Post-marketing regulation of medicines withdrawn from the market because of drug-attributed deaths: an analysis of justification

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ABSTRACT

Introduction: Several medicinal products have been withdrawn from the market because of drug-attributed deaths. However, there has been no investigation of whether such withdrawals were justified, and the extent to which confirmatory studies are used to investigate drug-adverse event relationships when deaths are reported is uncertain. We documented medicinal products withdrawn from the market because of drug-attributed deaths, identified confirmatory studies investigating the drug-adverse event relationships, examined whether withdrawals of medicinal products because of drug-attributed deaths after marketing were justified based on a mechanistic analysis, and examined the trends over time.

Methods: We searched electronic and non-electronic sources to identify medicinal products that were withdrawn because of drug-attributed deaths. We used a previously published algorithm to examine whether the withdrawals of products were justified. We then searched PubMed and Google Scholar to identify studies investigating the drug-adverse event relationships, used the Oxford Centre for Evidence-based Medicine criteria to document the levels of evidence, and assessed whether the evidence of an association was confirmed.

Results: We included 83 medicinal products. The reasons for withdrawal appeared to have been justified in 80 cases (96%). The median interval between the first reported adverse reaction that was related to the cause of death and the first reported death was 1 year (IQR = 1 to 3); products were withdrawn sooner when the interval between the first reported relevant adverse reaction and the first death was shorter. Confirmatory studies were conducted in 57 instances (69%), and there was evidence of an association in 52 cases (63%). Four products (5%) were re-introduced after initial withdrawal.

Conclusion: Regulatory authorities have been justified in making withdrawal decisions when deaths have been attributed to medicinal products, using the precautionary principle when alternative decisions could have been made. Medicinal products are likely to be quickly withdrawn from the market when there is a short interval to the first reported deaths. The use of an algorithm such as we have used in this study could help to expedite the process of decision making.

Key points

- Regulatory authorities have appropriately removed medicines from the market when they were suspected of causing deaths

- Harmful medicines are likely to be quickly removed from the market if the time period to first report of death is short

1. INTRODUCTION

Regulatory authorities grant marketing licenses when early-phase trials suggest a favourable benefit-to-harm balance. However, the harms may come to outweigh the benefits over time, and when the benefit-to-harm balance becomes unfavourable, the product may be withdrawn from the market. When adverse reactions that result in death are suspected, one would expect faster regulatory action, with suspension or withdrawal of a product from the market. However, if there is no convincing evidence of a causative relationship, withdrawal could result in removal of effective compounds, loss of confidence in medicines, negative incentives for drug manufacturers, and mistrust between physicians, patients, drug regulators, and pharmaceutical companies.

It was previously thought that drug-attributed deaths usually occurred in very ill patients undergoing therapy with highly toxic medicinal products [1]. However, it is now recognized that adverse drug reactions are not only a major cause of deaths in hospital [2,3,4], but are also important in the general population [5,6].

We have previously shown [7] that there are discrepancies in the patterns of withdrawal of medicines from the market when deaths are attributed to their use, and that formal confirmatory studies are rarely used in making withdrawal decisions. Although most withdrawal decisions are based on case reports, it is unclear whether other criteria are also used. Several signal detection algorithms are used to explore drug-adverse event relationships [8], but the extent to which confirmatory studies are used to investigate such relationships when deaths are reported is uncertain. We therefore decided (i) to determine whether withdrawals of medicinal products because of drug-attributed deaths were justified; (ii) to explore whether there is a relationship between the interval to first reports of deaths and time to first withdrawal of the product from the market; (iii) to examine how often confirmatory studies are performed to investigate associations between medicinal products and adverse reactions leading to deaths; and (iv) to document the levels of evidence of confirmatory studies and examine whether there is consistency across studies.

2. METHODS

We identified products for which death was documented as a reason for withdrawal between 1950 and June 2016, from the following sources:

- the World Health Organization's (WHO's) database of Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted, or not approved by governments (Issues 6, 8, 12 and 14);
- the WHO's Drug Information (Volumes 1–30);
- the WHO's Pharmaceuticals Newsletter (1997–Vol. 3, 2016);
- the database of withdrawn drugs of the European Medicines Agency (EMA);
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);
- the website of the US Food and Drug Administration (FDA);
- PubMed, and Google Scholar, using search terms including "drug withdrawal", "fatal*", "death(s)", "voluntary recall", and related terms;
- *Meyler's Side Effects of Drugs* volumes 1–8 and editions 9–15 and the *Side Effects of Drugs Annuals* 1–37;

[See Online Resource 1 for full search strategy].

To be included in the review, a product must have had death documented as a reason for withdrawal, but not necessarily the sole reason. Medicinal products that had previously been withdrawn in relation to deaths but had been re-introduced or made available in other formulations were included, excluding products that were first withdrawn before 1950. Medicinal products for which death was not specifically reported as a reason for withdrawal from the market were excluded, as were non-human medicines, herbal products, and non-

prescription medicines. We also excluded products withdrawn because of deaths caused by overdose.

We documented the launch year and the year in which any adverse reaction that was specifically related to death was first reported (e.g. if the death was due to liver failure, we searched for, and documented the first report of a hepatic abnormality attributed to the product after regulatory approval), the year in which deaths were first reported, the first year of withdrawal in any country, the total number of reported deaths before the first withdrawal, and the reported mechanism through which death occurred for each included product. For each documented first report of death attributed to a product, there had to be sufficient suspicion of a cause and effect relationship to warrant reporting it.

We used a previously published framework [9] to determine whether the first withdrawal decisions were justified. This framework comprises an algorithm for regulatory action when a new serious adverse drug reaction is suspected, and examines the following domains: (i) an identifiable susceptible population; (ii) the availability of an adequate monitoring strategy; (iii) the availability of an adequate preventive strategy; and (iv) a favourable benefit-to-harm balance in the population. We used information from case reports, case series, or confirmatory studies to determine whether each withdrawn product fulfilled the criteria in each domain. Depending on how many of the domains were fulfilled in the algorithm, we assigned a decision that the algorithm suggested was appropriate, as follows; decision A implies empowering the patient, B implies adding a caution, C implies adding a contraindication, and D implies licence revocation. [See Online Resource 2 for the schematic diagram].

We conducted searches in PubMed, Google Scholar (November 2016), and other non-electronic sources to compute the number of deaths attributed to the withdrawn product before the first withdrawal (or used any figures reported by the withdrawing regulatory authority). To assess whether any confirmatory studies were conducted, we searched PubMed and Google Scholar (November 2016) to identify studies investigating the drug-adverse event relationships using the following order of priority: meta-analysis > observational studies > case series/reports [see Online Resource 1 for a comprehensive search strategy]. We did not include animal studies unless they directly investigated drug-death relationships. We used the Oxford Centre for Evidence-based Medicine (OCEBM) criteria [10] to determine the highest levels of evidence for confirmatory studies; these criteria rank the levels as follows: Level 1: systematic review (highest); Level 2: randomized clinical trial; Level 3: non-randomized, cohort or follow-up studies; Level 4: case-series or case-control studies; and Level 5: mechanism-based reasoning (lowest). When two or more studies were identified, we assessed whether the evidence regarding the drug-adverse event relationship was consistent across the studies. When the deaths occurred primarily in children (n = 7), the confirmatory studies must have been conducted in children. One reviewer (IJO) applied the overall rating for each product and assessed the justification for withdrawal; a second reviewer (JKA) independently verified them. Disagreements were resolved by discussion.

2.1 Statistical analysis

We report the proportions for each domain fulfilling the criteria for assessing withdrawal decisions. Because the intervals to the first reports of deaths or confirmatory studies were skewed, we used medians and interquartile ranges (IQR) to express measures of central dispersion. Box and whisker plots were used to display the numbers of reported deaths by system, while scatter plots were used to explore relationships between the interval to the first reports of deaths and the time to the first withdrawal. We also used scatter plots to explore relationships between the first withdrawal and the interval to the first confirmatory study.

3. RESULTS

We included 83 medicinal products that were withdrawn from the market because of drug-attributed deaths (Table 1). The products were launched between 1951 and 2007, and the first withdrawals occurred between 1957 and 2011 (Online Resource 3). Excluding the products withdrawn worldwide (n= 23), the first withdrawals following reports of deaths by geographical region were in Europe (n = 41), North America (n = 16), Australasia (n = 2), and Asia (n = 1).

Table 1 shows that susceptible populations were identified in 21 (25%) instances; four of these were attributed to interactions with other medications. In 10 instances (12%), there was an adequate monitoring strategy, and in 3 cases (4%) there was an adequate preventive strategy or evidence of a favourable benefit-to-harm balance in the population for which the medicine was primarily intended. Based on analysis of the individual domains, outright revocation of the license was the appropriate decision in 62 cases (75%). Either revocation or empowering the patient was appropriate in 10 instances (12%), and revocation or adding a caution was appropriate in 7 instances (8%; Table 1). In 3 cases (4%), adding a contraindication would have been the most appropriate decision, and adding a caution should have been the most appropriate decision in 1 case (1%). Overall, the reason for first withdrawal appeared to be justified in 80 cases (96%). In 4 instances (5%), the withdrawn products were re-introduced in the countries of initial withdrawal.

In 51 instances (62%), the first reports of deaths occurred within a year of the initial adverse reaction reports, and reports of deaths with 9 products (11%) occurred within 2 years (web-Appendix Table 1); when deaths primarily occurred in children, all initial reports of deaths occurred within 1 year of the first adverse reaction report (with the exception of pemoline – 16 years). The median interval between the first reported adverse reaction and the first reported death was 1 year (IQR = 1 to 3). The number of reported deaths before initial withdrawal ranged from as low as 1 to as high as 1300 (benfluorex). The median number of reported deaths before initial withdrawal was 9 (IQR = 2 to 11). There was no relationship between the number of deaths and the interval to the first withdrawal (data not shown). When analysed by system, the median number of deaths before the initial withdrawal was highest with gastrointestinal toxicity (n = 13), followed by cardiotoxicity (n = 5) (see Figure 1). The median interval between the first report of a death and the first withdrawal was shortest when the adverse reactions involved the gastrointestinal system: median 0.5 years (IQR = 0 to 4.75); and longest when the causes of death were related to the metabolic system: median 3 years (IQR = 1.25 to 6.25) (Online Resource 4).

Confirmatory studies exploring the drug-adverse event relationships were conducted for 57 products (69%; web-Appendix Table 1). We identified two or more confirmatory studies for 36 of the 57. In 52 cases, confirmatory studies showed evidence of an association between the withdrawn product and the adverse reaction; in one of these (an interaction of sorivudine with 5-fluorouracil leading to bone marrow suppression), the authors investigated the relationship between the interaction and deaths in animals. We identified Level 1 evidence for 13 products (23%), Level 2 evidence for 20 products (35%), and Level 3 evidence for 21 products (37%). In 12 instances (15%), confirmatory studies were published before the year of the first withdrawal following reports of deaths. The median interval between the first withdrawal and the first confirmatory study was 3 years (IQR = 1 to 6). Figure 2 shows an inconsistent shortening in the interval to the first confirmatory study with more recent launch dates. Of the four products re-introduced after initial withdrawal, one death has since been attributed to one (L-tryptophan) [11].

Table 1: Determination of justification for withdrawal of 83 medicinal products to which deaths were attributed†

Medicinal product	Adverse reaction	Susceptible population	Monitoring strategy	Preventive strategy	Population benefit to harm balance*	Overall rating	Withdrawal justified?
Alosetron	Ischaemic colitis	Men > women	No	No	No	A/D	Yes
Alpidem	Hepatotoxicity	No	No	No	No	D	Yes
Azaribine	Thromboembolism	Hereditary homocystinuria	No	No	No	A/D	Yes
Beclobrate	Hepatotoxicity	No	Unclear	No	No	D	Yes
Benfluorex	Cardiotoxicity	No	No	No	No	D	Yes
Benoxaprofen	Hepatotoxicity	Elderly	No	No	No	A/D	Yes
Benzarone	Hepatotoxicity	No	LFT	No	No	B/D	Yes
Benzyl alcohol	Metabolic acidosis	No	No	No	No	D	Yes
Bicalutamide (150 mg)	"Accelerated deaths"	No	No	No	No	D	Yes
Bromfenac Na	Hepatotoxicity	No	LFT	Restrict duration of therapy	No	B/D	Yes
Bromocriptine mesylate [for suppression of lactation]	Cardiotoxicity, neurotoxicity	No	No	No	No	D	Yes
Buformin	Metabolic acidosis	Impaired renal function	Plasma concentration measurement predictive, but not practicable	No	No	A/D	Yes
Bunamiodyl	Nephrotoxicity	No	No	No	No	D	Yes
Celecoxib	Cardiotoxicity	No	No	No	No	D	Yes
Cerivastatin	Rhabdomyolysis; renal failure	Patients using other fibrates; high-doses	No	No	No	A/D	Yes
Cianidanol	Haemolytic anemia	No	No	No	No	D	Yes

Cisapride monohydrate	Cardiotoxicity (QT interval prolongation)	No	ECG	No	No	B/D	Yes
Clofibrate	"Accelerated deaths"	No	No	No	No	D	Yes
Clometacin	Hepatotoxicity	No	No	No	No	D	Yes
Clozapine	Agranulocytosis	No	WBC	No	Yes	B	No
Coumarin (synthetic)	Hepatotoxicity	No	No	No	No	D	Yes
Diiododiethyltin & isolinoleic ester	Cerebral oedema	No	No	No	No	D	Yes
Dithiazanine iodide	Metabolic acidosis	No	No	No	No	D	Yes
Domperidone (Inj)	Cardiotoxicity	No (high dose****)	No	No	Yes	C	No
Ebrotidine	Hepatotoxicity	No	No	No	No	D	Yes
Encainide	Cardiotoxicity	No	No	No	No	D	Yes
Felbamate	Hepatotoxicity; aplastic anaemia	Pre-existing blood dyscrasias or pre-existing immune disorders	Yes, but not helpful	No	No	A/D	Yes
Fenclofenac	Toxic epidermal necrolysis	No	No	No	No	D	Yes
Fenoterol	Increased mortality due to asthma	Children	No	No	No	A/D	Yes
Fipexide	Hepatotoxicity	No	No	No	No	D	Yes
Flosequinan	Cardiotoxicity	No	No	No	No	D	Yes
Gemtuzumab ozogamicin	"Accelerated deaths"	No	No	No	No	D	Yes
Grepafloxacin	Cardiotoxicity	No	No	No	No	D	Yes
Indoprofen	Gastrointestinal hemorrhage	No	No	No	No	D	Yes
Isaxonine phosphate	Hepatotoxicity	No	No	No	No	D	Yes

Isoxicam	Fatal skin reactions	No	No	No	No	D	Yes
Ketorolac injection	GI; renal	No	No	No	No	D	Yes
Levamisole [as an antihelminthic]	Neurotoxicity	No	No	No	No	D	Yes
Loperamide (syrups & drops)	Paralytic ileus	Children	No	No	No	D	Yes
Loxoprofen	Gastrointestinal hemorrhage	No	No	No	No	D	Yes
L-tryptophan	Eosinophilia-myalgia syndrome (EMS)	No	No	No	No	D	Yes
Lumiracoxib	Hepatotoxicity	No	No	No	No	D	Yes
Mibefradil	Drug interactions	Patients using other medicines	No	No	No	D	Yes
Muzolimine	Neurotoxicity/renotoxicity	No	No	No	No	D	Yes
Naftidrofuryl oxalate IV	Anaphylaxis	No	No	No	No	D	Yes
Nefazodone	Hepatotoxicity	Women > men	No	No	No	D	Yes
Nimesulide	Hepatotoxicity	No	LFT	No	No	D	Yes
Nitrefazole	Hepatotoxicity	No	No	No	No	D	Yes
Nomifensine	Haemolytic anaemia	Coombs'-positive patients?	Blood count	No	No	C	No
Orgotein	Anaphylaxis	No	No	No	No	D	Yes
Osmosin (indomethacin)	Adherence to intestinal wall	No	No	Short-term use	No	B/D	Yes
Oxyphenbutazone	Bone marrow suppression	No	No	No	No	D	Yes
Oxyphenisatine acetate	Hepatotoxicity	No	No	No	No	D	Yes
Pemoline	Hepatotoxicity	No	No	No	No	D	Yes

Phenformin HCl	Metabolic acidosis	Impaired renal function	Phenotyping for PMs, but not widely available at the time	No	No	B/D	Yes
Pirprofen	Hepatotoxicity	No	No	No	No	D	Yes
Practolol	Hypersensitivity	No	No	No	No	D	Yes
Prenylamine	Cardiotoxicity	No	No	No	No	D	Yes
Propofol	Hepatotoxicity, metabolic	Children	No	No	Yes	C	Yes
Propyphenazone	Hematologic	No	No	No	No	D	Yes
Pumactant	"Accelerated deaths"	Neonates	No	No	No	D	Yes
Rapacuronium bromide	Bronchospasm	Children	No	No (Sugammadex** was not available then)	No	D	Yes
Rofecoxib	Cardiotoxicity	No	No	No	No	D	Yes
Rosiglitazone	Cardiotoxicity	No	No	No	No	D	Yes
Sertindole	Cardiotoxicity	Patients at risk of cardiac dysrhythmias	ECG	No	No	A/D	Yes
Sibutramine	Cardiotoxicity	No (history of CVD***)	No	No	No	D	Yes
Sitaxentan sodium	Hepatotoxicity	No	No	No	No	D	Yes
Somatropin (pituitary-derived)	Creutzfeldt-Jakob disease	No	No	No	No	D	Yes
Sorivudine	Interaction with 5-fluorouracil	Patients taking fluorouracil	No	No	No	A/D	Yes
Sulfadimethoxine	Immunologic	Children	No	No	No	D	Yes
Suloctidil	Hepatotoxicity	No	No	No	No	D	Yes
Technetium (99mTc) fanolesomab	Cardiotoxicity	No	No	No	No	D	Yes

Temafloxacin	Haemolytic anaemia	No	No	No	No	D	Yes
Terfenadine	Cardiotoxicity	Patients on other medications	No	No	No	B/D	Yes
Thenalidine	Neutropenia	No	No	No	No	D	Yes
Tienilic acid	Hepatotoxicity	No	No	No	No	D	Yes
Tocainide	Hematologic	No	No	No	No	D	Yes
Tolcapone	Hepatotoxicity	No	LFT	No	No	B/D	Yes
Tolrestat	Hepatotoxicity	No	No	No	No	D	Yes
Troglitazone	Hepatotoxicity	No	No	No	No	D	Yes
Trovafloxacin	Hepatotoxicity	Children	No	No	No	D	Yes
Vitamin E (IV)	Hepatotoxicity	Children	No	No	No	A/D	Yes
Zomepirac Na	Anaphylaxis	No	No	No	No	D	Yes

*judgement at the time of first withdrawal

**agent for reversal of neuromuscular blockade

***recent studies have shown a low absolute risk of cardiovascular events in people without pre-existing CVD (https://www.ncbi.nlm.nih.gov/pubmed/25971925; https://www.ncbi.nlm.nih.gov/pubmed/20553061)

****possible overdose caused by physician administration of product in doses above that recommended by the manufacturer (the patient had failed to respond to therapeutic doses (https://www.ncbi.nlm.nih.gov/pubmed/6122831)

†Based on the Aronson et al criteria [11]. A Empower patient; B = Add caution; C = Add contraindication; D = Revoke licence

4. DISCUSSION

The withdrawal of medicinal products from the market by regulatory agencies because of drug-attributed deaths over the last 60 years has been largely justified, based on the available information at the time of initial withdrawal. Initial withdrawals following reports of deaths almost always occurred in either Europe or North America. The sooner deaths occurred following initial reports of the relevant adverse reactions, the sooner such products were withdrawn; this is consistent with our previous report, which showed that the shortened intervals between launch and withdrawal was largely due to quicker reports of deaths following product launch [7]. Regulatory authorities were also more likely to withdraw products from the market very quickly if the deaths involved children. The more recent the launch year, the quicker confirmatory studies were conducted after a product was removed from the market until 1980; although the interval to the first confirmatory study does not appear to have shortened afterwards, twice as many confirmatory studies were published when products were withdrawn, and the median interval was shorter (3 years versus 4 years). In most cases, the results of confirmatory studies investigating the association between the withdrawn products and adverse reactions suggested a true association.

Withdrawals were justified in the overwhelming majority of cases. When the decision algorithm suggested more than one possible course of action (17 cases), e.g., adding a contraindication or revoking the license, the regulatory authorities revoked the license, which suggests that they applied the precautionary principle [12]. The failure of initial withdrawals in Africa or South America suggests that concerted regulatory actions to withdraw products in those regions are taken only after actions have been taken in other regions.

4.1 Strengths and limitations

To our knowledge, this is the first review to examine whether post-marketing withdrawals of medicinal products because of drug-attributed deaths were justified, and also the first to examine the trends in the conduct of confirmatory studies when suspected drug-associated deaths are reported. We used a risk management algorithm to determine whether the initial withdrawals of products because of suspected drug-attributed deaths were justified. We comprehensively searched the literature to identify confirmatory studies exploring the drug-adverse event (or death) relationships; we accounted for the quality of the studies, and also went to great lengths to check for consistency across the studies. However, we recognize several limitations in this research. We may not have identified all medicinal products withdrawn from the market. We do not have data on the exact number of deaths attributed to each withdrawn product before withdrawal; indeed the number of deaths included in this research is probably an underestimation of the total number. Although we excluded deaths due to overdose, some of the reported deaths may have included patients who took overdoses, either deliberately or accidentally.

The algorithm we used for assessing regulatory actions when deaths are detected invokes population data and assumes causality. The final regulatory decision in any country will also depend on the capacity of the pharmacovigilance systems to account appropriately for the different domains of the algorithm; it is plausible that a lack of monitoring or preventive capacity could result in faster regulatory actions when new serious adverse drug reactions emerge. Economic considerations may also determine regulatory actions.

4.2 Implications for future decision making when deaths are suspected

Although it appears that regulatory authorities have appropriately revoked the marketing authorizations of medicinal products because of drug-attributed deaths, it is possible that effective compounds may have been hitherto removed from the market because of a lack of well-developed methods for risk assessment, monitoring, or minimization. Improved adverse

event monitoring and reporting strategies in clinical trials could identify the important feature of susceptibility, i.e. those who are at higher risk of adverse events, and therefore reduce the need to withdraw such products after approval, or lead to re-introduction after initial suspension. For instance, a clinical trial of felbamate, conducted in the context of a "black box" warning, showed that it was relatively safe in epilepsy [13], and alosetron was re-introduced for use restricted to women, who were thought to be less susceptible to the adverse outcome of ischaemic colitis [14]. Similarly, newer confirmatory evidence from public and industry funding has suggested that the risk of cardiovascular-related death with sibutramine is only significantly increased in patients with a prior history of cardiovascular disease [15,16].

Greater co-ordination of drug post-marketing surveillance across regulatory authorities should lead to consistency in the patterns of withdrawal across geographical regions when deaths are suspected; this will also minimize unnecessary exposure of the public to potentially fatal hazards, especially in settings with weak pharmacovigilance systems. The use of an algorithm such as we have used in this study could help to expedite the process of decision making.

In two cases (domperidone and loperamide) withdrawal was occasioned by deaths when the products were either administered inappropriately by physicians in doses above those recommended by the manufacturers [17,18] or used indiscriminately in children [19]. We therefore suggest that training of physicians in appropriate prescribing [20] should be a priority for undergraduate medical training, as should promotion of the rational use of medicines [21].

4.3 Implications for future monitoring of adverse drug reactions

Signal detection (e.g. from pharmacovigilance databases) does not prove a drug-adverse event association. Integrated evidence synthesis and algorithms that combine data from spontaneous adverse reaction databases and systematic reviews or observational studies (teleoanalysis) could be used to investigate drug-adverse event relationships, especially when deaths are suspected.

Drug manufacturers and regulatory authorities should ensure that there is consistency in how medications are used, irrespective of settings. For instance, there were discrepancies in the lower age limit for the use of loperamide in children [22]; the minimum age at which the product could be prescribed was two years in the USA and four years in the UK, but one year in developing countries. All the reported deaths associated with this product occurred in children aged less than six and a half months.

4.4 Implications for the future conduct of confirmatory studies

We identified confirmatory studies for a majority of the products we studied, and the results across the studies were largely consistent. In the very few instances where the direction of the effect estimate for a risk of adverse reactions was inconsistent (n = 3), the sources of funding for the studies differed. For example, publicly funded confirmatory studies showed that fenoterol was associated with an increased risk of asthma deaths in New Zealand and Japan [23,24,25] and in women aged over 35 years in Italy [26]. However, a similar study funded by a drug manufacturer did not find an association between fenoterol and an increased risk of asthma deaths [27]. Similarly, sertindole (used in the management of schizophrenia) was initially withdrawn because signals detected in adverse reactions databases suggested that its use was associated with a 10-fold increase in the risk of death, and publicly funded research showed that the product significantly increased the risk of adverse cardiovascular events [28]; however, confirmatory studies funded by the manufacturer did not suggest an increased risk [29,30] and the product was re-introduced. Furthermore, the number of deaths estimated to have been caused by the weight loss product benfluorex (1300) was based on the results of a publicly funded study [31], but another group of authors with financial ties to the manufacturer

has described the number of reported deaths as an overestimate [32]. While public-industry partnerships in drug development are being fostered [33,34], similar partnerships appear not to have been considered for monitoring serious adverse reactions. Collaborative research between public and independently funded entities when deaths are suspected could be considered for future confirmatory studies on harms, especially when the product has a favourable population benefit-to-harm balance.

5. CONCLUSIONS

Regulatory authorities have been largely justified in making withdrawal decisions when suspected deaths have been attributed to medicinal products. Medicinal products suspected of causing drug-attributed deaths are more likely to be withdrawn from the market quickly when there is a short interval between the first adverse reaction reports and the first reported deaths. New methods for regulatory courses of action when deaths are suspected should be developed, and research aimed at determining whether specific susceptibilities predispose particular patient groups to severe reactions should be instigated. Collaborative research involving both publicly and independently funded institutions should be encouraged, to help strengthen monitoring and evaluation processes when drug-related deaths (and other serious adverse drug reactions) are suspected.

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