ELSEVIER

If it does no harm, does it also mean it does no good?

Communicating the risks and benefits of medicines

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Pharmaceutical innovation, together with rising education, sanitation and wealth, prolonged life expectancy in industrialised countries throughout the 20th century. At the turn of the 21st century, with many, formerly common, lethal diseases confined to the developing world, the benefits of medical intervention are taken for granted in industrialized countries, and the expectations of safety have risen considerably. The perception and tolerance of risk has changed largely in the absence of immediate, population-wide health threats. Here, we review selected examples of drug withdrawals and adverse drug effects, and their impact on public perception. We analyse the role of major players, such as the media, patients, prescribers, regulators and pharmaceutical companies, and what actions are needed to better describe and communicate the risks and benefits of medicines to the public.

Introduction

Health suppliers, including the pharmaceutical industry, are experiencing higher demands on product safety than ever before. Recent high-profile drug withdrawals from the market, combined with a legal profession that offers 'no win – no fee' services, have led to some large litigation payouts in the USA. Such litigation invariably leads to headline news in the mass media. Although the safety of medicines today is monitored more closely than ever before, reported adverse events appear to be increased (Figure 1), giving the impression that drugs today are less safe than they were previously. However, is this true or is it a reflection of a changing risk–benefit tolerance of the population at large?

Perceiving risk

Cognitive psychology has provided insights into how individuals perceive risk. Factors that lead to overestimation of risk include publicity, severity and immediacy of impact, and lack of trust in the information source [1,2]. In relation to adverse drug effects, such psychological disposition might influence how a medicine is perceived, particularly one whose benefits are deferred (e.g. preventative medicine) but carries immediate risk, and/or receives high levels of negative media

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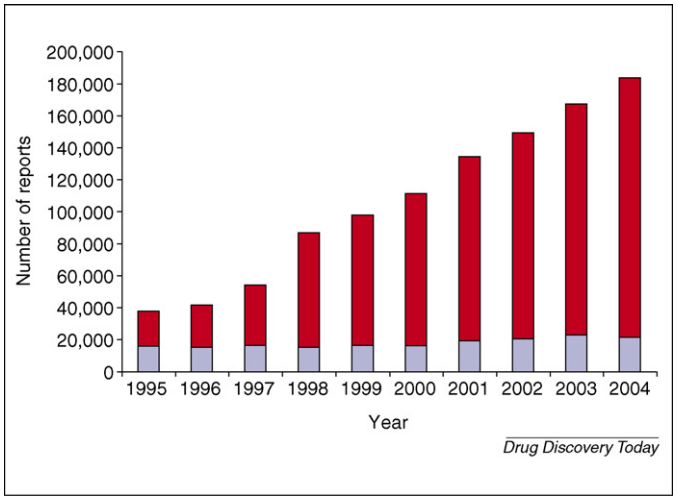

FIGURE 1

Serious adverse event reports to the FDA between 1995 and 2004. Red bars indicate 15-day reports (where manufacturers must report serious or unexpected adverse events within 15 days); blue bars indicate direct MedWatch data (voluntary reports that can be submitted by anybody if they suspect that there is a link between an event and a medication). Data from the FDA (http://www.fda.gov).

attention. Combined with cognitive processes that simplify complex probabilities to simpler, qualitative terms (either safe or unsafe), and a lack of trust in regulators, government and pharmaceutical companies as a source of information [2], it is perhaps not surprising that the safety of new medicines today is seen in such a negative light. This was especially true, for example, during the debate about the measles-mumps-rubella (MMR) vaccine, which is one of the case studies highlighted in this paper. We also analyse the efforts made by pharmaceutical companies to react to post-marketing safety issues, and discuss whether more testing during development will make medicines safe or whether risk–benefit needs to be communicated in a more understandable context. The current product-specific advertising campaigns (in the USA) are drawing much, sometimes warranted, criticism in terms of the potential overuse of medicines. However, the regulatory approach of inserting more frequent, stronger warnings into product labels (black-box warnings appear at the beginning of a product label) has the potential to confuse and scare the public who find it increasingly difficult to make informed risk–benefit decisions.

Hormone-replacement therapy as a case study of risk perception by the public

The Women's Health Initiative estrogen/progesterone study of 16,000 post-menopausal women found an increased health risk, including an increased risk of developing cancer [3]. The scientific presentation of this study referred to the risk in terms of hazard ratio, which is a complex statistical term. For example, for breast cancer, the risk was based on 245 (Prempro) versus 185 (placebo) cases of breast cancer (including non-invasive) out of a total of almost 16,000 women over a five-year period [3]. Despite relatively balanced media reporting of these USA study results, and of studies conducted in the UK, the overall impression was that hormone-replacement therapy (HRT) was 'unsafe' (this was the headline view that the media chose to promote), while failing to provide benefits. This perception was exacerbated by the regulatory guidance, with the US Food and Drug Administration (FDA) requiring a black-box warning for estrogen and estrogen–progestin-based HRTs (http://www.fda.gov), and the Committee on the Safety of Medicines in the UK issuing guidance that the risk–benefit was unfavourable for the prevention of osteoporosis (http://www.dh.gov.uk). However, viewing these data against a backdrop of 'normally' occurring breast cancer, which gives individual women a 5% risk of developing breast cancer over the 20-year period between the ages of 50 and 70 in the absence of risk factors such as genetic disposition and the use of medicines, the additional risk, for an individual woman on combination HRT for <15 years, of developing breast cancer over the same 20 years is <0.1% [4]. By contrast, alcohol (2–5 drinks a day) raises a woman's risk, compared to a non-drinker, by 40%; however, this 40% relative risk equates to an additional 2% risk added to an individual woman's risk of breast cancer [5]. Although a 2% additional risk is still low, it is 20-fold higher than the risk of HRT, and weight gain of >20 kg adds >4% risk [4], which increases individual risk to 9% over 20 years. In other words, one in 11 overweight women at age 50 will be diagnosed with breast cancer by the time they are 80-years old, compared to only one in 20 women that have either been on HRT for <15 years or that have not taken HRT. After these studies were reported the use of combination HRT dropped by >60% within one year in the USA [6], with similar trends in other countries.

Ironically, some women, who find the effects of menopause intolerable, have turned to natural estrogens, in the belief that these might be safer than HRT, even though comprehensive safety versus efficacy studies have not been conducted on these products. Black cohosh, one of these products, has been linked to liver injuries and now requires warning labels in Australia (http://www.tga.gov.au).

Herbal remedies are mainly unregulated (i.e. clinical studies to prove benefit and absence of risk are not conducted) and available over-the-counter. The absence of data gives herbal medicines a 'must be safe because it is natural' and 'it might do some good' perception to patients. It is, perhaps, not surprising that patients often exceed the recommended dose, even though this is an arbitrary one. The 'natural' product also hides the fact that these products are produced for profit and bypass the scientific rigour of conventional medicines.

The example of HRT highlights one of the shortcomings in communicating with patients, which is the fine line between interpreting and simplifying scientific data for patients, and providing them with the full set of scientific source data, which is often hard to interpret. Examples of patients as passive recipients of pre-interpreted medicinal information include black-box labelling, media reporting and pharmaceutical advertising (in the USA). A more active approach is taken by relatively few, mainly well-educated, patients, who conduct their own research on the internet and by other means. However, even this approach can be fraught with problems, as our next case study on the MMR vaccine demonstrates.

The MMR vaccine hysteria

In 1998 a potential link between the MMR vaccine and autism in children was claimed by Dr Andrew Wakefield in the peer-reviewed medical journal *The Lancet* [7]. A flurry of scientific responses followed, most of which either challenged

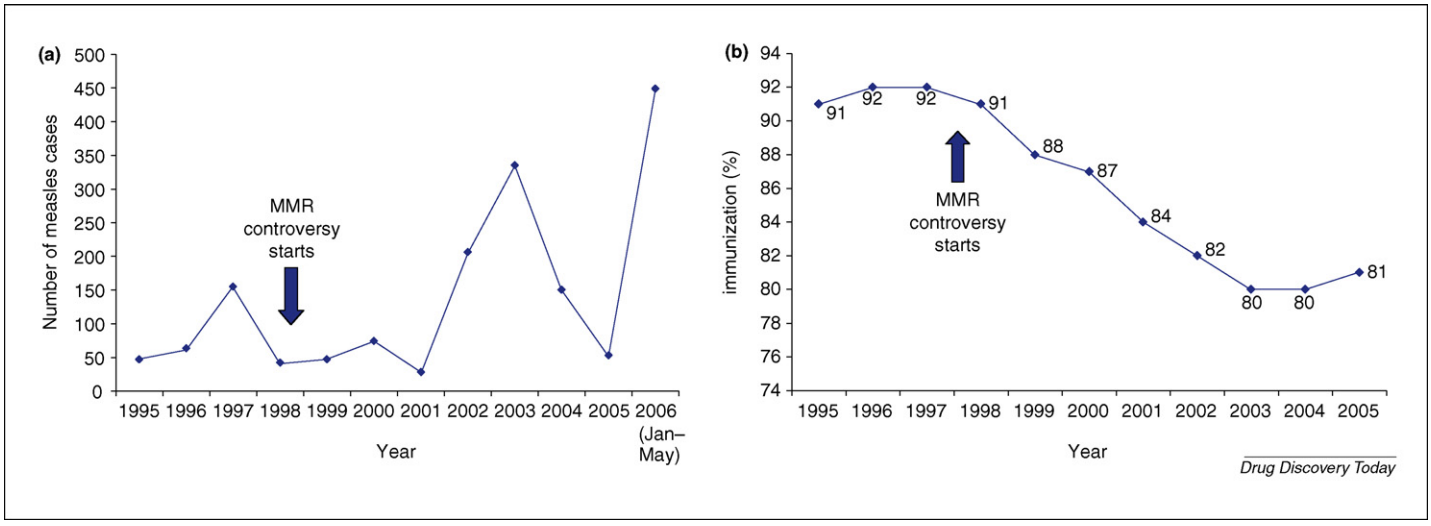

FIGURE 2

Impact of the MMR debate on measles cases and vaccination rates. **(a)** Numbers of confirmed measles cases in England and Wales between 1995 and 2006. Data from each quarter were added to derive the full-year figure. Data for 2006 are for the five months from January to May. **(b)** Immunization rates in England and Wales since 1995. Data from http://www.hpa.org.uk.

Dr Wakefield's results [8] or cast doubt over the scientific rigour of his analysis [9]. In addition, a potential conflict of interest emerged [10] that was later substantiated [11] and led, eventually, to the partial retraction of the paper. Unfortunately for the paediatric population in the UK and elsewhere, who had enjoyed a 92%, epidemiologically-effective, immunization coverage in 1998 (http://www.dh.gov.uk/PublicationsAndStatistics), Dr Wakefield's initial paper was publicised widely in the media, which led to an immediate drop in MMR vaccinations across the UK [12]. Vaccination now stands at ~80% coverage (Figure 2), which is insufficient to prevent measles epidemics. Similar vaccine fears were observed in other European countries and the USA. In the UK, concerned parents demanded that the National Health Service (NHS) provide single vaccines, a request without any scientific basis, which was refused by the NHS. In the eight years since, there has been a significant rise in cases of measles across the UK, despite slowly recovering vaccination rates (Figure 2). What parents were not told in 1998 was that measles alone claimed 100 lives each year in the UK before vaccinations were introduced [13]. Measles is also a major cause of child mortality in developing countries today with over half a million deaths each year (http://www.who.int). Epidemiologists warn that 92–95% vaccination coverage is required to prevent epidemics (http://www.who.int) and there is now a real risk that measles, mumps and rubella will re-emerge in developed countries. For example there were >50,000 cases of mumps in 2005 in England and Wales (http://www.hpa.org.uk), and 449 cases of measles in the first five months of 2006 (http://www.hpa.org.uk) (Figure 2) and one death. In the USA, after a measles outbreak in 2005 (which originated in Romania) parents stated that fear of the supposed side-effects of the vaccine (autism) prevented them vaccinating their children [14].

Is there a communication gap? The manufacturer–regulator–prescriber–pharmacist–patient contract

Various patient groups and other non-profit, non-governmental organisations provide information services that vary in the degree of simplification of complex medical information. However, our case studies show that there remains a gap in how complex information, particularly information on individual risk, is conveyed to patients. For example, black-box labelling (a regulatory intervention) is targeted at prescribers to communicate the presence of a risk and the need for heightened caution in prescribing the affected drugs. However, boxed or black-box labelling is introduced as soon as a credible link to safety issues arises. This can affect drugs for which there are either few or no switching alternatives, leaving prescribers and patients with a dilemma. Theoretically, prescribers should adapt their prescribing and monitoring behaviour to the specific risks associated with the black box-labelled drug. In addition, they should communicate the meaning of such a label for a particular drug to their patients by either contrasting the relative risk of taking the medicine compared to not taking the medicine or by presenting another relevant comparator of risk. In reality, few prescribers have the time to describe the magnitude and nature of the risk to their patients. Moreover there is a big fear that by implying risk a patient might not take the medicine and do themselves considerably more harm. This silent benefit/risk analysis (i.e. the prescriber has performed some analysis but imparts only implied benefits: take this and you will get better) means that patients are not informed of the risk. There is also difficulty in changing behaviours. Education and information need to be presented constantly and in novel forms to inform successfully; simple, repeated warnings are tolerated and ignored. Cigarettes and alcohol sales show no decrease despite high profile media campaigns and labelling, and consumers are resistant to the warnings. So contra-indicated drugs continue to be prescribed, monitoring is not performed and the scenario plays out until a large problem explodes.

NSAID black-box warning

The following is the standard template for the black-box warning for non-steroidal anti-inflammatory drugs (NSAIDs), which is inserted at the beginning of labelling.

Cardiovascular risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS and CLINICAL TRIALS).
- TRADENAME is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See WARNINGS).

Presented as such, what is the impact on the average prescribing physician and a patient in pain with, for example, backache? Apart from the firm contra-indication, what steps should be taken? How much time should be spent in discussing the risks and benefits between the patient and doctor? Because some NSAIDs are available over the counter, what level of information should be imparted to a purchaser in an airport pharmacy? What tools does the doctor really have at his disposal around this?

Some drugs have very high risks in particular conditions but still have very high value to the patient. Examples include Lotronex (alosetron) and Accutane (isotretinoin) for the treatment of diarrhoea-predominant irritable bowel disease in female patients and acne, respectively. Lotronex can cause ischemic colitis probably as a side-effect of its mechanism of action [15] and because of the severe effects of exaggerated constipation. Accutane is a powerful teratogen (because it is a retinoic acid derivative, which have known polypharmacology) that causes birth defects even after short duration at the clinical dose. Both drugs are licensed for use, and involve prescriber training, full-risk explanation to the patient and signed contracts between each of the parties. For example, Accutane is distributed and prescribed under the iPLEDGE program, which is a binding contract to ensure that Accutane is never taken by a patient at risk of pregnancy. Lotronex also is prescribed under a 'contract'. Typical of the signed patient conditions for Lotronex are:

'I will follow instructions in the Medication Guide about:

telling my doctor, before taking LOTRONEX, about any illnesses I have, or other medicines I am taking or planning to take.

taking LOTRONEX exactly as my doctor prescribes it.

stopping LOTRONEX and calling my doctor right away if I get constipated, if I have new or worse pain in my abdomen, or if I see blood in my bowel movements.

calling my doctor again if the constipation I called about before has not gotten better.

not starting LOTRONEX again unless my doctor tells me to do so, if I stopped taking it because I got constipated.

talking with my doctor 4 weeks after starting LOTRONEX to recheck my IBS symptoms.

stopping LOTRONEX and calling my doctor if my IBS symptoms have not improved after 4 weeks of taking 1 mg 2 times a day'.

These examples indicate the methods that are used to limit the known risk and allow 'safe' prescribing, but even with these sorts of programmes there is still risk. Accutane can cause lipid elevation, acute pancreatitis, hearing impairment, hepatotoxicity, inflammatory bowel disease, changes in bone mineral density, hyperostosis and visual impairment. This list appears overwhelming, but a glance at the label of any prescription medicine will reveal a similar list of side-effects usually observed in a small minority of patients. No similar contract to pregnancy testing and two forms of contraception can be written for these side-effects because precautions do not mitigate the risk. Moreover, the judgement that society in general makes about the value of a medicine and the burden of the disease, and the judgement made by the patient who is suffering might be very different, and both might vary considerably with hindsight. The dangers of cigarette smoking are often described as a lowered median life expectancy of ~4–5 years. In many smokers' minds this equates to a slightly shorter life enriched by the pleasure of nicotine. The median does not portray the horror of a 35–40-year old parent who is told he has contracted throat or lung cancer with, at best, a 12-month life expectancy.

Irritable bowel syndrome and acne do not sound like diseases of high medical need, but the shortage of available therapy and the effects these diseases have on individual patients warrants the continued use of these drugs. From what is outlined above there is a gap between the standard adverse effects labelling, black-box warnings and the types of programs outlined here. It is also noticeable that the guidance for Lotronex described above might, in a modified form, apply to every drug, particularly the compliance and the regular checks and balances. Even then it seems impossible to remove all risk. The iPledge programme was announced in 2005 (http://www.fda.gov/cder/drug/advisory/isotretinoin2005.htm). A previous programme, the Kaiser Permanente programme, which had many of the elements of iPledge and included electronic capture of all prescriptions and pregnancy-testing documentation, has been studied at length [16]. Even with multiple safeguards, foetal exposure still occurred (0.21% patients per course of therapy), the major reason being failure to use two forms of birth control. That it is impossible to eliminate all risk all the time is demonstrated by foetal exposure occurring in one patient in which full compliance was documented with every safeguard (1 in 11 508 prescriptions). Below these carefully monitored schemes are safety campaigns that use targeted warnings and rely on professionals to respond. Examination of the success of these illustrates a sudden fall-off in safe prescribing.

The prokinetic heartburn medicine cisapride (Janssen) was withdrawn in 2000 because of 340 cases of abnormal heart rhythm and 80 deaths (http://www.fda.gov) out of 30 million prescriptions. It is now known that interaction with other drugs that inhibit metabolizing enzymes can increase plasma concentrations of cisapride to levels that can lead to prolongation of the cardiac QT interval by inhibition of the cardiac inward rectifying K^+ channel (IKr). This can trigger abnormal heart rhythms and, in some cases, cause fatal torsades de pointes. Today, all major pharmaceutical companies screen both preclinically and clinically for the inhibition of IKr as well as performing clinical drug-interaction studies well ahead of marketing application. The risk of cisapride was managed initially with strong warnings around the

covariates [17]. A 'Dear Healthcare Professional' letter in 1995 described a risk of prolonged QT intervals and serious ventricular arrhythmia in patients who received macrolide antibiotics and imidazole antifungals in conjunction with cisapride. A further letter in June 1998 that expanded the list of contraindicated co-medications had wider distribution, and was accompanied by substantial internet and media coverage, and complemented by an effort to inform large pharmacy dispensing-information organizations of the warnings against concurrent use of the named drugs: the Dear Healthcare Professional letter of October 1995 had no discernible effect on prescribing practices, as measured at the pharmacy. The 1998 letter and surrounding activity were followed by a 66% decline in same-day dispensings to patients of cisapride and the contra-indicated drugs and a smaller, but pronounced, decline in dispensings in the wider time windows. Although this study shows some degree of response, it is not at a level that might be termed safe prescribing. Other studies around this programme have been even more negative. For example, Smalley *et al.* [18] conclude that: 'The FDA's 1998 regulatory action regarding cisapride use had no material effect on contra-indicated cisapride use. More effective ways to communicate new information about drug safety are needed'. Clearly the warnings have to be multimedia and widespread to be effective, and even then they might not have the desired effect of reducing the impact of a known risk factor.

The diabetes drug troglitazone (Parke-Davis) was withdrawn in the same year after 63 deaths from acute liver failure (out of >1 million users) (http://www.webmd.com; http://www.pfizer.com). Soon after initial marketing in March 1997, troglitazone, the first thiazolidinedione antidiabetic agent, was found to cause life-threatening acute liver failure, and it was removed from the market in March 2000. Before withdrawal, the US FDA had a comprehensive risk-management programme, including repeated labelling changes and 'Dear Healthcare Professional' letters, on the requirement for periodic monitoring of liver enzymes in patients taking troglitazone [19]. The programme consisted of four, progressively more stringent, liver-monitoring recommendations. Baseline testing increased from 15% before any FDA monitoring recommendations to 44.6% following the most severe warnings. But this monitoring was highest following one month of therapy and had fallen back to the baseline value after three months. The risk-management efforts therefore did not achieve the sustained improvement in liver-enzyme testing that is necessary for the safe prescribing of troglitazone.

The dilemma seems to be that to really inform the patient, the prescribing clinician and the dispensing pharmacist, the risks of medicines have to be presented repeatedly to a much higher degree than the benefits. This is counterproductive to the compliant use of medicines for the maintenance and improvement of health.

How safe are medicines today?

The perspective of a member of the public and even patients, as shown above, is unlikely to be influenced by the package inserts (labels) of drugs. Most consumers do not read the labels, packages and, even, instruction manuals of any products they buy (whether electrical goods, cars or furniture flatpacks) until a problem is encountered. Most people's opinion reflects either their own experience or recent opinions expressed in the media. The media will distil its message as much as possible for impact, and balance is rare. Typical headlines following a drug withdrawal or even a black-box warning is 'MILLIONS TOOK KILLER DRUG'. This is not untrue and certainly grabs the attention more than the fully correct 'fatalities occurred in fractionally small proportion of the millions whose serious illness benefited'. Moreover some drugs are more newsworthy than others. The treatments for male erectile dysfunction, particularly inhibitors of phosphodiesterase type 5 (PDE5), have probably collectively more column inches in the popular press than any other. Side-effects are just as newsworthy in this class and the recent labelling change (http://www.fda.gov/cder/foi/label/2006/020895s023lbl.pdf) concerning non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, which was reported post-marketing in temporal association with the use of PDE5 inhibitors, was major headline material (e.g. 'SEX DRUG MAKES YOU BLIND'). This occurred even though the labelling states specifically that the finding was very rare and that most patients affected had underlying anatomic and vascular risk factors for developing NAION, including, but not necessarily limited to low cup:disc ratio ('crowded disc'), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking.

The impression can be that serious adverse drug reactions are increasing, 'defective' products are brought to market that have not been adequately tested, and that pharmaceutical companies suppress the findings to maximise profit. In short, fuelled by the media, and several high-profile events over the last five years, there is a perception that current medicines are not safe. But is this really the case and how should it affect communication about risks (and benefits)?

What are the potential reasons for drug safety issues?

(i) A drug has a side-effect that was not expected at the time of marketing and has either not been tested specifically for the side-effect during the R&D process, or has been tested and toxicity was not discovered because of low incidence rates. This might be due to: primary pharmacology (toxicity of Type A1), for example Vioxx; secondary pharmacology (toxicity of Type A2), for example cisapride; and general toxicity of types B (immunological) and C (chemical reaction with tissue) [15].

(ii) There is an expected safety issue, for example cytotoxic oncology drugs, which are often designed to cause type C toxicities to kill tumor cells.

(iii) A medicine is genuinely defective because it has been manufactured inappropriately (e.g. it contains either contamination or residues)

(iv) A drug has either been prescribed inappropriately in violation of the drug label (e.g. overdosed, prescribed with other contra-indicated drugs, and prescribed in contra-indicated patient populations) or it has been inappropriately monitored so that early signs of side-effects were missed

(v) The side-effects of the disease overlap with the potential side-effects of the medicine, making a distinction between cause and effect either difficult or impossible (e.g. antidepressants and suicide).

TABLE 1

Examples of safety issues in marketed drugs and the subsequent R&D response

Decade	Medicine affected	Issue	R&D response	Predictive ability of screen to avoid previous safety issue
1960s	Thalidomide	Reproductive toxicity	Routine reproductive toxicology testing	High
1990s	Terfenadine	Drug interactions	Cytochrome P450 panel screening; clinical drug interaction studies	High
1990s	Fenfluramine, d-fenfluramine	Secondary pharmacology	Broad ligand profiling in Discovery	High
1990s	Terfenadine, cisapride	Secondary pharmacology (QT prolongation)	QT – prolongation testing preclinically and clinically	High
1990s	Troglitazone, bromfenac	Idiosyncratic hepatotoxicity	Chemical 'alerts' system (avoidance of known reactive structures and reactive metabolites) Attempts to develop *in vitro* markers of hepatotoxicity Preclinical and clinical screening for markers of liver injury	Medium–low

As much as drugs improve life expectancy and quality-of-life for millions of patients, adverse drug reactions also kill thousands of patients. At the extreme, one meta-analysis estimates that 106,000 deaths in the USA in 1994 might have been caused by adverse drug reactions [20]. This would make drug side-effects the sixth leading cause of death in the USA (4.6% of all deaths due to adverse drug reactions). This estimate (which was based on admission rates in 1994 and adverse drug reactions before 1981) is quoted widely in grant applications, publications and presentations by scientists working in the area of adverse drug reactions (e.g. drug–drug interactions). These repeat messages rapidly raise the apparent validity of this estimate because the audience is not exposed to the caveats and accepts it as a fact. It is important in understanding the actual risk that other studies that used death certificates and/or the US MedWatch data report that only between 0.1% and 0.3% of deaths are caused by adverse drug reactions.

It is unclear which percentage is correct and, importantly, what fraction of these deaths is attributable to which reason listed above. However, a detailed analysis of hospitals in Liverpool [21] gives a similar figure to the Lazarou study of fatal adverse drug reactions per hospital admission. In this study, 28 deaths were related to adverse drug reactions out of 18 820 admissions (with 1225 admissions due to adverse drug reactions). Almost all of these adverse reactions stemmed from the primary pharmacology. The 'most dangerous drug' was aspirin, which was either the sole medicine or in combination (particularly with other NSAIDs and warfarin) and a factor in 17 of the 28 deaths. Another over-the-counter medicine, paracetamol, has a narrow therapeutic index and is responsible for many cases of liver failure due to inappropriate dosing (self-medicated). The figures somewhat reflect the huge numbers of patients treated: 30 million people take NSAIDs daily and an estimated 16 500 deaths each year in the USA are caused by NSAIDs [22]. There is also evidence that prescription errors and expected side-effects account for a substantial proportion of these deaths. For example, >7000 deaths per year in the USA are thought to result from medication errors [23].

Taking a closer look, the greatest impact drug manufacturers can have on drug safety is through reducing the numbers of unexpected safety issues while, at the same time, trying to ensure the medicine is used appropriately. However, this requires learning from the market place and establishing feedback loops into R&D to implement screens that can measure such safety problems early, which has been ongoing since the thalidomide disaster.

Table 1 lists several screens that have been introduced by most major drug companies in response to safety issues identified in the market place. An important detail in Table 1 is the difference between predictive and non-predictive screens. Predictive screens might, theoretically, eliminate the numbers of unexpected safety issues, whereas less-predictive screens cannot. It is unlikely that a new medicine will have an unrecognized drug–drug interaction or QT liability before marketing.

The difference in incidence versus severity of reaction of adverse events between 'preventable' and 'non-preventable' adverse drug reactions has been outlined by Frattarelli [24]. In his analysis, preventable drug reactions fit a linear model (and can, theoretically, be reduced to zero), but non-preventable reactions fit a power law equation (and, thus, cannot be reduced to zero). The previous example of alosetron is unpreventable because the mechanism of action leads to the side-effect. Cilansetron is a newer 5-hydroxytriptamine (5-HT_3) receptor antagonist of the same class as alosetron. This compound has an identical risk (0.4% per year of patient exposure) of ischaemic colitis to alosteron, which indicates the link to the antimotility effects of the primary pharmacology. Cerivastatin (Bayer) is the most potent of a group of drugs that inhibit hydroxymethyl glutanyl-coenzyme A (HMG-CoA), known as statins. These drugs lower the incidence of mortality from cardiovascular disease dramatically. Muscle toxicity (myopathy) is a low incidence adverse effect of all HMG-CoA inhibitors, the extreme form of which is rhabdomyolysis. The occurrence of rhabdomyolysis with cerivastatin is up to 10-fold greater than with other HMG-CoA inhibitors. In addition, the systemic bioavailability of cerivastatin is the highest of any statin drug and metabolism gives rise to circulating, active metabolites. In this context, bioavailability can be viewed as the ratio between systemic burden (muscle toxicity) and hepatic burden (liver efficacy), and might point to a key factor that differentiates cerivastatin from similar drugs. This balance was changed further when the drug was prescribed with gemfibrozil. Gemfibrozil and its glucuronide metabolite inhibits [25] the hepatic uptake of cerivastatin (actively transported into the liver by Organic Anion Transporting Polypeptide) and its metabolism (by CYP2C8). Because of the inhibition of hepatic uptake, dose adjustments do not alter the impact of the drug interaction, and efficacy is

always accompanied by increased rhabdomyolysis. Here, the withdrawal of this drug was possible because other examples in the class reduced, but did not eliminate, the risk.

There are very few reported cases of truly defective drugs that lead to patient deaths; that is medicines that have been manufactured in a way that leads, unintentionally, to a substandard product (e.g. the clotting factor for hemophiliacs that contained live-virus contamination). Unfortunately, litigation lawyers and the media like to use the term 'defective' for any safety issue that is associated with medicines. This furthers the impression that any newly arising safety issue is caused by negligence of the manufacturer, rather than (in many cases) a genuinely unexpected finding that leads to new scientific insights and appropriate R&D responses to prevent the incidence from recurring.

Unexpected side-effects and withdrawals of high-profile drugs

In recent years, several 'blockbuster' drugs have been associated with safety concerns. Most notable are the withdrawals of dexfenfluramine (Wyeth-Ayerst), fenfluramine (American Home Products) and fenfluramine/phentermine (Wyeth-Ayerst) in 1997. These drugs, which were intended to treat obesity, contained a similar active principle, and had the side-effect of heart valve disease and associated cases of pulmonary hypertension. Approximately 1.2–4.7 million patients took one these drugs (http://www.fda.gov) and, at the time of withdrawal, there were 113 confirmed cases of drug-induced valvulopathy, of which 27 patients required valve replacements and three died. It is now known that Redux- and Pontimin-induced heart valve disease is likely to be caused by secondary pharmacology (type A2 toxicity) as a result of the activation of 5-HT_{2B} receptors. The causal relationship was unknown at the time, but screening (broad ligand profiling) of prospective medicines makes this toxicity unlikely to recur in the future.

These withdrawals were followed by the lipid-lowering drug cerivastatin in 2001 because of rhabdomyolysis with ~100 deaths out of 6 million patients treated, as outlined previously. The painkiller Vioxx (rofecoxib, Merck) was withdrawn in 2004 because of cardiovascular side-effects (heart attacks and strokes) with a clinical impact that is yet to be determined.

The reality of drug safety

These events, perhaps because they were widely publicised, affect many patients and support the image that the pharmaceutical industry makes profit on the back of unsuspecting patients and have led to the impression that newer drugs are less safe than older drugs. However, the available data indicates that this is not the case. A cohort of older drugs approved between 1971 and 1992 had 14 safety-based withdrawals out of 488 medicines (2.9%), and those approved between 1992 and 2005 had 10 withdrawals out of 325 medicines (3.1%) (http://www.fda.gov). Fisher's exact test yields $P = 0.8012$, which is not significant. Looking at a different set of data, for example a 20-year period of drugs approved between 1979 and 1998 divided into five-year cohorts, the rate of subsequent withdrawals was 3.2% (1979–83), 3.5% (1984–88), 1.6% (1989–93) and 1.2% (1994–98) (http://www.fda.gov). The difference between the cohorts is not statistically significant.

By contrast, reporting of serious adverse events has increased year on year, based on FDA published data (Figure 1). In addition, if

TABLE 2

Recent drug withdrawals and their estimated risk–benefit profile

Drug	Year of with-drawal	Number of serious adverse events or deaths	Number of patients	Other drugs of the same class remain available after withdrawal?	Health benefits	Medical need of health condition treated by withdrawn drugs	Refs
Fen-Phen	1997	113	1.2–4.7 million	No, and no effective alternatives to treat obesity exist	Reduced weight, and improved morbidity and mortality	Estimated >100,000 excess deaths in USA each year through obesity[a]	[26]
Cisapride	2000	80	30 million prescriptions[b]	No, and few drug classes treat heartburn	Reduced acid reflux (thereby avoiding some esophageal cancers)	Estimated 8000 esophageal cancers in USA each year caused by acid reflux[c]	[27]
Troglitzone	2000	63	~1 million	Yes, several options in the same class emerged at the time of withdrawal	Avoided potentially lethal complications of diabetes	Estimated >70,000 deaths in USA each year through diabetes	[d]
Cerivastatin	2001	100	6 million	Yes, several statins provide options post-cerivastatin withdrawal	Avoided heart attacks and stroke	Estimated >900,000 cardiovascular disease deaths in USA each year through hypertension and high blood lipids	[d]
Rofecoxib	2004	Unknown (10,000 court cases filed); estimated 16,500 deaths from NSAIDs in arthritis patients in the USA in 1997	90 million prescriptions[b]	Yes, other COX-2 inhibitors provide options	Improved quality of life	Gastrointestinal side-effects associated with the use of non-selective NSAIDs	[22]

[a] Obesity defined as BMI ≥30.
[b] http://www.cancer.org.
[c] Number of prescriptions is given where patient numbers are not available.
[d] http://www.cdc.gov.

withdrawals are counted by the year of withdrawal rather than the year of approval, it appears that withdrawals are becoming more frequent: between 1970 and 1979 there were no withdrawals, between 1980 and 1989 there were five withdrawals, between 1990 and 1999 there were 10 withdrawals and in the five-year period between 2000 and 2005, nine drugs were withdrawn for safety reasons (http://www.fda.gov). This points to improved monitoring of drug safety and an increasingly effective regulatory response in protecting the public from drugs that are deemed to have an undesirable benefit:risk ratio. Table 2 identifies some major drugs that have been withdrawn in recent years. Interestingly, all but one are from drug classes in which either safer alternatives exist, for example, atorvastatin (Pfizer), simvastatin (Merck) and others, in the case of cerivastatin, or where other drug classes can substitute, as with cisapride. Incidentally this highlights the need for a selection of drugs with similar mechanisms (popularised as MeToos), thus, ensuring the best benefit:risk ratio. At the time of launch and certainly during development some of the subtle differentiating features (such as liver:blood concentration ratio in the case of statins) might not be fully known or recognized. As in the case of the MMR vaccine, the perception of drug safety and risk–benefit is influenced by the availability of safer alternatives. As more treatment options become available, it is conceivable that safety-based drug withdrawals will increase, not because drugs are becoming less safe, but because the option to switch to the best risk:benefit ratio increases as more medicines are tried and tested in the market place. Combined with improved monitoring in the market place, faster regulatory responses and improved R&D safety testing that remove overtly toxic drugs before they reach the market, the exposure of the general public to safety issues will continue to be limited.

The safety of drugs must be a concern and addressed with the utmost diligence by all parties, including the manufacturer (usually the innovator because by the time medicines are off-patent their safety is generally established), the prescriber, the regulator, the pharmacist and the patient. All these parties must

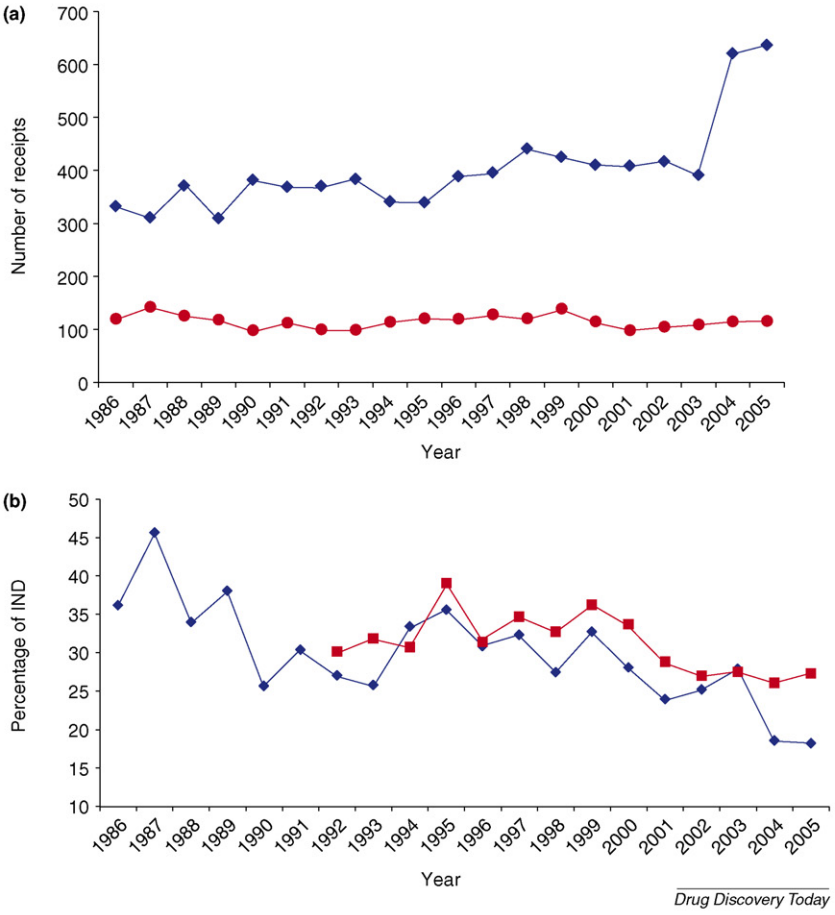

FIGURE 3

The growing gap between clinical trial candidates (INDs) and new drug applications (NDAs). **(a)** IND versus NDA applications to the FDA each year. Diamonds indicate number of Center for Drug Evaluation and Research (CDER) commercial IND receipts, circles indicate CDER NDA receipts. **(b)** IND per NDA application based on a six-year development phase between IND and NDA application. Diamonds depict the ratio in each year of NDA over IND receipts [taken from (a)]. This line shows a sharp decline in the ratio of NDAs to INDs, which indicates that attrition has been increasing between clinical trial application (IND) and seeking marketing approval (NDA). Squares are calculated with a six-year time delay between IND and NDA, which is approximately the current average speed of development between IND and NDA. This links attrition to the same cohort of drugs, but shows the same trends as the non-time-adjusted squares. This means that attrition is probably the true causative factor in the current decline of new drug applications, not a lack of development compounds.

keep sight of the benefit part of the risk–benefit equation. One measure is the risk of the consequences of a disease compared with the risk of therapy. Table 2 lists the death toll from disease, but does not claim that all these deaths would be avoided by using the example medicines, although effective drug treatment might reduce the death burden significantly, as is the case with statins [28–30]. The disease burden, in this case the mortality statistics, provides the theoretical maximum benefit a medicine can provide. Compared to this are the mortality figures incurred by the example medicines that are judged to have too high a risk to be used (Table 2). Data are now available for the statistical impact on reduction in mortality for some of the major drug classes. These data provide a realistic backdrop to the discussion of risk–benefit and point to the fact that drugs such as cerivastin (and troglitazone) might have remained on the market had alternative, safer statins (and glitazones) not been available (see above).

A more complex situation arises when a new drug has a different safety profile to the existing therapy. Warfarin (an oral inhibitor of thrombin) is a difficult drug to prescribe safely because of large inter-patient variability and a narrow therapeutic index in all patients. This limits the use of the drug in several indications including high risk of hemorrhagic stroke. Ximelagatran (Exanta, AstraZeneca), is a novel, oral inhibitor of thrombin with a far superior safety profile in patients apart from a risk of hepatotoxicity (possibly severe) in a small minority. The drug has been approved in Europe, but following post-approval data in Europe, approval in the USA was not granted.

Conclusion

No drug is completely safe, or as Paracelsus stipulated: 'the dose makes the poison'. Today, this ancient wisdom has been transformed by the lessons from the growing repertoire of medicines on the market. Only ~3% of all medicines cause such severe adverse events that they are withdrawn from the market, but all these events have enriched the knowledge about the mechanisms of toxicity. Learning from the adverse events of marketed drugs has improved safety testing during R&D. The increased battery of safety tests has, conceivably, contributed to the widening gap between the rapidly growing rate of new investigational new drug applications and the slow increase in new drug applications (Figure 3). Drugs with QT-prolongation issues or other known, potentially toxic, secondary pharmacology, no longer reach the market. Known toxicities in areas of high medical need are expected to reduce in future through advances in delivery (e.g. Gliadel Wafer, Mylotarg and Zevalin) and novel, safer mechanisms (e.g. Herceptin and Gleevec).

However, unless there is a major step in knowledge acquisition and science, unpredictable, idiosyncratic toxicities cannot be eliminated completely; neither is it likely that a true understanding of the benefit–risk association will emerge when the possible side-effects of a drug mirror either the effects or the side-effects of the disease they are treating. Examples of this include drugs for depression and the risk of suicide. Furthermore, as the launch of new medicines based on novel targets increases, so does the likelihood that some will have unexpected side-effects through primary pharmacology, which might only become apparent later in the drugs life. The cardiovascular risk of herceptin is an example. As a society we can opt to increase regulation with a view to reducing medicinal risk further. Consequences of such a step are, most likely, a further increase in the costs of developing new medicines and, almost certainly, fewer new classes of drug brought to market. In the present system, increased regulation, in the form of contra-indications, boxed warnings and even 'Dear Healthcare Professional' letters, does not seem effective in its present form. In fact, the only regulatory activity that reduces risk is to make a drug non-approvable (e.g. Ximelagatran) or to withdraw it (Cisapride and Troglitazone). The solvable gap seems to be in safer prescribing; the information exists for this to be practiced, but it seems often it might not reach the people it is meant to. If we accept that drugs are dangerous if used wrongly (which is obvious), why do we, apparently, allow this to happen so often? The shortfalls include training and information formats, surveillance and regular checks on what is being prescribed, when, with what and to whom. Somehow, the manufacturer–prescriber–patient contract must become a reality. In an Editorial, Wooseley [31] states that 'Unfortunately, the medical care infrastructure lacks an integrated coherent system for optimal delivery of prescription medications to patients. Myriad conglomerations of uncoordinated mechanisms from mail order or internet pharmacies to pharmacies in grocery stores to physician-dispensed samples and drugs have succeeded in making medication purchases convenient, but without full appreciation for the increasing complexities of therapeutics and the potential risks of medications. A more uniform system would make it simpler to correct the serious problems that exist, but this is unlikely to occur in our free-market society. It is in everyone's best interest that these efforts to promote safe use of medications succeed. The pharmaceutical industry cannot afford to spend more than $500 million to develop a new drug only to remove it from the market because physicians prescribe it in ways contraindicated in the label. Physicians cannot afford to waste valuable time learning new treatments and adverse effects, only to have the treatment withdrawn from the market. Most importantly, patients should no longer be harmed by otherwise safe medications that are used in ways known to be potentially dangerous.' It would be encouraging to think that six years later these statements are outdated, but they seem as true today as when they were written, except the cost of development now exceeds $1 billion.

To significantly advance the presentation and understanding of risk–benefit with pharmaceutical therapies, we propose a five-point call-to-action:

(i) Clearer, more succinct, well-written product labels. Both for healthcare professionals and for patients.

(ii) Better education of all healthcare professionals on the issue and analysis of risk–benefit. These healthcare professionals would then play the key 'front guard' role in communicating risk–benefit to patients.

(iii) Clearer presentation of risk–benefit by all pharmaceutical product sponsors. A basic template, similar to the templates or outlines used for preparation of standard regulatory submission documents, could be developed.

(iv) Commitment to assure that better, more complete, more understandable product information is presented to patients. This includes information on relevant risk–benefit compara-

tors and, using objective data, the consequences of taking and not taking the medicine. This would cover efficacy as well as safety endpoints.

(v) Commitment by all healthcare and health-field communicators to be balanced, comprehensive and complete in their presentation of risk–benefit issues; doing this will help educate everyone about risk–benefit analysis and issues, not doing this will add to the current confusion and inappropriate understanding of risk–benefit.

In summary, we have outlined here the necessity of pharmaceutical products to the healthcare system. Like all products, the huge benefit comes with some risk. Co-ordinated action resulting in the correct prescribing of these medicines to an informed patient population will make the benefit–risk equation even more favourable.

Conflict of interest

All authors declare a conflict of interest as they are each employed by Pfizer and own equity in the company.

References

1 Taylor, S. (1991) Asymmetric effects of positive and negative events: the mobilization-minimization hypothesis. *Psychol. Bull.* 110, 67–85

2 Lloyd, A.J. (2001) The extent of patients' understanding of the risk of treatments. *Qual. Health Care* 10 (Suppl. 1), i14–i18

3 Chlebowski, R.T. *et al.* (2003) Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative randomized trial. *J. Am. Med. Assoc.* 289, 3243–3253

4 Archer, D.F. (2005–2006) Hormone therapy and breast cancer: issues in counselling women. *Menopausal Med.*13, 5–12.

5 Smith-Warner, S.A. *et al.* (1998) Alcohol and breast cancer in women: a pooled analysis of cohort studies. *J. Am. Med. Assoc.* 279, 535–540

6 Hersh, A.L. *et al.* (2004) National use of postmenopausal hormone therapy. *J. Am. Med. Assoc.* 291, 47–53

7 Wakefield, A.J. *et al.* (1998) Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 351, 637–641

8 Peltola, H. *et al.* (1998) No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study. *Lancet* 351, 1327–1328

9 Walker, D.R. (1998) Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 351, 1356–1357

10 Rouse, A. (1998) Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 351, 1356

11 Horton, R. (2004) A statement by the editors of The Lancet. *Lancet* 363, 820–821

12 Begg, N. *et al.* (1998) Media dents confidence in MMR vaccine. *BMJ* 316, 561

13 Gay, N.J. *et al.* (1995) Interpretation of serological surveillance data for measles using mathematical models: implications for vaccine strategy. *Epidemiol. Infect.* 115, 139–156

14 Manning, A. (2006) Measles remains a threat despite 'eradication'. *USA Today* 2nd August

15 Smith, D.A. and Schmid, E.F. (2006) Drug withdrawals and the lessons within. *Curr. Opin. Drug Discov. Devel.* 9, 38–46

16 Cheetham, C.T. *et al.* (2006) A risk management program aimed at preventing fetal exposure to isotretinoin: retrospective cohort study. *J. Am. Acad. Dermatol.* 55, 442–448

17 Weatherby, L.B. *et al.* (2001) Contraindicated medications dispensed with cisapride: temporal trends in relation to the sending of 'Dear Doctor' letters. *Pharmacoepidemiol. Drug Saf.* 10, 211–218

18 Smalley, W. *et al.* (2000) Contraindicated use of cisapride impact of food and drug administration regulatory action. *J. Am. Med. Assoc.* 284, 3036–3039

19 Graham, D.J. *et al.* (2001) Liver enzyme monitoring in patients treated with troglitazone. *J. Am. Med. Assoc.* 286, 831–833

20 Lazarou, J. *et al.* (1998) Incidence of adverse drug reactions in hospitalised patients. *J. Am. Med. Assoc.* 279, 1200–1205

21 Pirmohamed, M. *et al.* (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* 329, 15–19

22 Wolfe, M.M. *et al.* (1999) Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N. Engl. J. Med.* 340, 1888–1899

23 Hampton, T. (2006) Medication errors. *J. Am. Med. Assoc.* 296, 384

24 Frattarelli, D.A.C. (2005) Adverse drug reactions and avalanches: life at the edge of chaos. *J. Clin. Pharmacol.* 45, 866–871

25 Shitara, Y. *et al.* (2004) Gemfibrozil and its glucuronuide inhibit the organic anion transporting poypeptide 2 (OATP2/OATP1B1: *SLC21A6*) mediated hepatic uptake and CYP2C8 mediated metabolism of cerivastatin: analysis of the mechanism of the clinically relevant drug-drug interaction between cerivastatin and gemfibrozil. *J. Pharm. Exp. Therap.* 311, 228–236

26 Flegal, K.M. *et al.* (2005) Excess deaths associated with underweight, overweight, and obesity. *J. Am. Med. Assoc.* 293, 1861–1867

27 Pohl, H. and Welch, H.G. (2005) The role of over diagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J. Natl. Cancer Inst.* 97, 142–146

28 Sytkowski, P.A. *et al.* (1990) Changes in risk factors and the decline in mortality from cardiovascular disease. The Framingham Heart Study. *N. Engl. J. Med.* 322, 1635–1641

29 Horwich, T.B. *et al.* (2004) Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. *J. Am. Coll. Cardiol.* 43, 642–648

30 Sever, P.S. *et al.* (2003) Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. *Lancet* 361, 1149–1158

31 Wooseley, R.L. (2000) Drug labelling revisions, guaranteed to fail? *J. Am. Med. Assoc.* 284, 3047–3049