I
General Aspects

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Why Drugs Fail – A Study on Side Effects in New Chemical Entities

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1.1
Introduction

Drug development is a long and cost-intensive business. Only after years of lead identification, chemical optimization, *in vitro* and animal testing can the first clinical trials be conducted. Unfortunately, many projects still fail in this late stage of development after a considerable amount of money has been spent. According to estimates, preapproval costs for a new drug exceed US$ 800 million [1].

Approximately 10% of new chemical entities (NCEs) show serious adverse drug reactions (ADRs) after market launch. Such events usually result in 'new black box warnings' by the US Food and Drug Administration (FDA), label change or market withdrawal. The most common causes for these actions are hepatic toxicity, hematologic toxicity and cardiovascular toxicity [2]. Reasons for such ADRs, which are identified only after NCEs are launched on the market, include the narrow spectrum of clinical disorders and participating patient profiles in clinical studies as well as the fact that serious ADRs are often rare and that the number of patient exposures required to identify such occurrences sometimes may range over a few millions [3].

To avoid the occurrence of ADRs in the future, specific trials to detect them should therefore be conducted before an NCE is launched on the market. Before this can be done, however, the major reasons leading to the withdrawal of drugs and termination of NCE-to-drug development should be identified and analyzed.

In this chapter, reasons why 17 drugs were withdrawn from the Western market between 1992 and 2006 are discussed and facts on 63 terminated clinical development projects presented, so as to identify the most common reasons for the failure of drugs in this late stage of drug development. This analysis is then compared with two previous related studies published more than 18 years ago by Prentis *et al.* [4] and Kennedy [5].

The study by Prentis *et al.* [4] included an analysis of 198 NCEs, developed between 1964 and 1985 by British pharmaceutical companies but had not been marketed for reasons presented in Figure 1.1. Kennedy [5] further analyzed these data and noticed that a high number of anti-infective drug development projects were all terminated

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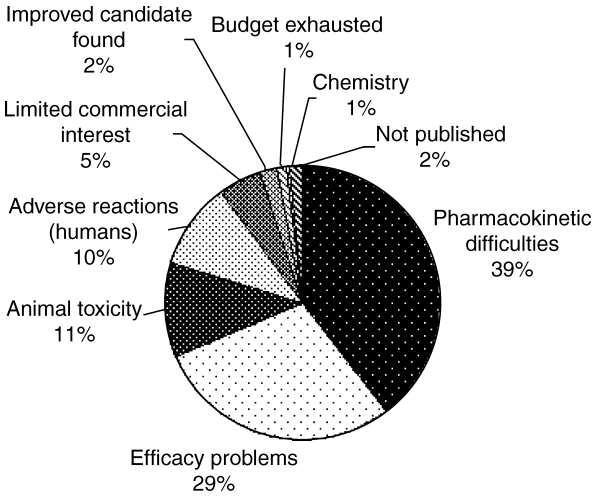

Figure 1.1 Reasons for drug development termination from 1964 to 1985 ($n = 198$).

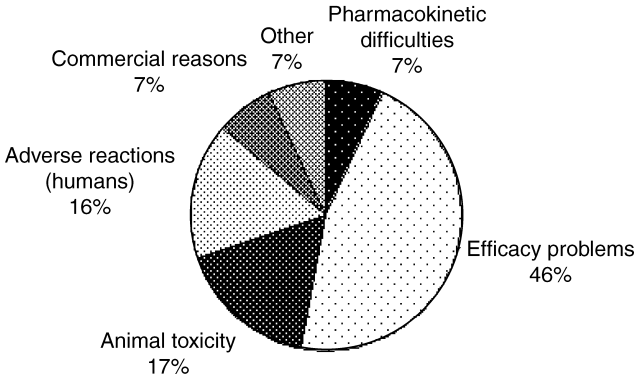

Figure 1.2 Reasons for drug development termination, excluding anti-infectives ($n = 121$).

because of pharmacokinetic difficulties. He therefore excluded the anti-infective NCEs from the statistics and presented the facts as illustrated in Figure 1.2.

1.2
Drugs Withdrawn from the Market between 1992 and 2006 Listed Alphabetically

1.2.1
Amineptine

The atypical tricyclic antidepressant amineptine (Survector) is an indirect dopamine agonist, which selectively inhibits dopamine uptake and induces its release, with additional stimulation of the adrenergic system. Its antidepressant effects are similar to those of other tricyclic antidepressant drugs. However, it acts more rapidly, is better

tolerated and has little cardiovascular, analgesic or anorectic effects [6]. Amineptine was launched on the market in 1978 for the treatment of dysthymia and was marketed by Merck and Servier [7]. Microcystic and macrocystic acne and toxicomania were observed as its common side effects. Also, a major risk of addiction was reported [8]. More females than males were found to suffer from acneiform eruptions resulting from amineptine therapy. The very florid, only slightly inflammative, retentional acne lesions with multiple comedones and microcystic and macrocystic lesions appeared mainly on the face, ears and neck of the patients. The incidence of acne was dose-related [9]. In comparison with other tricyclic antidepressants, amineptine – as tranylcypromine – was considered to have a clinically significant liability to cause addiction, which was attributed to its dopaminergic and stimulant properties [10]. In addition, cases of hepatotoxicity were reported, thought to be related to oxidation of amineptine forming a reactive metabolite. Especially, patients of the extensive metabolizer phenotype and those with an increased susceptibility to amineptine reactive metabolites – probably related to a genetic deficiency in a cell defense mechanism – suffered from liver injury [11]. The overconsumption of amineptine was expressed by the appearance of neuropsychotic disorders such as agitation, confusion, anxiety and insomnia, as well as weight loss and severe cutaneous reactions (acne) [12]. In 1999, France, Italy and other countries decided to suspend the marketing authorization for amineptine. In the United States of America, amineptine has never been approved. All regulatory authorities withdrew this substance because of the risk of its potential abuse and dependence on it [13] – in other words, addiction. In some developing countries, however, amineptine is still in use; although hepatotoxicity associated with amineptine, along with acne eruption and anxiety, and the availability of safer antidepressants have all made amineptine therapeutically less useful [6].

1.2.2
Aminophenazone (Aminopyrine)

In December 1999, the FDA suspended aminophenazone, an analgetic, antipyretic and antirheumatic substance. The drug had been introduced way back in 1887 and used for over 100 years in the clinic. Aminophenazone caused agranulocytosis, a condition characterized by a decrease in the number of granulocytes – a type of white blood cells – and lesions on the mucous membrane and skin. Some of the cases of agranulocytosis were fatal [14]. Another reason for suspending this drug from the market was its ability to react with nitrite-containing food, thus forming carcinogenic nitrosamines [15]. Aminophenazone is a metabolite of metamizole, an analgesic, which is still marketed in Germany and Austria.

1.2.3
Astemizole

This second-generation histamine H1 receptor blocker was put on the world market in the 1980s for the relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria [14]. Janssen Pharmaceuticals marketed this drug under the brand name Hismanal. The major benefit of these antihistamines was their

nonsedating character. Although this new class of medication was launched as highly selective and specific H1 antagonists, several of them were later found to cause prolongation of the QT interval in the electrocardiogram (ECG) and therefore induce severe cardiac arrhythmias [16]. The manufacturer withdrew the drug from the market in June 1999 [14]. Although its proarrhythmic effects are known, a second compound of this generation – terfenadine (Seldane) – is still available on the market [17].

1.2.4 Bromfenac Sodium

In 1998, Wyeth-Ayerst Laboratories announced to withdraw their nonsteroidal anti-inflammatory drug (NSAID) Duract (bromfenac sodium) [18].This drug had been submitted in 1994 and approved in July 1997 for the short-term management of acute pain. The use was indicated to 10 days or less, as there was a higher incidence of liver enzyme elevations in patients treated in long-term clinical trials [19]. The company withdrew the drug after postmarketing reports implicated it in severe hepatic failure that lead to four deaths and eight liver transplants. All but one of these 12 cases involved patients using Duract for more than 10 days. The exception involved a patient with preexisting significant liver disease. The company decided that steps to limit the use of a potent NSAID pain reliever such as Duract to just 10 days would not be feasible or effective and therefore withdrew the product [19].

1.2.5 Cerivastatin

Ever since lovastatin was launched in 1987 as the first potent HMG-CoA reductase inhibitor to reduce altered low-density lipoprotein (LDL) levels, statins are widely used to prevent thrombotic events. In 1997, Bayer launched cerivastatin (Lipobay, Baycol), a 50–200-fold more potent HMG-CoA reductase inhibitor than other statins [20]. At that time, it was known that the use of statins can lead to rhabdomolysis, a severe and potentially life-threatening condition. This risk is increased when statins are taken along with fibrates, for example, gemfibrozil, another group of substances used to treat blood lipid disorders [21]. Although the package insert of cerivastatin carried several warnings concerning the combination with fibrates, there were 52 deaths reported under treatment with cerivastatin. In the United States alone, 31 of these deaths were counted, of which 12 occurred as a result of using cerivastatin in combination with gemfibrozil [20]. In August 2001, Bayer withdrew cerivastatin because of the serious side effects or even deaths associated with the improper use of the drug [21].

1.2.6 Chlormezanone

Since 1958, chlormezanone was marketed by Sanofi-Winthrop, under the brand name Trancopal, as a centrally acting muscle relaxant in lower back pain [22,23]. Evidence of the efficacy of chlormezanone was, however, limited and of poor quality. In comparison to other centrally acting muscle relaxants in lower back pain, there

were no studies performed according to current standards. Considering the overall safety profile of chlormezanone, the most relevant risk involving the use of the drug was concluded to be life-threatening cases of toxic epidermal necrolysis and other bullous reactions [24]. Chlormezanone was shown to produce an increased relative risk of toxic epidermal necrolysis, also known as Stevens–Johnson syndrome [24]. Serious skin reactions may also occur with other muscle relaxants, but the available data suggested that the relative frequency of serious skin reactions was greater with chlormezanone [25]. In November 1996, Sanofi-Winthrop announced to discontinue this drug in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) report [26].

1.2.7
Fenfluramine and Dexfenfluramine

A dextrorotatory enantiomer of fenfluramine, dexfenfluramine (*Isomeride*) was introduced on the market in 1992, as its racemic fenfluramine (Ponderax), a serotonergic substance, had already been used for 25 years to treat obesity. However, like most of the anorexigenic drugs, it showed benefit for short-term treatment but failed to show significant benefit over placebo in long-term studies. Dry mouth, headache, fatigue, drowsiness and gastrointestinal disorders were reported as side effects [27]. When in 1997, such serious side effects as pulmonary hypertension and changes in the heart valves – especially in patients taking *fen-phen* (a combination of fenfluramine and phentermine) – were found, the FDA suspended both substances. This action came after physicians who had evaluated patients taking these two drugs with echocardiograms found that approximately 30% of the patients evaluated had abnormal echocardiograms, even though they had no symptoms [28].

1.2.8
Flosequinan

Flosequinan has a positive inotropic effect and shows a tendency to increase the heart rate, atrioventricular conduction in patients with atrial fibrillation and neurohormonal activation. Although the precise mechanisms involved have remained unclear up to now [29], this drug has been used to treat congestive heart failure (CHF). The FDA approved flosequinan (Manoplax) in 1993. However, the drug was withdrawn a year later because the PROFILE (prospective randomized flosequinan longevity evaluation) study indicated that flosequinan had adverse effects on survival, and that beneficial effects on the symptoms of heart failure did not last beyond the first 3 months of therapy, after which patients on the drug had a higher rate of hospitalization than patients taking a placebo [14].

1.2.9
Glafenine

A nonulcerogenic analgetic, antipyretric and nonsteroidal anti-inflammatory drug, glafenine was introduced in 1965 and was marketed under the brand names

Glifanan (Roussel Diamant) or Adalgur. Its main adverse effects included severe allergic reactions leading to anaphylactic shock, intrarenal crystallization of glafenine metabolites after long-term use and – in rare cases – liver toxicity [30,31]. Glafenine-induced anaphylactic shock was reported several times in the literature and was associated with cutaneous and respiratory manifestations [32]. In a study covering 20 years of drug surveillance in the Netherlands, glafenine was associated most often with probable or possible anaphylactic reactions (326 of the 992 reported cases) [33]. However, it was not until 1990 that Belgium ordered its withdrawal, the first country to do so. Two years later, the manufacturers withdrew glafenine worldwide. Some generic versions of this drug, though, may still be available in developing countries [34].

1.2.10
Grepafloxacin

Ever since its marketing began in August 1997, Raxar (grepafloxacin), an oral fluoroquinolone antibiotic, had been prescribed to an estimated 2.65 million patients in over 30 countries for a variety of infections including pneumonia, bronchitis and some sexually transmitted infections [35]. When severe cardiovascular events were reported implicating the drug, Glaxo Wellcome, its manufacturer, stated that it was no longer convinced the benefits of grepafloxacin outweighed the potential risk and considering that alternative antibiotics were available in the market withdrew the drug in 1999 [35]. Grepafloxacin binds to the human ether-a-go-go-related gene (hERG) potassium ion channel, which is responsible for repolarization in cardiac cells. Blocked by substrates such as fluoroquinolone antibiotics, repolarization is delayed, and a prolongation of the QT interval in the ECG can be observed. This symptom is also known as *torsade de pointes* (twist of points). As a result, cardiac arrhythmias can occur [36].

1.2.11
Levacetylmethadol

Levacetylmethadol, a synthetic opioid receptor agonist, was approved for the management of opiate dependence by the FDA in 1994 and was marketed as Orlaam by Roxane Laboratories since 1995. The European Commission granted a marketing authorization for the European Union to Sipaco Internacional Lda. in July 1997. However, in December 2000, following 10 cases of life-threatening cardiac disorders including ventricular rhythm disorders such as *torsade de pointes* reported in patients treated with levacetylmethadol, the EMEA recommended suspend ion of the marketing authorisation for Orlaam. The market suspension in the European Union took place in March 2001 [37]. However, levacetylmethadol remained on the US market as an orphan drug for the management of opioid dependence in patients who failed to show acceptable response to other adequate treatments. Meanwhile, Roxane Laboratories received more reports of severe cardiac-related adverse effects, including arrhythmias because of QT-interval prolongation

(15 cases), *torsade de pointes* (8 cases) and cardiac arrest (6 cases), as well as other cardiac-related adverse effects, such as arrhythmias, syncope and angina. In August 2003, Roxane Laboratories discontinued the sale and distribution of Orlaam, and levacetylmethadol is no longer available in the Western market [38].

1.2.12 Mibefradil

This calcium channel blocker, used to treat essential hypertension and stable angina pectoris, was marketed by Roche (as Posicor) and Astra Medica (as Cerate) [39]. As mibefradil turned out to be a potent inhibitor of certain liver enzymes of the cytochrome P450 (CYP) family, multiple drug interactions were observed. Mainly CYP 3A4 and CYP 2D6, two subtypes of the cytochrome P450 enzyme family, were found to be inhibited by this drug. This inhibition does not allow other substrates of CYP 3A4 or CYP 2D6 to be metabolized at the usual rate, which results in higher than usual concentrations of these substrates in the plasma. In such circumstances, the probability of side effects rises sometimes to a life-threatening level. Other kinds of interactions include interactions with terfenadine, cyclosporin A and metoprolol. Concomitant use of these drugs with mibefradil was either contraindicated or bound to a dose reduction of these drugs [39]. Cardiac effects have been reported as another side effect of mibefradil, while it has been associated with slowing down or complete suppression of sinoatrial node activity. Ventricular rates have been found to be as low as 30–40 beats per minute (bpm). Many patients were symptomatic. As this adverse effect occurred mainly in elderly patients who were on concomitant β-blocker therapy, it was warned against combining these substances. Use of mibefradil in patients suffering from sick sinus syndrome and possessing no pacemaker was contraindicated.

The FDA approved mibefradil for angina in August 1997. Until its removal from the market, over 25 interacting drugs had been identified, several labeling changes with additional warnings and contraindications were performed and continued reports of adverse effects from interacting drugs were received. As mibefradil showed no special benefits compared to other agents [40], Roche decided in June 1998 to withdraw Posicor from the market. In August 1998, Asta Medica followed suit with the removal of Cerate [41].

1.2.13 Rapacuronium Bromide

For the past 30 years, there have been efforts to find a nondepolarizing muscle relaxant to replace succinylcholine for endotracheal intubation. The goal has been to develop a fast-acting, short-duration drug without the side effects of succinylcholine such as bradycardia, rhabdomyolysis and malignant hyperthermia [42]. The injectable aminosteroid rapacuronium bromide (Raplon), launched by Organon Inc. in August 1999, seemed to be a promising substitute for succinylcholine. In

comparison with other neuromuscular blocking agents, it had a rapid onset and a short duration of action. However, a pharmacologically active metabolite seemed to be responsible for a delay in spontaneous recovery after repeated bolus doses or infusions [43]. Several case reports and observations indicated that rapacuronium bromide could induce severe and potentially life-threatening bronchospasm in certain patients. The precise cause of incidence was unknown, but it seemed to be more frequent in patients with respiratory afflictions [42]. Histamine release, muscarinic receptor (M2) antagonism and cholinergic facilitation via airway stimulation were suggested as possible mechanisms for bronchospasm [44]. On 27th March 2001, Organon Inc. voluntarily withdrew Raplon [45].

1.2.14 Rofecoxib

The FDA approved this selective cyclooxigenase (COX)-2 inhibitor (Vioxx) for the treatment of pain and inflammation in 1999. This NSAID demonstrated to have a lower risk of side effects such as gastrointestinal ulcers and bleeding than nonselective COX inhibitors, for example, ibuprofen. In 2004, a long-term study of Vioxx in patients at increased risk of colon polyps was halted because of an increased cardiovascular risk (heart attack, stroke) in the rofecoxib group. Subsequently, Merck withdrew the drug from the world market at the end of September 2004 [46].

1.2.15 Temafloxacin

In late January 1992, Abbott Laboratories received the FDA approval for temafloxacin (Omniflox), a fluoroquinolone broad-spectrum antibiotic for treatment of infections with gram-negative pathogens, for example pulmonary infections. The drug had been marketed before in several European countries such as Germany and the United Kingdom. It was marketed in the United States from mid-February till 5th June 1992. However, Abbott halted all marketing and further distribution of this drug worldwide [47], as within 3 months of its use, the FDA received some 50 reports of serious adverse events including three deaths. These side effects included hypoglycemia in elderly patients as well as a constellation of multisystem organ involvement characterized by hemolytic anemia, frequently associated with renal failure, markedly abnormal liver function tests and coagulopathy [48]. There were also a substantial number of reports about allergic reactions, some causing life-threatening respiratory distress [49].

1.2.16 Troglitazone

Pfizer introduced troglitazone in 1997 and marketed it as Rezulin, an oral treatment for type 2 diabetes. Warner Lambert Co., which was acquired by Pfizer in June 2000, discontinued marketing this drug in March 2000. In January 2003, the company

withdrew its new drug application [49]. In Europe, troglitazone was never marketed. Its use was associated with a markedly increased risk of acute idiopathic liver injury and acute liver failure [50].

1.2.17 Ximelagatran

The first orally bioavailable thrombin inhibitor prodrug ximelagatran was introduced on the German market in June 2004 and subsequently marketed as Exanta. Approved for the prevention of thromboembolic events such as venous thromboembolism (VTE) [51], its use was restricted to 11 days as elevated liver enzymes had been reported from clinical trials. On 14th February 2006, Astra Zeneca withdrew Exanta from the market because of a report of serious liver injury from the EXTEND clinical trial. This trial investigated whether ximelagatran could also be used in extended VTE prophylaxis after orthopedic surgery up to 35 days and so involved a longer duration of therapy than was currently approved for marketing [52].

Table 1.1 summarizes the reasons for the withdrawal of drugs in the past 14 years.

Figure 1.3 shows the percentage of substances withdrawn for toxicity reasons and illustrates the toxicity profile of these drugs.

Especially cardiovascular toxicity and hepatotoxicity played a crucial role in the decisions for withdrawing drugs from the market. These data suggest that there are

Table 1.1 Drugs withdrawn from the market from 1992 to 2006.

Drug name	Reason	Detailed information
Amineptine	Toxicity	Hepatotoxicity, addiction and neuropsychotic disorders
Aminophenazon	Toxicity	Cardiovascular (agranulocytosis)
Astemizole	Toxicity	Cardiovascular (hERG block)
Bromfenac sodium	Toxicity	Hepatotoxicity
Cerivastatin	Toxicity	Locomotor system (rhabdomolysis)
Chlormezanone	Toxicity	Serious skin reactions
Fenfluramine	Toxicity	Cardiovascular
Flosequinan	Lack of efficacy	
Glafenine	Toxicity	Anaphylactic reactions
Grepafloxacin	Toxicity	Cardiovascular (hERG block)
Levacetylmethadol	Toxicity	Cardiovascular (QT-interval prolongation, arrhythmias, angina)
Mibefradil	Toxicity	Hepatotoxicity, cardiovascular and interactions via the CYP450 enzymatic system
Rofecoxib	Toxicity	Cardiovascular (heart attacks, stroke)
Rapacuronium bromide	Toxicity	Bronchospasm
Temafloxacin	Toxicity	Multiple side effects
Troglitazone	Toxicity	Hepatotoxicity
Ximelagatran	Toxicity	Hepatotoxicity

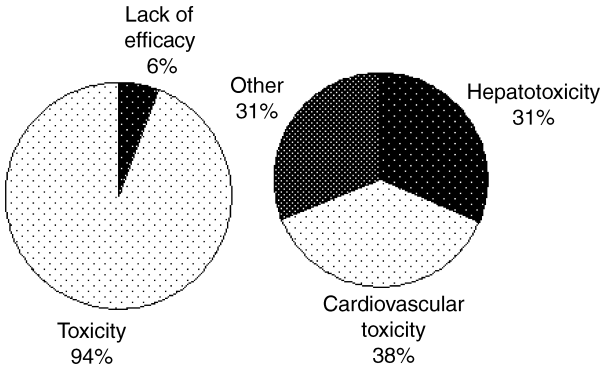

Figure 1.3 Reasons for the market withdrawal of the investigated drugs ($n = 17$, left). Toxicity profile of the withdrawn drugs (right).

currently no reliable test models for such toxicity problems available, for otherwise these drugs would never have entered the market at all.

1.3 Borderline Cases

To show a more complete picture on failed drugs, drugs that have been removed from the market and have been reintroduced later on with some restrictions as well as drugs that have been suspended from most drug markets but still remain on the market in only a few countries are listed in Table 1.2. As these drugs remain available on the Western market, they are not included in our statistics.

1.4 Investigational Drugs That Failed in Clinical Phases from 1992 to 2002

1.4.1 A Case Study: Fialuridine

Nucleoside analogues such as acyclovir, didanosine or zidovudine have been most widely evaluated as potential therapeutics for chronic hepatitis B. After gaining a better insight into hepatitis B virus (HBV) infection, a second generation of nucleoside analogues was developed, containing lamivudine, famciclovir and fialuridine. Fialuridine (1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil, FIAU) led to prompt and marked suppression of serum HBV DNA levels in two first phase II trials [60]. These two previous dose-finding studies – performed over a 2- and a 4-week course – led to the conclusion that longer therapy courses would be more efficacious in achieving a sustained loss of viral DNA in patients. In March 1993, a 6-month course of

Table 1.2 Drugs suspended from most but not all markets in the European Union and the United States.

Drug name	Indication	Important ADRs	Year	References
Alosetron (Lotronex)	Irritable bowel syndrome	Serious gastrointestinal events, especially ischemic colitis and constipation	2000	[53]
Cisapride (Propulsid)	Gastroesophagal reflux disease	Cardiovascular (QT-interval prolongation, arrhythmias)	2000	[54]
Phenylpropylamine (e.g. Proin)	Nasal decongestant, weight control	Hemorrhagic stroke	2000	[55,56]
Sertindole (Serdolect)	Schizophrenia	Cardiovascular (QT-interval prolongation, potentially fatal arrhythmias)	2000	[57]
Terfenadine (Seldane)	Allergy	Cardiovascular (potentially fatal heart condition)	1998	[58]
Tolcapone (Tasmar)	Parkinson's disease	Hepatic toxicity	1998	[59]
Trovafloxacin (Trovan)	Antibiotic	Hepatic toxicity	1999	[59]

fialuridine started. After 13 weeks, however, the study was terminated immediately when hepatic failure and lactic acidosis occurred in one of the 15 patients. The following side effects had been reported earlier in the study: intermittent crampy abdominal pain, paresthesias in the feet, fatigue, nausea, numbness and tingling in the feet or hands, crampy lower abdominal pain, constipation and mild thrombocytopenia. Three patients had already discontinued therapy with fialuridine between weeks 10 and 12 [60].

Severe fialuridine-induced toxicity included the following:

(i) Hepatic failure and lactic acidosis: Seven out of 15 patients showed varying degrees of hepatic failure and lactic acidosis. Common symptoms in these patients were fatigue, nausea, constipation, abdominal pain, steadily worsening jaundice, decreasing hepatic synthetic function, gradually worsening prothrombin times and increasing serum levels of ammonia and lactate. In two patients, the hepatic failure and lactic acidosis were rapidly progressive, so they had to be transferred to liver-transplantation centers. However, they both died 22 and 36 hours, respectively, after the transplantation. The other five patients showed a more gradual progression of hepatic failure and lactic acidosis. Their condition worsened over a period of several weeks. Two patients died of hemodynamic

collapse caused by pancreatitis and lactic acidosis before liver transplantation could be performed on them. Another patient died of complications of pancreatitis after transplantation. The remaining two patients underwent a successful liver transplantation and survived. During 24 months of follow-up, they have had only little evidence of residual fialuridine-induced toxicity. However, a mild peripheral neuropathy remained [60].

(ii) Pancreatitis: The seven patients who showed severe hepatotoxicity had biochemical evidence of pancreatitis. Three of these patients had severe abdominal pain and clinically apparent pancreatitis, which ultimately led to their death. All five patients who died showed evidence of pancreatitis at autopsy [60].

(iii) Neuropathy and myopathy: Five of the seven patients with severe hepatotoxicity also had symptoms or signs of peripheral nerve injury. They reported paresthesias and dysesthesias, mild to moderate in severity, in the feet or toes. Two patients reported muscle pain or weakness [60].

Several mechanisms of fialuridine-induced hepatotoxicity have been suggested: fialuridine and its metabolites inhibit mitochondrial DNA replication, leading to decreased mitochondrial DNA and mitochondrial ultrastructural defects [61]. Another mechanism suggested lies in pyruvate oxidation inhibition [62].

1.4.2 A Recent Case Study: Torcetrapib

The recent years have seen the success of statins like Lipitor (atorvastatin) as hypolipidemic agents that help treating cardiovascular disease primarily by lowering low-density lipoproteins ('bad cholesterol') levels. Another novel strategy is to tackle the same problem by elevating high-density lipoproteins (HDL or 'good cholesterol') levels via inhibition of cholesteryl ester transfer protein (CETP).

On 2nd December 2006, Pfizer, whose CETP inhibitor torcetrapib (CP-529414) was the first compound aimed at this target, announced that its development had to be stopped in phase III. Of 7500 patients who were given a combination of torcetrapib and atorvastatin, 82 had died, while in the other arm of the study, where patients were given atorvastatin alone, only 51 of 7500 patients had died. There was also a significant rise in blood pressure observed in the group that received torcetrapib.

Many people had high hopes in this new class of therapeutics, which should act against the number one cause of death and disability in the United States and most European countries. While this chapter is being written, there is still a lot of speculation going on as to why this promising heart drug failed, but there is some support that CETP remains a rewarding drug target [63,64]. Both Roche and Merck, which have their own, structurally unrelated CETP inhibitors under development (Roche: JTT-705/R1658, Phase IIb; Merck: MK-859, Phase II), claim that their compounds do not elevate blood pressure.

1.4.3
General Reasons for Project Failing in Clinical Phases I–III

The termination of fialuridine and torcetrapib can be considered as 'worst case scenarios' in drug development. In over 50% of all cases, project termination occurs due to less spectacular reasons such as a lack of efficacy or liberation–absorption–distribution–metabolism–excretion (LADME) problems (Figure 1.4) [65].

Taking together all three clinical phases, it has been observed that most drug candidates fail because of a lack of efficacy. The second major problem is toxicity that leads to the termination of approximately one third of all projects. More details on other reasons are given in Figure 1.5.

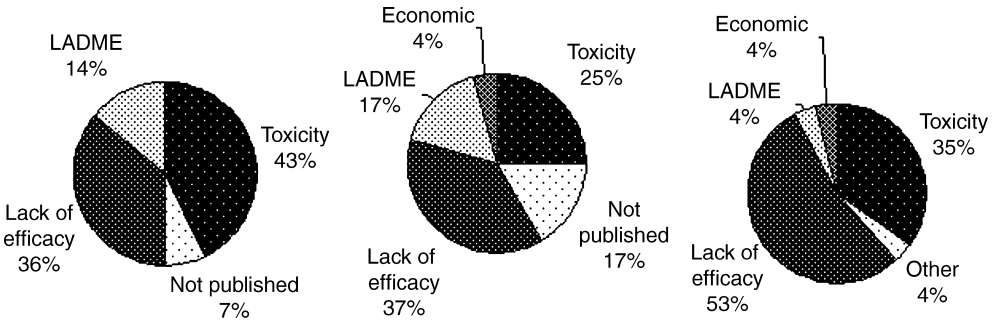

Figure 1.4 Reasons for project termination in clinical phases I (left), II (middle) and III (right) from 1992 to 2002.

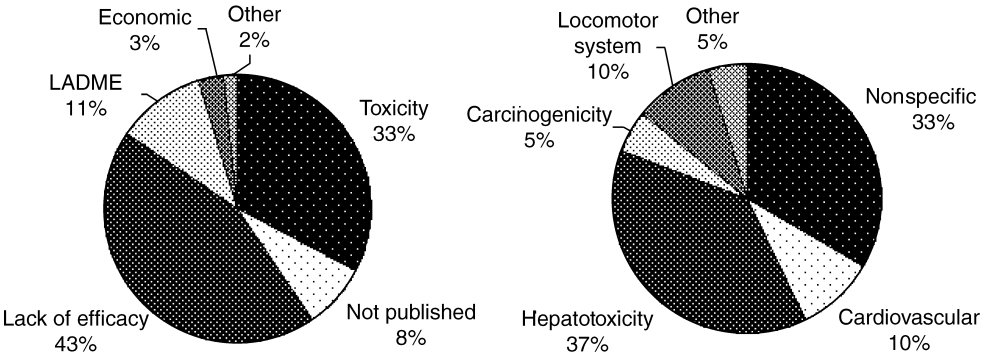

Figure 1.5 General reasons (left) and toxicity issues (right) leading to project termination in clinical phases I–III from 1992 to 2002.

1.5 Strategies for Avoiding Failure

The recent example of torcetrapib, where the world's largest drug company lost its potentially biggest drug, underlines the continued need for strategies to avoid failure during drug development. Despite the increased efforts in synthesis and testing via combinatorial synthesis and high-throughput screening (HTS) methods, the number of new drugs being approved is slowly declining and companies' drug pipelines are drying up. A recent study showed that the number of drugs that are the first to act at a new target has been relatively constant over the past 20 years [66]. The trend toward mergers and acquisitions (M&A) continues, though M&A have failed to provide long-term solutions in the past years, and only less than half of the new medical entities approved by the FDA in 2006 originated from the top 10 pharma companies [67,68].

Although HTS can process up to a million compounds per day, it has a high possibility of producing both false-negative and false-positive results. Replicate measurements in combination with statistical methods and careful data analysis may help to identify and reduce such errors [69].

In accordance with the credo 'fail early, fail cheap', there is a growing trend toward applying parallel screening and so-called *in vitro* safety pharmacology profiling methods at an earlier stage now [70]. Since the early 1990s, several contract research organizations such as Cerep, Euroscreen, MDS and Novascreen have emerged that offer profiling services against hundreds of different targets, to rapidly assess specificity and off-target effects, including absorption, distribution, metabolism, excretion and toxicity (ADMET) properties, for the selection of new lead candidates and for compound optimization. High-content screening, using whole cells, provides the possibility to monitor multiple targets or pathways and to directly identify toxic effects [71,72].

At the same time, *in silico* methods are expected to gain largely in importance with improved models that are able to address different aspects of ADMET [73], including metabolic effects at cytochromes [74,75] and nuclear receptors [76] as well as effects at antitargets such as certain GPCRs [77] and the hERG potassium channel [78]. Efforts to simulate *in vivo* effects by predicting drug disposition from demographic, physiological, genomic and *in vitro* data are also under way [79]. Our group recently presented the promising concept of parallel virtual screening with pharmacophoric methods, which allow for the fast profiling of molecules against a large number of drug targets and antitargets *in silico* [80,81]. A similar concept has been presented by Cleves and Jain [82].

One of the problems in creating reliable computer models for certain targets and antitargets is the lack of available data on inactive compounds, because this is widely regarded as an unimportant information. Furthermore, results from large-scale HTS are usually not available to the public scientific community. A notable project that may help to improve this situation is currently underway as part of the Molecular Libraries Initiative at NIH, screening more than 100 000 compounds against multiple targets and making the results available to the public via PubChem [83]. Other publicly accessible sites providing resources for *in silico* screening are listed in a recent paper by Strachan *et al.* [84].

1.6 An Unusual Case: The Revival of Thalidomide

The story of thalidomide (Contergan, Thalidomid) is certainly the most prominent example of a drug that had to be withdrawn from the market because of its severe side effects. First introduced in 1957 as a sedative that lacked both the addictive properties of barbiturates and the risk of death by accidental or intentional overdosing, it was marketed in 46 countries worldwide, including many European countries, Canada and Australia. It was also prescribed to pregnant women as an antiemetic for morning sickness. By the end of 1961, it was found that thalidomide caused severe teratogenic effects, with strong fetal malformations like phocomelia (shortened or absent arms and legs). The drug was quickly withdrawn from the market, but in between 5000 and 12 000 deformed babies were born worldwide, with an unknown number of aborted fetuses. It was found that as little as a single dose of 50 mg, taken between day 35 and 49 after the last menstrual period, could produce the characteristic birth defects.

In 1964, it was discovered by chance that thalidomide is also one of the most highly active agents in the treatment of erythema nodosum leprosum (ENL), a complication of leprosy. Later on, it was found that it is also an effective treatment for multiple myeloma and related plasma cell disorders. The use of thalidomide (Thalidomid, Celegene Corporation) was approved by the FDA for the treatment of ENL in 1998, and, in combination with dexamethasone, for the treatment of multiple myeloma in 2006. Because of the above-mentioned high risk of teratogenic effects after just one single dose of thalidomide, severe restrictions were imposed on its distribution. For this purpose, the System for Thalidomide Education and Prescribing Safety (STEPS) program was established to ensure that every patient is well informed about the associated risks and that no uncontrolled distribution of the drug is possible. The history and current use of thalidomide is summarized in some recent reviews [85–87].

New derivatives of thalidomide have been developed, such as lenalidomide (CC-5013, marketed as Revlimid) – approved by the FDA in 2005 for patients with myelodisplastic syndrome – and actimid (CC-4047), which is planned to enter phase II trials as an orally available treatment for myelofibrosis and sickle cell anemia, both by Celegene. These immunomodulatory drugs have a potency between 2000 and 20 000 times higher than thalidomide in inhibiting the drug's primary target tumor necrosis factor α, while the teratogenic effect is most likely to be retained [88].

Abbreviations

ADR	adverse drug reaction
CETP	cholesteryl ester transfer protein
EMEA	European Agency for the Evaluation of Medicinal Products
ENL	erythema nodosum leprosum
FDA	Food and Drug Administration

HBV	hepatitis B virus
HTS	high-throughput screening
LADME	liberation–absorption–distribution–metabolism–excretion
NCE	new chemical entity
NSAID	nonsteroidal anti-inflammatory drug

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