laboratory studies for the study popuation.[21] A pharmacy professor reported being denied corporate permission to publish results of an industry-sponsored clinical trial in the *Journal of the American Medical Association* although she had designed the trial, had been the study's principal investigator, and had received an acceptance letter from an editor at the journal.[69] A radiologist reported being denied permission to report bone radiograph findings at a medical conference in Europe from a pharmaceutical company–sponsored phase III clinical trial that had been completed eight years previously and for which the study data had been stored at her academic institution.[24] A hematologist confidentially reported to the Hospital for Sick Children's Research Ethics Board that data from then unpublished phase II and phase III clinical trials identified lack of sustained effectiveness of the then-investigational iron chelating drug.[20] She revised the consent forms, submitted revised forms to the Research Ethics Board, and these were approved. Four days later, the corporate sponsor prematurely terminated the clinical trials and issued threats of lawsuits. Study patients enrolled prior to the termination continued to receive the experimental drug under revised forms. Relevant safety data, with the hematologist as first author, were subsequently published in the *New England Journal of Medicine*.[20] Lawsuits against the hematologist followed many threats issued by the corporate sponsor and were filed many years after the *New England Journal* publication. An epidemiologist reported identifying rofecoxib-associated cardiovascular toxicity following review of a phase III clinical trial study report.[40] The epidemiologist, who is a senior investigator at the Food and Drug Administration, was informed by his superiors that he would not be allowed to present his findings at a medical conference in Europe. Subsequently, these findings were published a year later in an article that appeared in *The Lancet*.[42]

**Table 2. Communications by scientists and clinicians.**

| Communication by scientists contrary to corporate interests | Corporate statement (or corporate consultant's statement) reporting findings contrary to the scientists' findings or identifying purported methodologic limitations of the scientists' studies | Third party statement on the specific drug or device | Retraction of report or statement of concern |
|---|---|---|---|
| Drug or device withdrawn from marketing (n=5) | | | |
| 2001 (rofecoxib): Topol, Mukherjee, Nissen, et al (JAMA) reported increased risk of cardiovascular events with COX-2 inhibitors. (Findings were from clinical trial data from the Bombadier et al study that had not been initially reported.[6] | 2000: Bombadier et al [NEJM] Merck sponsored clinical trial reports no cardiovascular risk data for rofecoxib.[72] | 2004: Topol reported to a Senate committee that the 2000 NEJM publication did not include the actual number of deaths in the two arms of the Bombadier NEJM publication in 2000.[73] | Curfman, Drazen. NEJM (2005). Expression of concern: Bombadier et al[74] |
| 1999 (phenylpropanolamine or PPA): Brass communicated safety concerns with PPA-containing cold products to scientists at Roche pharmaceuticals[75] | 1999: Upon learning that the study by Brass and others found an association of stroke with PPA use, pharmaceutical makers opened an assault on methodology and integrity of the researchers.[75] | 2004: FDA officials said they did not move faster [to withdraw PPA] because industry's efforts to discredit Yale results delayed the final report. "There were obvious concerns that we weren't getting the data because it was being held up by the people who sponsored the study," said the director of FDA's Division of Over-the-Counter Drug Products.[75] | 2004: FDA recommended withdrawal of > 100 PPA products, including popular cough and cold brands such as Robitussin CF and Dimetapp, and appetite suppressants such as Dexatrim and Acutrim.[75] |
| 2009 (benfluorex): Frachon reports case series identifying severe valvular disease with benfluorex to France's Agencie nationale du medicament et des prduits de sante (ANSM).[76] | 2021: Lawyers for Servier (benfluorex's manufacturer) stated that they were unaware prior to 2009 of links of benfluorex with heart valve or lung disease.[50] | Benfluourex was withdrawn from Spain, Italy, the United States, and the European Union (between 1997 and 2004), and France (2009).[77] | 2021: Servier was found guilty of "aggravated deception" and "manslaughter and involuntary injury" for its benfluorex marketing.[78] |
| 2000 (atrazine): Unpublished Syngenta report on adverse effect from atrazine. Hayes was told that his Syngenta contract did not allow him to publish. With NSF funding, Hayes published same findings using independent funding. Male frogs were demasculinized and feminized after atrazine exposure.[55,79] | 2003: Atrazine's manufacturer (Syngenta)-funded researchers who reported that laboratory treatment of Xenopus laevis at 25 parts per million atrazine, but not at lower concentrations, led to intersex frogs.[80] | 2003: A special Environment Protection Agency panel concluded that there is inconsistency across studies and more studies are needed.[79] In 2003, European regulators banned atrazine due to an inability to keep atrazine levels in water below 0.1 parts per billion.[81] | None |
| 1982 (amrinone): Wilmshurst communicated lack of benefit and increased risks of serious adverse events with amrinone based on case series to the manufacturer, Sterling Winthrop.[12,82] | 1978: Harvard Medical School cardiologists and Sterling-Winthrop employees and consultants reported improved cardiac function among eight amrinone-treated congestive heart failure patients.[82,83] | 1983: Wilmshurst reported to the Netherland Committee for the Evaluation of Medicine that Sterling-Winthrop had sent the Committee falsified clinical records on amrinone-treated patients with adverse event information deleted.[12,82] | 1985: The Guardian newspaper reported that Sterling-Winthrop submitted fabricated clinical trial data from Wilmhurst's study to regulatory agencies.[82] |
| Drugs where black box warnings were added to product label (n=5) | | | |
| 2007 (epoetin and darbepoetin): Bennett shared draft manuscript and meta-analysis which identified mortality risks of erythropoiesis stimulating agents with a then Vice-President for Research at an | Glaspy et al (2010) published an Amgen sponsored meta-analysis finds no mortality risks with erythropoiesis stimulating agents[84] | Bohlius et al published a [Lancet] (2009) German Federal Ministry of Education and Research grant-funded meta-analysis identified mortality risks with erythropoiesis stimulating agents.[85] | FDA 2008 Oncology Drug Advisory Committee (ODAC). Identified mortality risks with erythropoiesis stimulating agents[86] |

| Communication by scientists contrary to corporate interests | Corporate statement (or corporate consultant's statement) reporting findings contrary to the scientists' findings or identifying purported methodologic limitations of the scientists' studies | Third party statement on the specific drug or device | Retraction of report or statement of concern |
|---|---|---|---|
| erythropoiesis stimulating agent manufacturer (now a Vice-President for research at a different large pharmaceutical manufacturer)[29,62] | | | |
| 2007 (rosiglitazone): Nissen and Wolski report a meta-analysis in NEJM that identified increased risk of myocardial ischemic events associated with rosiglitazone.[87] | 2007: GlaxoSmithKline statistician reports at an FDA Advisory Committee meeting results from a meta-analysis that did not identify increased myocardial ischemic risks with rosiglitazone.[88] | 2007: FDA statisticians report at an FDA Advisory Committee meeting results from a meta-analysis that identified increased risk of myocardial ischemic events associated with rosiglitazone.[89] | 2010: FDA Statement of concern letter. This letter was addressed to the FDA Commissioner and reported that the "totality of the evidence suggests that GSK was aware of possible cardiac risks associated with rosiglitazone years before such evidence became public."[90] |
| 2003 (paroxetine): Mosholder submits a memorandum to FDA supervisors indicating that his analysis of two clinical trials did not identify any benefits of paroxetine for children with depression.[30] | 2007: GlaxoSmithKline statisticians reported to an FDA Advisory Committee that pooled analysis of the two trials found positive benefit with paroxetine.[88] | 2007: An FDA statistician reported to an FDA Advisory Committee that his analysis of individual clinical trials identified no benefit with paroxetine for children with depression.[89] | 2004: New York Attorney General requires GlaxoSmithKline to post entire clinical information for all sponsored trials. NY Attorney General reported GSK had previously withheld data.[91] |
| 2007 (gadodiamide): Thomsen reports at a scientific conference 20 cases of gadodiamide-associated nephrogenic systemic fibrosis.[30] | 2008: Danish Medicines Agency reports that a 2007 White Paper from the manufacturer of gadodiamide (General Electric) identifies no risk of nephrogenic systemic fibrosis | 2008: Danish Medicines Agency report on gadodiamide identified several cases of gadodiamide-associated nephrogenic systemic fibrosis.[92] | 2008: Danish Medicines Agency requested that General Electric respond to allegations that safety-related information had been withheld from radiologists at Herlev Hospital.[92] |
| 1991 (paroxetine): Creaney and Healy published two cases of paroxetine-associated suicide.[93] | 2001: Keller al reported efficacy and no suicide risk with paroxetine treatment of adolescents with depression.[94] | 2004: FDA reviewer reports meta-analysis identifying increased suicide risks with selective serotonin release inhibitor (SSRI) anti-depressants. This report is leaked to the public by the Alliance for Human Research Protection[95] | None |
| Device for which the manufacturer withdrew its application for approval from the FDA (n=1) | | | |
| 2006 (cardiac device): Wilmshurst, a co-principal investigator of the Migraine Intervention with StarFlex Technology (MIST) trial communicated serious safety concerns with the patent foramen ovale closure device.[12] | 2008: Andre Dowson MD and other NMT Inc funded researchers reported that migraine intervention with STARFlex was beneficial. A co-principal investigator, Wilmshurst, was not a co-author of this report.[96] | 2006: Wilmshurst and others showed that the manufacturer (NMT Inc) submitted data to the FDA by NMT Inc that were not consistent with the actual clinical findings.[81] A review of the original case report forms indicated that data submitted by NMT Inc were falsified.[97] | 2008: The Guardian newspaper reports that NMT Inc had submitted fraudulent data to the FDA in 2008.[12] |

| Communication by scientists contrary to corporate interests | Corporate statement (or corporate consultant's statement) reporting findings contrary to the scientists' findings or identifying purported methodologic limitations of the scientists' studies | Third party statement on the specific drug or device | Retraction of report or statement of concern |
|---|---|---|---|
| Drug for which the manufacturer's application to the FDA was delayed for several years (n=1) | | | |
| 1996 (deferiprone): Oliveri et al reported to the relevant Research Ethics Board lack of adequate effectiveness and increased hepatic iron concentrations among deferiprone treated persons in clinical trials. This information was also presented at the 1996 American Society of Hematology Conference | 1999: A paper by Diav-Citrin et al reports on an Investigation into variability in therapeutic response to deferiprone using selected clinical trial data[98] | None | 2019: The senior author of Diav-Citrin et al was ruled by a University of Toronto committee to have committed research misconduct with respect to this publication. Request to the University of Toronto for retraction of this paper. Public assurance for this retraction had been initially announced in 2002.[99] |
| Drug for which no regulatory changes were made (n=3) | | | |
| 1999 (thyroxine): Draft report of a study submitted to Boots Pharmaceuticals by Dong et al. finds bioequivalence of generic and branded drug. | Mayor et al (1995). Limitations of comparing branded versus generic thyroxine (clinical trial data). Focused on research questions.[25] | None | None |
| 2007 (risedronate): Blumsohn et al report a relationship of fracture risk to bone resorption in a clinical trial study initially reported in 2003[22] | 2003: Eastell et al report an abstract with 40% of the clinical trial data purposely omitted. Blumsohn as co-author was unable to see the entire data set. In 2007, Eastall reports a statistical re-analysis of the 2003 data and could not confirm one of the three of findings reported in 2003 from the trial.[100,101] | 2009: Eisman, Lorenzo write that the Journal of Bone Mineral Research did not view itself as an investigative body. They had requested in 2006 that Blumsohn submit a publishable letter and if accepted, Eastell would be asked to respond. Eastell responded to the journal late in 2007. Addressed scientific research considerations.[102] | Journal of Bone Mineral Research: Statement of concern. [2006] Concern was expressed that a statistical re-analysis of the Eastell 2003 data, as promised in 2006, had not been received.[17] This re-analysis was then received in 2007.[102] |
| 1997 (textile fibers): Kern submitted a draft version of an abstract to Microfibres that described eight patients with interstitial lung disease following occupational exposure at a textile factory[31] | 1998: A Microfibres spokesperson noted that the draft abstract listed chemicals for production that they considered proprietary; Kern's abstract purportedly violated confidentiality agreement; and abstract reached premature conclusions.[103] | 1997: The Centers for Disease Control and Prevention recognized a new syndrome "Flock Worker's Lung, based on the abstract information."[32] | Not applicable. |

Five communications were from clinicians and scientists who were prevented from presenting findings of phase III clinical trial results. A radiation oncologist publicly reported and published findings in the Lancet of increased mortality rates with erythropoietin administration to cancer patients during an industry-sponsored phase III clinical trial.[14]

A gastroenterologist and a cardiologist independently and publicly reported cardiovascular toxicity with rofecoxib administration.[4,9] An endocrinologist reported rosiglitazone-associated cardiovascular mortality after reviewing results of several phase III clinical trials.[109]

Case series were published by five clinicians describing patient safety concerns. One pulmonologist and one cardiologist reported pulmonary and cardiac safety concerns following short-term off-label use of a diabetes drug, benfluorex.[63,64] A radiologist and a nephrologist reported chronic kidney disease patients who developed nephrogenic systemic fibrosis following magnetic resonance angiograms performed with a gadolinium-based contrast agent.[65]

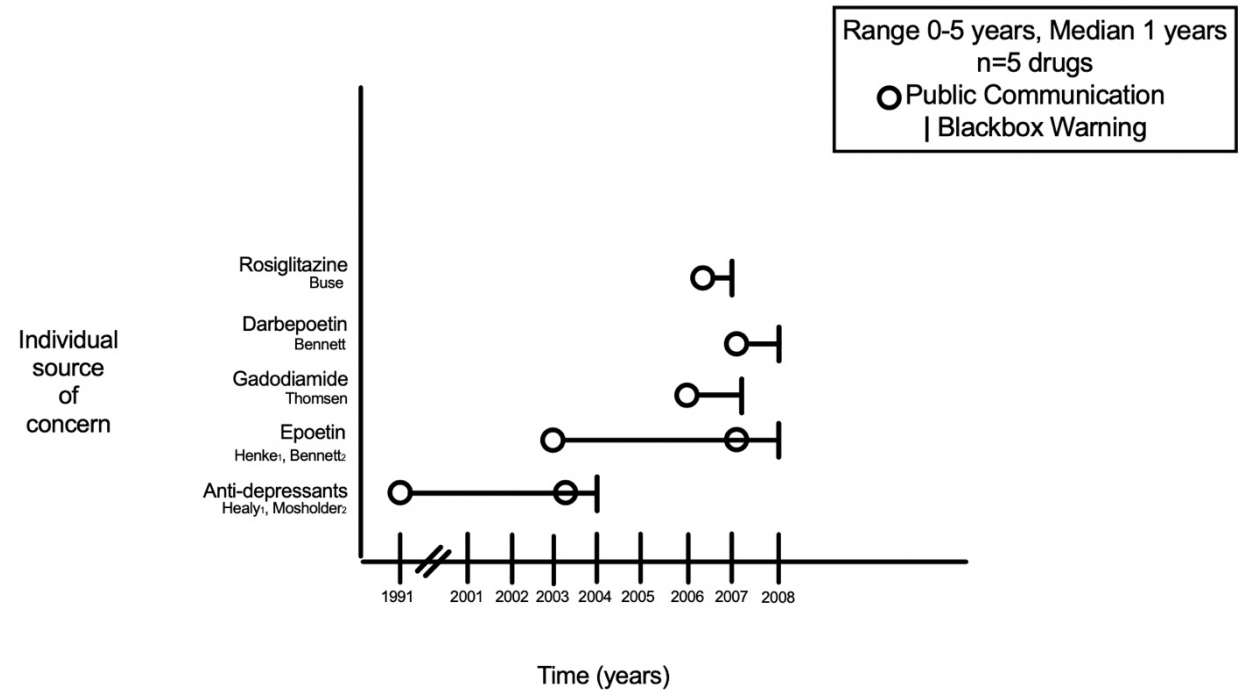


**Figure 1A. Time in Years from Public Communication to Drug/Device Black Box Warning**

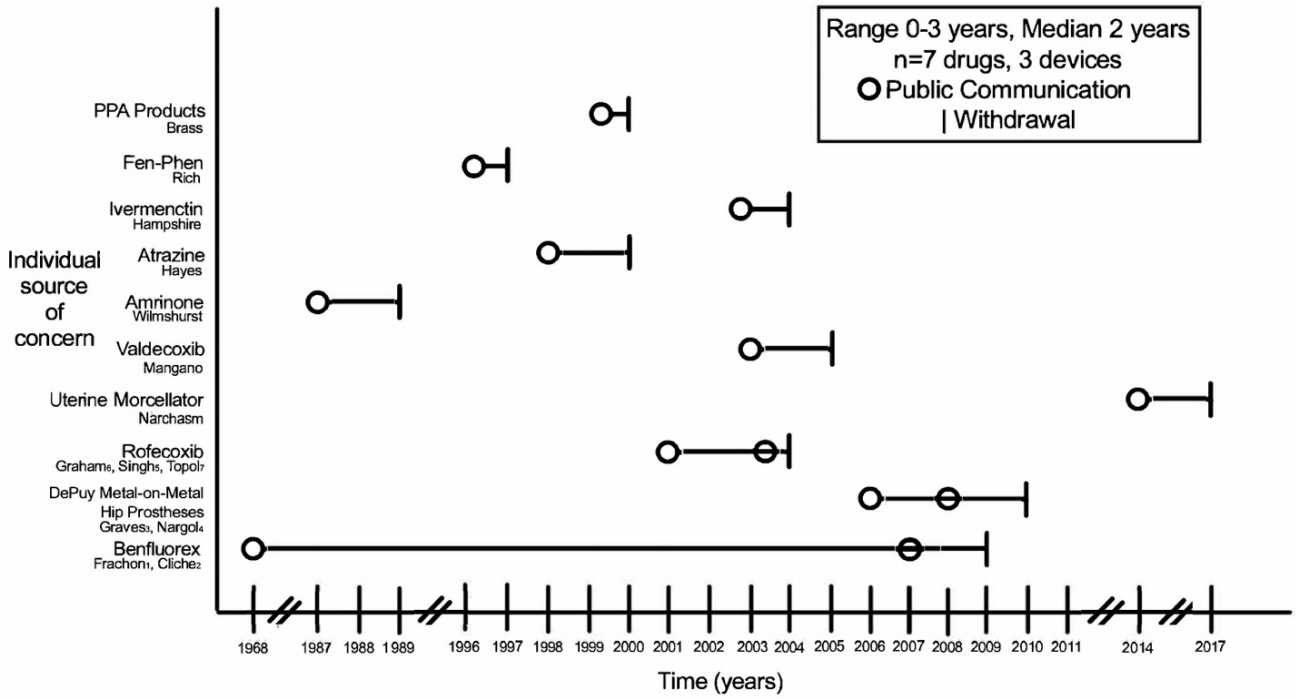


**Figure 1B. Time in Years from Public Communication to Drug/Device Withdrawal**

Personal clinical observations informed toxicity reports from three clinicians. A surgeon reported development of metastatic sarcoma after his wife underwent uterine morcellation.[68] One orthopedic surgeon in Australia reported that several of his patients had developed serious complications following DePuy metal-on-metal hip prostheses.[52] A psychiatrist reported two patients had committed suicide after initiating anti-depressant therapy.[93]

Four case-control studies (one on phenylpropanolamine, two on anorectic drugs, and one on rofecoxib),[43,47,64,106] two meta-analyses (one on erythropoiesis stimulating agents and one on anti-depressants),[62,95] one review of FDA reports (on ivermectin pyrantel),[53] and two basic science reports (one on frogs and one on corn)[55,67] informed additional communications.

Five instances involved clinicians and scientists who were initially prevented from presenting their findings. An epidemiologist reported identifying rofecoxib-associated cardiovascular toxicity following review of a phase III clinical trial study report.[40,106] The epidemiologist, who was also a senior investigator at the Food and Drug Administration, was informed by his superiors that he would not be allowed to present his findings at a medical conference in Europe. Subsequently, these findings were included in an article that appeared in *The Lancet*.[42]

## INSTANCES WHERE SCIENTISTS AND CLINICIANS IDENTIFIED FRAUDULENT DATA SUBMISSIONS FROM PHARMACEUTICAL CORPORATIONS

The communications identified seventeen individuals who identified eleven instances where corporate employees had submitted data to government or regulatory agencies that were subsequently identified as differing from source data belonging to clinician investigators of the same drug. These communications were related to two anorectic drugs (benfluorex and phenfluramine-fentermine), two cox-2 inhibitors (valdecoxib and rofecoxib), three devices (uterine morcellators, artificial hip implants, and a patent foramen ovale closure device), a cardiac drug (amrinone), a diabetes drug (rosiglitazone), anti-depressants, gadolinium-based contrast agents, an iron-chelating drug, a skeletal anti-resorptive agent, and a pesticide.[6,9–11,18,21,30,33,34,40,42,43,55,56,63,65,68,70,71,87,109–114]

Primary motivations for clinicians and scientists included concerns over drug/device safety (twenty-one individuals), drug/device efficacy (five individuals), or data integrity (one individual). Personal statements described negative interactions by tweny-three individuals with corporations, eleven individuals with university personnel, and four individuals with regulatory agency personnel.

## THREATS AND INTIMIDATION EFFORTS (TABLES 1, 2, AND 3)

Overall, twenty-three individuals received twenty-four threats from pharmaceutical employees generally within weeks of communicating concerns. Threats to fourteen individuals began shortly after presenting findings to pharmaceutical corporation employees. For ten individuals, threats began following presentations at medical conferences, or after being prevented by supervisors from presenting their concerns. Three individuals received threats from supervisors at regulatory agencies.

Intimidation efforts included: threats of lawsuits (eighteen individuals), public disparagement at conferences (eleven individuals), threats of loss of academic positions (six individuals), threats of loss of grant funding (two individuals), delays in decisions regarding tenure (two individuals), and threats of reassignment to a low-level position (one individual). Several documents identified complex efforts to intimidate scientists and clinicians.[5,12,20,22,25–27,31,34–37,51,53,54,56–61,75,82,92,110–113,115–136]

Two clinicians incurred personal expenses over $1 million in attorney fees. One scientist described episodes where corporate scientists threatened his family.[56] The Federal Office of Internal Affairs investigated an FDA reviewer after the reviewer's account of selective serotonin reuptake inhibitors was forwarded to his supervisor.[53] One clinician described receiving lawsuit threats after rejecting a financial offer by a pharmaceutical corporation to suppress publication of his findings.[123] For twenty-three individuals, threats and intimidation efforts were sustained over long periods of time.

Threats and intimidation occurred for a median of three years (range: one to eighteen years). Some threats ended following regulatory actions. In two instances, threats were discontinued after executives for pharmaceutical corporations were contacted by academic department chairpersons.[9,15] For two clinicians, threats persisted for more than a decade. Senior university and/or FDA officials took actions against twelve clinicians and four research scientists beginning a median of two years after the clinicians and scientists had publicly communicated their concerns (range: zero to five years).

## HARMS

For fifteen clinicians and scientists, threats were followed by harms. Harms were inflicted a median of one year after threats or intimidation began (range: zero to two years). Harms included personal payments of attorney fees (fifteen individuals), loss of hospital positions (nine individuals), loss of faculty positions (six individuals), loss of federal grants (two individuals), delayed tenure decisions (two individuals), removal as lead of a multi-national clinical trial (one individual), removal as a journal editorial board member (one individual), and job demotion (one individual). In fourteen cases, university employers provided support, overt or covert, to pharmaceutical companies against the clinicians and scientists. For three clinicians who lost university or hospital positions, their attorneys negotiated financial settlement agreements that also included non-disparagement clauses under which the clinician or scientist could not disparage the university. For twelve individuals, documentation of harms coordinated by a corporation was identified. In eleven instances, no university employee assisted a clinician or scientist. In one case, one clinician was awarded $39 million in damages and $19 million in interest from Pfizer and a statistician purportedly hired by Pfizer who had been charged with stealing data from the clinician's laboratory. This data identified valdecoxib-associated cardiac toxicity.[123] Before the case went to trial, Pfizer offered the clinician $24 million to settle.[123] In 2009, a judge dismissed the verdict against Pfizer. The clinician reported that his attorney fees had been $15 million.[123]

## CORPORATE-UNIVERSITY INTERACTIONS

Clinicians and scientists received threats from executives at eleven publicly traded corporations. These corporations ranged from smaller public corporations ($1.1 billion in market capitalization) to extremely large public corporations (market capitalization of $483 billion). Executives at two privately held companies also threatened three individuals. Twelve individuals who identified findings contrary to corporate interests were employed at eleven academic uni-

**Table 3. Clinicians' and scientists' statements about communicating findings contrary to corporate interests.**

| Reporter, Position at the time of successful or attempted communication (relevant drug or device) | Statement |
|---|---|
| Drug or device withdrawn (n=10) | |
| Irene Frachon MD, pulmonologist, Universite Europeene de Bretagne, Breast France (anorexin drug (benfluorex)) | "The [court] trial [against Servier] comes as a huge relief. Finally, we are able to see the end of an intolerable scandal."[137] |
| Georges Cliché MD, cardiologist, Marseilles, France (anorexin drug (benfluorex)) | "[Servier's drug safety expert] comes to tell me that my [adverse event] observation] is null and that it must be withdrawn…. She gave me a biology lesson and explained to me that I was talking nonsense." |
| Lucien Abenheim MD PhD MS. Professor, Epidemiology/ Biostatistics, McGill University, Canada (anorexin drug (phenfluramine-fentermine) | "Serious questions need to be asked about a drug approval process that gives more weight to drug company lobbyists than independent medical researchers."[138] |
| Stuart Rich MD, Director, Rush Hospital Heart Institute, Associate Professor, Division of Cardiology, Rush College of Medicine, Illinois (anorexin-drug (phenfluramine-fentermine) | When I got back to my office at the medical center earlier that morning, he [the company vice-president] called me directly. He told me he saw my interview on the Today show, and warned me that it was very dangerous for me to talk to the press about that; that if I had any issues regarding their product that I wanted to publish in a scientific journal, so be it. But if I spoke to the media about their drug, bad things would happen."[44] |
| Dennis Mangano MD PhD 2006, Professor of Medicine, Vice-Chair, Department of Anesthesia, University of California/San Francisco (cox-2-inhibitor (valdecoxib) | "They [Pfizer] did not want to deal with me because my mandate has always been, whatever I find, I publish, good, bad, indifferent."[123] |
| Eric Topol MD, Professor, Chairman, Cardiovascular Medicine Department, Cleveland Clinic Medical Center, Chief Scientific Officer, Cleveland Clinic Medical College, Ohio (cox-2-inhibitor (rofecoxib) | "I am bothered by continued outrageous lies of Merck with the full-page multiple ads that 'they published everything' and that they never had a trial which showed any harm of Vioxx before September 2004."[5] |
| David Graham MD, Associate Director for Science and Medicine, Office of Drug Safety, FDA, Silver Spring, Maryland. (cox-2-inhibitor (rofecoxib) | "The [FDA] response from senior management in my Office, the Office of Drug Safety, was equally stressful. I was pressured to change my conclusions and recommendations, and basically threatened that if I did not change them, I would not be permitted to present the paper at the conference."[40] |
| Gurkipal Singh MD. Adjunct Clinical Professor, Medicine, Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University School of Medicine, California. (cox-2-inhibitor (cox-2-inhibitors (rofecoxib) | "I persisted in my enquiries [about rofecoxib safety]– I was warned that if I continued in this fashion, there would be serious consequences for me. I was told that Dr. Louis Sherwood, a Merck senior vice-president, and a former Chief of Medicine at a medical school, had extensive contacts within the academia.. Dr. Sherwood called several of my superiors at Stanford to complain."[9] |
| Stephen Graves MD, Professor of Surgery, University of Melbourne/the Australian Orthopedic Association's National Joint Registry, Australia (Articular Surface Replacement Hip Prostheses) | "It is a complete untruth that DePuy did not have reason to withdraw the ASR [hip prostheses] before now; we have been telling them since 2007, but they allowed it to be used on thousands of people…. There's a natural tendency for companies [to think] it's probably factors other than a device, because they have invested a lot of time in it."[90] |
| Antoni Nargol MD, Consultant Surgeon, University Hospital of North Tees, England (Articular Surface Replacement Hip Prostheses) | "They [DePuy] put the blame on myself and colleagues."[52] |
| Hooman Narchasm MD PhD, Instructor, Harvard Medical School and cardiothoracic surgeon, Brigham and Women's Hospital, Mass (morcellator) | "Congress must ask how it is that a surgical error becomes standard of practice."[60] |

| Reporter, Position at the time of successful or attempted communication (relevant drug or device) | Statement |
|---|---|
| Lawrence Brass MD, Professor of Neurology and Epidemiology and Public Health, Yale University School of Medicine (phenylpropanolamine) | "Supposed experts in the field are willing to say we somehow put the public at risk by publishing the results. They're willing to do that in the courtroom while paid tens of thousands of dollars, but they are not willing to write a letter to be judged in a peer-reviewed forum — that's the worst kind of professional. That's despicable."[75] |
| Victoria Hampshire DVM, Safety Officer, FDA Center for Veterinary Medicine, Commissioned Officer at the FDA, Silver Spring, Maryland. | "To take this much stress home [after reporting tumors among ivermectin/pyrantel-treated dogs] and not to sleep for weeks is not worth it."[139] |
| Tyrone Hayes PhD, Professor, University of California/ Berkeley, California (atrazine) | "Ultimately they [Syngenta] told me I could not publish the data outside their closed panel…. Tim Pastoor [a Syngenta vice-president] threatened him and his family"[25,133] |
| Peter Wilmshurst MB ChB BScD, cardiologist and cardiology research registrar, Saint Thomas' Hospital, London, England (amrinone) | "Company employees asked us to exclude some patients from the analysis. These were ones where there was a downward trend in contractility. The effect of excluding them would have been to produce an apparent but spurious increase in contractility in the remainder. We refused. My supervisor and I were then threatened with litigation. …When you are threatened by a multinational with infinite amounts of money, some people might find that a good reason not to go ahead.[12,111] |
| Black box warning added (N=5) | |
| Henrik Thompsen MD, Professor and Chairman of Radiology Department at Copenhagen University Hospital, Denmark (gadodiamide) | "I believe that the lawsuit [filed by General Electric] is an attempt to silence me."[140] |
| John Buse MD PhD, Professor of Medicine, Chief, Division of Endocrinology, University of North Carolina School of Medicine, Chapel Hill, North Carolina (rosiglitazone) | "There was a high-ranking member of the company that had a longstanding professional relationship before he joined the company with my chairman… [The conversation between the two men] was characterized to me as being disturbing. The phrases that I remember…involved that number, $4 billion [sought by the company via a lawsuit]. The second was that I was characterized as a liar. And the third was that I was characterized as being for sale."[15] |
| Charles Bennett MD PhD MPP. Buehler Professor of Medicine and Economics, Northwestern University Schools of Medicine and Management, Hematologist/Oncologist, Northwestern University, Illinois | "We have a safety signal [for ESAs] on deep vein thrombosis, and we now have a safety signal that we see on survival…. How much more do we need to show you to stop overuse of these drugs? How many safety signals do we need before we get to the idea that we have to reconsider what we are doing here?"[107] |
| Michael Henke MD PhD, Associate Professor, Head of Clinical Research Section, and Vice-Chairman of the Department for Radiation Oncology, University of Freiburg, Freiburg, Germany. | "Everyone claims to want to protect cancer patients, and if there is agreement on this, it should be easy to come to a conclusion. Nevertheless, the doctor is making a little money prescribing erythropoietin, the scientist is making money, the manufacturer is making money."[141] |
| David Healy MD, Director of the North Wales Department of Psychological Medicines, Professor of Psychiatry, University of Wales College of Medicine, Walse, United Kingdom | "The guest lecturer gave the opinion that I had no right to present data like this [on SSRI-associated suicides]. Even when it was pointed out that these data were consistent with other data in pharmaceutical company files, he still insisted I had no right to present the data. He said it would ruin my career. Both a witness and I found the conversation disturbing."[51] |
| Product application not submitted to FDA for consideration of regulatory approval (n=1) | |
| Peter Wilmshurst MB ChB BScD, consultant cardiologist at the Royal Shrewsbury Hospital and Senior Lecturer in Medicine at Keele University in Keele, England (related to the patent foramen ovale closure device). | "My experience suggests that corporations can use the English defamation laws to misrepresent the results of clinical research, A corporation can propagate a misleading version and can use the defamation laws to bully those who object to remaining silent….Truths should not be decided by those with the greatest wealth using bullying and threats to make a scientist retract what he or she knows is true."[136] |
| Delayed FDA approval (n=1) | |

| **Reporter, Position at the time of successful or attempted communication (relevant drug or device)** | **Statement** |
|---|---|
| Nancy Olivieri MD, Professor of Paediatrics and Medicine, University of Toronto. Director, Thalassemia Program, Hospital for Sick Children and University Health Network (deferiprone) | "The company [Apotex] was very much against informing the patients [about lack of efficacy and serious toxicities]."[26] |
| No regulatory action (n=4) | |
| Aubrey Blumsohn MD, Senior Lecturer/Laboratory Head, Bone Metabolism Research, Sheffield University, England | "The company failed to allow investigators access to randomization and event codes from the study. They continued to refuse access to this information to authors even after ghost-authoring work in the names of myself and Dr. Eastell, and after substantial and increasing information emerged to suggest that the company data analysis could not be trusted."[21–23] |
| Igancio Chapela PhD, Assistant Professor, University of California/Berkeley, California (maize) | "I don't want to be a martyr by any means, but I cannot avoid now realising that this is a very, very well concerted, and coordinated and paid for campaign [by Monsanto] against me."[57,128] |
| David Kern MD, Associate Professor, Brown University; Director, General Internal Medicine/Occupational and Environmental Health Service; Memorial Hospital; Director, Occupational Medicine, Brown University, Rhode Island. | "There were many courageous folks who stood up for me, but most looked the other way. I'm mightily discouraged by the failure of the community to do more."[31,129] |
| Betty Dong Pharm D, Associate Professor, University of California, San Francisco School of Pharmacy, San Francisco, California | "They [the pharmaceutical corporation] accused me of falsifying data. They sent private investigators after me to investigate my personal and professional life…The part of that is very difficult is that none of it is true and you can't always get your reputation back in place."[26] |
| Guiring Jiang MD, Research Radiologist, Sheffield University. | No statement could be identified. |

versities, each of which has more than 20,000 students. The University of California/Berkeley, the University of Toronto, the University of Sheffield, Northwestern University, and the University of North Carolina each had in-place or pending financial agreements with manufacturers who employed individuals who threatened eight scientists at the five universities.[20,22,27,51,56,57,107,116–122,127,133] At Senate hearings, Drs. Buse, Singh, and Topol testified about communications from pharmaceutical executives to university officials requesting that these individuals be removed from their academic positions.[5,9,15,142] Other examples of corporate-university interactions against scientists and clinicians involved Dr. Dong, at the University of California/San Francisco, Drs. Hayes and Chapala at the University of California/Berkeley, and Dr. Kern at Brown University, who were informed that their universities would not provide legal support against actions brought by pharmaceutical corporations.[25,26,31,56,57,127,133,135]

### CRIMINAL MISDEMEANORS AND FINES AGAINST CORPORATIONS (AND ONE CORPORATE EXECUTIVE)

Of the 13 pharmaceutical companies included in this report, four companies pled guilty or were found guilty in criminal trials (Table 4). The findings were related to six products (Table 4). Fines accounted for $5.7 billion in payments to the United States (for five products) and $3.3 million to the French government. The criminal pleadings were for misbranding, providing false information for commerce, failing to report clinical trial data, manslaughter, and causing patient deaths (Table 4).[48,91,108,143–145] These guilty findings were related to pharmaceutical or device manufacturers knowingly reporting false data to regulatory agencies or marketing products that had known serious or fatal toxicities, while none related to misbranding.

## DISCUSSION

Our findings of threats and intimidation following communication attempts or actual communication of scientific findings contrary to corporate interests have not been described previously. In interpreting our findings, several factors should be considered.

Threats and intimidation were long-lasting and were first noted following public presentations. Careers of thirteen clinicians and two scientists were affected for years. Abraham and Davis note the significance of legal threats and explain that even if litigation threats are not converted to lawsuits, threats can impact when evidence becomes publicly known.[150]

We found that university employers actively discredited reputations of clinicians who had publicly communicated findings contrary to corporate interests. Our study extends the analysis of Rhodes and Stain who posited that scientific disagreements between academics and pharmaceutical corporations cause academic establishments to fear the loss of industry and grant dollars.[151] A related consideration is that academic leaders are concerned that lawsuits might be filed by corporations if toxicities are reported by academic scientists. These concerns were borne out in our study.

Another concern was that after threats were made by corporations to fourteen clinicians and four scientists, regulatory agencies discovered that these corporations had submitted applications for regulatory approval or for documentation of governmental regulation requirements that included data that differed from source information in each of these clinicians' or scientists' files. Subsequent investigations found that, in most cases, the data submitted by the corporations was fraudulent.

In one of the most frequently cited reviews of a case involving disagreements between a senior clinician and pharmaceutical company in 1996, a pharmaceutical company prematurely discontinued two clinical trials led by Dr. Nancy Olivieri following generation of data potentially adverse to commercial interests and after attempting to discredit her.[20] In 2009, an FDA review by the Division of Scientific Investigations of Olivieri's clinical data from 1996 identified differences in data included in a 2009 sponsor's application for FDA approval of deferiprone.[152] A FDA site visit carried out in 2009 confirmed that, where source data were available from 1996, the 1996 data were accurate.

At the other end of the public awareness spectrum, in a serious but infrequently cited example of pharmaceutical fraud, the Netherlands Committee for the Evaluation of Medicines contacted Peter Wilmshurst in 1983 about discrepancies between published toxicities with amrinone and amrinone toxicities reported by the sponsor. Comparison with original reports of phase III clinical trial data revealed that the sponsor had altered case report findings.[11] The pharmaceutical sponsor attempted to discredit Dr. Wilmshurst before prematurely discontinuing a phase III clinical trial with amrinone.

Following threats and intimidation of clinicians and scientists, regulatory agencies delayed taking safety-related actions that would have positively affected public health (Figures 1A and 1B). The priority of profits over people resulted in delays of several years for withdrawals or black box warnings for most drugs and devices reported herein.

Fourteen clinicians or scientists experienced personal harms. Harms ranged from loss of professional positions (nine individuals) to payments of attorney fees of $1 million (two individuals) and $15 million (one individual). A distinguishing characteristic between the fourteen individuals who experienced harms versus the twelve individuals who experienced threats and intimidation but no harms was that individuals who experienced harms had generally been disciplined by university or regulatory authority employers after publicly communicating findings contrary to corporate interests.

The circumstances involving disciplinary actions against six clinicians and three scientists were reviewed extensively by committees or external reviewers. In each case, detailed investigations concluded that the university or a regulatory agency had purposefully intimidated and threatened the clinicians and scientists and the clinicians and scientists had not been at fault. It should be noted that following disciplinary actions taken by four universities or medical centers against four individuals, the university or hospital paid financial settlements to these four individuals. Three settlements required the clinician to sign non-disparagement clauses (only the financial settlement involving Healy

**Table 4. Regulatory and Governmental hearings, publicly reported costs (fines or settlements) of associated legal actions, criminal findings, and number of persons injured by adverse drug reactions that were identified contrary to corporate interests**

| Serious adverse drug reaction (sales-pre/ post FDA meeting) | Year of initial threat | # of affected Pts (year of 1st report) | Legal fines to companies | Regulatory and Congressional hearing | Criminal findings against corporations (and employees, if any) |
|---|---|---|---|---|---|
| Epoetin ($5.4 billion/$1 billion) 2007 | 2007 | Not Available (2003) | $610 million; $95 million[77,91] | 2004, 2006, 2007, 2008, 2010, 2011 | None |
| Darbepoetin ($4.1 billion/$1.7 billion) 2007 | 2007 | Not Available (2003) | $610 million; $95 million[77,91] | 2004, 2006, 2007, 2008, 2010, 2011 | 2012: Amgen plead guilty to one criminal count of illegally introducing a misbranded drug and providing false information (for darbepoetin) into commerce. ($150 million fine).[91] |
| Rosiglitazone ($3 billion/$0.2 billion) 2007 | 1999 | 47,000 (2007)[42] | 2011 GlaxoSmithKline set aside $3.4 billion to pay patients to settle individual lawsuits for injury[108] | 2007, 2010, 2013 | 2012: GSK pled guilty to federal and charges of failing to report clinical data. ($3 billion in Federal penalties and $319 million for state penalties).[108] |
| Rofecoxib ($2.5 billion/ 2004, withdrawn in 2004) | 2001, 2001, 2001 (three persons) | 88,000-140,000 (2005) | Merck paid $4.85 billion (to patients for injuries).[5] | 2004,2005 | 2011: Merck pled guilty to criminal misdemeanor of illegal promotional activity ($321 million fine).[143] |
| Fenfluramine-phentermine ($0.3 billion 1996/ drug withdrawn 1997) | 1996 (two clinicians) | 300,000 (1996) | Wyeth paid $22 billion (to patients for injuries)[106] | 2000 | None |
| Benfluorex ($500 million 2008/drug withdrawn in 2009) | 2007 | 2,000 deaths; 6,500 injured patients (2010) | Servier paid $146 million- patients $3.2 million and $0.5 million to the ANSM, the French pharmaceutical regulatory agency[50] | 2011, 2021 (French courts) | 2021: Manslaughter and criminal deceit- Servier and former Servier executive (four-year suspended sentence). ($3.3 million fine against Servier)[146] |
| Gadodiamide ($0.54 billion/ $0.2 billion 2020) | 2007 | Not known (2006) | General Electric $500 million (to patients) (reportedly) | 2009 | None |
| Atrazine (still sold) | 2002 | Not known (2002) | Syngenta paid $105 million (to 105 counties to settle class action lawsuit related to public water contamination)[147] | 2012, 2020 | None |
| Ivermectin (no known sales numbers) | 2004 | 5,552 dogs with toxicity (2004) | No fines were paid by Fort Dodge Animal Health | 2004,2005 | None |
| Paroxetine - 2009 use returned to 2004 levels | 2004 | Many cases (1991) | GlaxoSmithKline pain patients $3 billion[144] | 2004 | 2012: GlaxoSmithKline pled guilty to a 3-count criminal information charge, including one count of misbranding paroxetine. (Criminal fine of $956 million)[144] |
| Risedronate | 2002 | Not | Not applicable | 2005- UK | None |

| Serious adverse drug reaction (sales-pre/ post FDA meeting) | Year of initial threat | # of affected Pts (year of 1st report) | Legal fines to companies | Regulatory and Congressional hearing | Criminal findings against corporations (and employees, if any) |
|---|---|---|---|---|---|
| (risedronate) | | known | | | |
| Phenyl-propanolamine (drug withdrawn) ($200 million 1999/$0 in 2000) | 2000 | Not known | Not available. Cases were settled privately. | 2000 | None |
| Articular surface hip replacements (US recall-2010) | 2007 | 8,000 persons | $4 billion to patients for faulty hip prostheses[104] | 2011 (Australia); 2012 (FDA) | None |
| Synthroid | 2004 | None reported | $42 million (states) $98 million (class action settlement)[147,148] | None | None |
| Valdecoxib | 2004 | 1,100 persons (2005) | Pharmacia paid $745 million (personal injury claims settlement). Also paid $1 billion in civil settlement for False Claims Act violation.[145,149] | 2005 | 2009: Pharmacia pled guilty to a federal violation of misbranding valdecoxib with the intent to defraud or mislead. Paid $1.3 billion in criminal fine.[145] |

did not). Only one university-convened committee reported that a clinician's personal action supported a disciplinary decision. The University of Sheffield had disciplined a radiologist for submitting an abstract to a medical conference without receiving permission to submit the abstract to the conference. Following this action, the clinician was dismissed from the university. Grant funded research was a major component of the academic careers of five clinicians. Only one of these five clinicians continued with an active grant-funded research career.

Our study included individuals who reported threats or intimidation. Roy Poses, editor of the well-respected blog *Health Care Renewal*, described in detail intimidation efforts involving five clinicians.[116,117,120] He concluded: "I am convinced that for every Aubrey Blumsohn, there are dozens who are aware of deception, other unethical conduct, even crime and corruption that could harm patients and patient care, but are afraid to speak out."[116] Moreover, though several SONAR/RADAR investigators and collaborators published clinical findings contrary to corporate interests, no documented threats or intimidation acts could be identified after the findings were published.[153–162]

Our study has limitations. There might be whistle-blowers who have been publicly threatened by corporations and were not identified by our search methodology. However, our findings suggest that based on the search criteria that we developed, the likelihood of having missed many of these scientists or clinicians is small. Our estimate of $25 billion in financial settlements/payments and one million injuries or fatalities represents significant damage. If individuals were omitted from our search, then the financial and human cost estimates might be much larger (i.e. the "tip of the iceberg").

There are additional data about each case that were not identified in our searches. These data include sealed judicial documents and undisclosed financial settlements, findings of university investigations that are not publicly disclosed, an in-press report (i.e. a review of the Bennett-Amgen and Bennett-Northwestern University cases by Jack Getman JD, emeritus Earl E Sheffield Regents Professor of Law at the University of Texas and former general counsel to the American Association of University Professors),[163] and secrecy clauses between universities and/or corporations and scientists or clinicians that prevented dissemination of additional information.[29,103,120,129,135] Also, while some of the claimed threats and harms (e.g. harms such as loss of grant funding, loss of position) could be spurious, this is unlikely. Clinicians and scientists in this study testified under oath at Congressional hearings, had corroboration of individual claims in an external report from professors at other universities (for Chapela), a report from the Canadian Association of University teachers (for Olivieri), an in-press report on the Amgen-Northwestern University case (for Bennett), and as part of presentations made when receiving an honorary doctorate or an award from the American Academy of Advancement of Science (for Oliveri) or after receiving excellence awards from various honorary societies and organizations (for Wilmshurst and Hampshire).[20,29,53,54,127,128,133,135,164]

It should be noted that these twenty-six individuals differ from the usual description of qui tam relators ("whistleblowers") who file fraud claims involving federal funds, are

frequently characterized as disgruntled employees, and, if successful, receive significant financial remuneration for their efforts. None of the twenty-six individuals received any financial remuneration for communicating findings contrary to corporate interests. Several clinicians and scientists faced libel lawsuits after reporting their findings.[12,35,36,136,140]

To our knowledge, this is the first case series reviewing threats and intimidations experienced by clinicians and scientists who identified significant findings contrary to corporate interests. Our results indicate that while commitment to accurately reporting findings related to patient safety, drug efficacy, or data integrity was the most common motivating factor for twenty-six individuals, clinicians and scientists should be aware that extended threats or intimidation efforts can occur after these communications are publicly disseminated. Schafer and Krimsky summarized approaches to mitigate effects of pharmaceutical and academic threats when reporting findings potentially contrary to corporate interests.[130,165] The first option, termed the regulatory approach, focuses on managing risks that accompany pharmaceutical funding. The second approach eliminates corporate sponsorship of academic research. These approaches could have assisted some individuals in this study who received direct manufacturer funding but would not have helped others.

Our study suggests that corporations (and pharmaceutical employees, if their role is known) who knowingly submit fraudulent data to support regulatory agency requirements for drugs or devices should be tried for criminal violations. There is some precedent for this. In 2021, former Servier Incorporated executive Jean-Philippe Seta received a four-year suspended sentence in a case that involved thousands of patient deaths and severe injury to tens of thousands of patients.[146] Between 2009 and 2021, four of the thirteen corporations accounting for six drugs or devices and included in this study pled guilty to varying criminal charges (Table 4).[48,91,108,143–145] Going forward, more criminal activities conducted by pharmaceutical or device corporations are likely to be uncovered, as in the case of Purdue Pharma. As in the Servier executive case, focused efforts are needed to hold corporate executives accountable. The many examples of threats and intimidation that resulted from medical researchers exposing corporate wrongdoing discussed in this paper show that corporate executives must be held responsible for these actions.

## DATA SHARING AGREEMENT

All data were obtained from publicly available data sources as cited in the methods, tables, and references. Each co-author had full access to the entire study database.

## GUARANTOR

Charles L Bennett MD PhD MPP is the guarantor of the accuracy of this manuscript.

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