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ATTRITION IN DRUG DISCOVERY AND DEVELOPMENT

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1.1 "THE GRAPH"

If we had a confident grasp of the underlying reasons for attrition of projects and compounds in drug discovery and development, we would not need to write this book. But we are not confident, not confident at all. While attrition is a problem for both small and large molecules, and they share some common factors, it is small-molecule attrition that is currently crippling the industry. In some senses, the perceived greater success rates achieved with large-molecule drugs have increased the focus on large-molecule therapeutics.

With only 1 in 20 or fewer small molecules that enter clinical development reaching the market, greater than 95% of our innovation fails during the phases of clinical development [1]. A heated debate is currently raging in the scientific literature over the reasons for our dismal success rates. Many papers have been written concerning reasons for attrition, and many lectures given, often with contradictory messages. Substantial progress has been made in identifying new targets and rapidly designing small molecules active at these targets. However, converting these molecules into drugs has become more difficult [1]. Furthermore, to create value for patients and investors and to meet the health economic targets of those who pay for these drugs, let alone sustain a drug on the market for many years in the face of constant scrutiny and challenge, seems at times to be a superhuman task. Some limited progress has been made, but many great leaps in understanding are still to be taken. This books aims to help project teams and drug hunters in what is still a great endeavor.

One thing that everyone agrees on is that output from drug discovery industry is declining. "The graph" is a common first slide or figure in many public presentations.

Attrition in the Pharmaceutical Industry: Reasons, Implications, and Pathways Forward,
First Edition. Edited by Alexander Alex, C. John Harris and Dennis A. Smith.

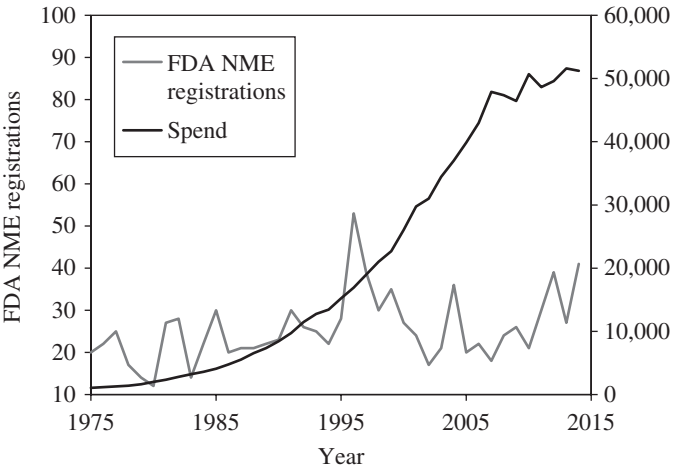

FIGURE 1.1 "The Graph"—Number FDA New medical entity registrations per year (gray curve) and total R&D expenditure/$ millions (black curve) [2, 3].

It shows the FDA new drug approvals and the costs of drug discovery and development per year [2, 3]. While investment in research and development (R&D) has dramatically increased, new drug registration has remained flat. It is shocking, we keep looking at it, we keep talking about it, and it is resulting in fundamental changes in the pharmaceutical industry (Figure 1.1).

The reasons for decreasing output are highly complex and poorly understood. Often cited reasons include, but are not limited to, higher regulatory hurdles required for drug safety, the requirement for adequate differentiation of new drugs versus existing therapies for reimbursement, inadequate choice of biological targets linked to disease, poor control of compound quality, and human decisions over which drugs to support through development and which to not support, so-called portfolio reasons.

The pressure is on; companies aspire to decrease attrition by implementing changes in the way they operate, but they do not just rely on their aspiration. They "manage" attrition by playing the numbers game. In order to "live" with attrition, you just need to run more projects. A recent 2010 review on R&D productivity[1] suggests that at a 7% success rate for small-molecule drugs reaching the market from a phase I entry and a 13.5-year development time, a company would need 11 phase I entries per year to yield 1 marketed drug per year. To sustain that level of availability of development compounds, a company would need a steady-state work in progress volume of 25, 20, and 15 projects in the target to hit, hit-to-lead, and lead optimization stages, respectively. Many large pharmaceutical companies have been attempting to maintain such a "volume" model. But this "volume" model is becoming unsustainable, for a number of reasons. First, the pharmaceutical industry cannot afford to sustain the volume model. While it was thought that the average cost of delivering a drug to market was $1.8B, Matthew Herper in *Forbes* magazine recently published the "real" costs of drug development [4]. By taking 10-year R&D costs of the top 100 companies and dividing by the number of drugs they delivered to market, the median cost for companies releasing more than three drugs was cited as greater than five billion dollars. For some companies, the figures were even worse. Topping the poll

of worst performers were Abbott ($13B), Sanofi ($10B), and AstraZeneca ($9B). These staggering numbers are the result of higher than average failure in delivering drugs to market during the period of measurement despite somewhat similar overall levels of R&D investment. For companies that released only one drug in the 10-year period, the median costs were only $350M, but the attrition in this segment was likely in *companies* rather than projects. With the costs of delivery of drugs to market spiraling, the return from those few drugs that do reach the market needs to be higher; hence, the industry has continued its pursuit of blockbuster drug status (able to achieve >$1B/year sales). Where the number of treatable patients is limited by the disease, for example, for some cancers, increased prices are required to achieve commercial viability, with consequent issues in some health economic assessments. The industry's reaction to the failing output and increasing costs has been to experiment with changes to business models:

- Mergers to bolster weak portfolios and drive size and scale efficiencies, as exemplified by the 2014 attempted acquisition of AstraZeneca by Pfizer
- Closures or "virtualization" of "difficult" high-attrition disease areas, such as GSK's and AstraZeneca's minimized investment in neuroscience
- Outsourcing of synthesis and screening to lower cost base countries (although with demand, costs are increasing there)
- The scramble to develop a biologics business by partnerships, in-licensing, and acquisitions, based on perceived lower risks, higher returns, and lower generic competition with biologic drugs
- The move away from diseases apparently well controlled on standard therapy
- The hunt to build new markets in developing countries
- "Playing to company strengths" in discovery, clinical science, or sales and marketing expertise
- An increased focus on first in class drugs, as "innovative" drugs for new mechanisms are more likely to suffer less competition than follower drugs
- And lastly a focus on "quality" projects and "quality" compounds. How to achieve "quality" is perhaps the main aim of this book

However, many of these are essentially business operational strategies. What are we doing to address attrition head-on?

1.2 THE SOURCES OF ATTRITION

An early study by Prentis, Lis, and Walker in 1988 focused on reasons for attrition in the development pipelines on the then seven major UK pharmaceutical companies and categorized sources of attrition as shown in Figure 1.2a [5].

They highlighted 39.4% development compounds failed due to inappropriate human pharmacokinetics, with a further 29.4% failing due to lack of clinical efficacy. Pharmacokinetics are determined in phase I trials, while it is not until phase II that clinical efficacy results are uncovered. Anti-infectives comprised 30% of the database, and if they were excluded, clinical efficacy failure rose to 50%. At that time, drug metabolism and pharmacokinetics were not a part of preclinical optimization. Many companies began to invest in the discovery of drug metabolism and pharmacokinetic departments, where

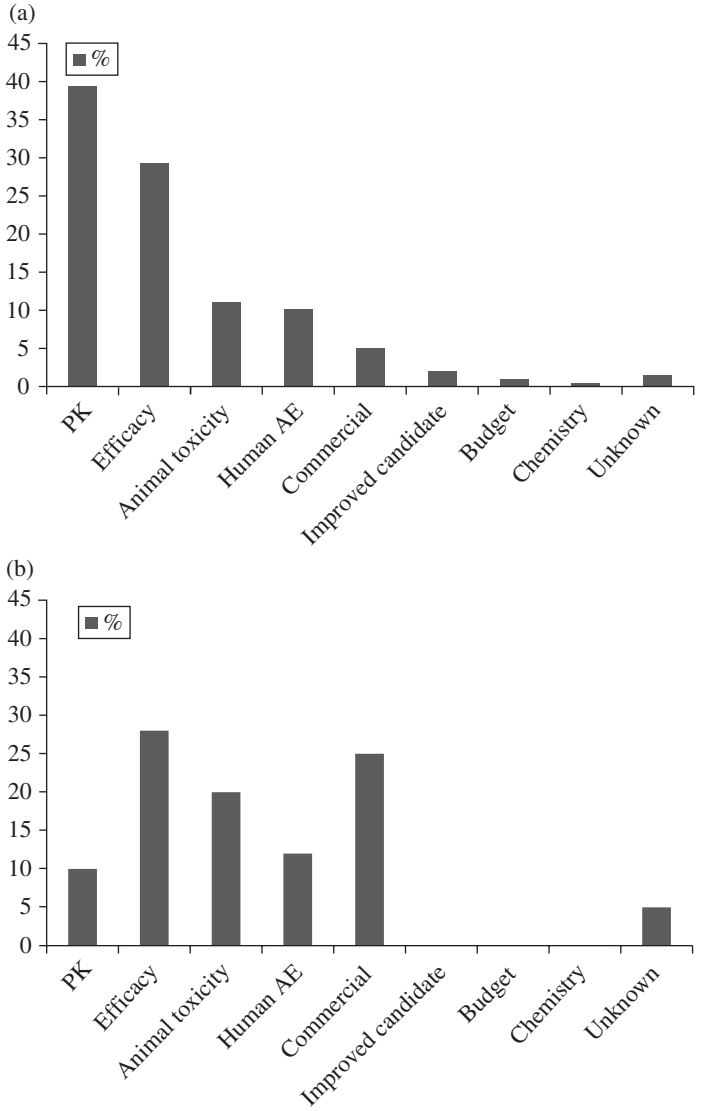

FIGURE 1.2 (a) Reasons for attrition. Data from Prentis and Walker [5]. (b) Reasons for attrition. Data from Kola and Landis [6].

compound weaknesses could be addressed during lead optimization. Reassuringly, it appeared that the investment was worthwhile, as in a 2004 follow-on review, attrition due to pharmacokinetics had apparently been reduced to around 10%. The major source of attrition remained lack of efficacy [6]. Poor pharmacokinetics was certainly a problem that needed fixing. But fixing it uncovered an unaddressed problem and moved attrition to phase II, a more expensive place to fail. The failure was that of translation of our mechanistic hypothesis into clinical efficacy. It had always been the major problem and remains the major challenge the industry faces. Attrition in phase II is now thought to be the highest of any phase, with some estimates putting it as high as 66% [1].

1.3 PHASE II ATTRITION

The problem of translation of mechanistic hypotheses into clinical efficacy is being tackled on a number of fronts. The choice of biological target on which to base a discovery program is receiving increased scrutiny at the earliest possible opportunity. Even before potent selective compounds are available, gene knockdown or gene editing can be conducted using siRNA knockdown, TALENs, or CRISPR-Cas technologies even using primary human cells. These experiments can probe the biological hypothesis and safety liabilities can be inferred [7, 8]. As potent selective compounds become available, experiments can be conducted with chemical probes that provide subtler control over the degree of modulation of the biological target than can be achieved with knockouts or generic mutations and indicative of the eventual candidate drug. As the discovery project progresses and compounds become closer to candidate drugs, further studies can be conducted, including *in vivo* testing. Although important questions are being asked about the value of animal models of disease [9, 10], such models can allow a more detailed pharmacokinetic–pharmacodynamic relationship to be explored, providing information on the concentration-time-biological mechanism relationship informing the design of clinical studies.

The definition of "patient populations to treat" is a further important focus, and the emerging paradigm is personalized healthcare. Identification of likely-to-respond patients maximizes the chances of observing a clinical efficacy signal without the dilution of nonresponding patients. It also avoids the risk of exposing nonresponding patients to possible drug-induced toxicity. Hence, personalized healthcare is of interest to patients, pharmaceutical companies, regulators, and payers alike. A recent PhRMA survey suggests that most clinical trials are now personalized [11], although very few diseases are understood at the genetic level.

Much of medical disease classification is empirical by nature, largely based on clinical manifestations, where a collection of similarly exhibited symptoms are used to classify indications. This is a major problem for drug development, which approaches disease from a molecular perspective. Where patients do not share a common molecular basis for disease, variability in drug response will, unsurprisingly, ensue.

Cystic fibrosis (CF) is a good case study to exemplify these points. CF was first described in 1938 by Dorothy Andersen, a pathologist, who noted the pancreatic lesions on a child who had presented with symptoms of celiac disease [12]. Prior to Andersen's description, there was increasing recognition that children with celiac disease were not uniform, and some of them presented with distinct pancreatic abnormalities, often identified post mortem. Up until this point, sporadic cases of infant deaths had been ascribed to pancreatic insufficiency, and some of the children were noted to have severe respiratory disorders also. At this time, infant death due to gastroenteritis and pneumonia, even in non-CF patients, was a relatively common occurrence, which had prevented the recognition of CF as a distinct disease. Andersen researched the post mortem records of similar patients to her own, which provided the evidential basis for her to classify CF as a distinct clinical entity.

The disease pathology was now understood at the level of clinical manifestations, but it would be years before a molecular understanding was provided. Andersen held on to the hypothesis that CF was caused by vitamin A deficiency, due to the similarities with celiac disease. We would now not be surprised that vitamin A supplementation was hardly

likely to be effective. The hint to the underlying pathology can be traced as far back as 1857, to a passage in the "Almanac of Children's Songs and Games from Switzerland," which warned that "the child will soon die whose forehead tastes salty when kissed." This idea was proven in 1953 when Paul di Sant' Agnese revealed the increased salt content of sweat in people with CF, and this remains a cornerstone of CF diagnosis today. It was not until 1985 that Professor Lap-Chi Tsui, Dr. Francis Collins, and Professor Jack Riordan identified the first specific faulty gene mutation responsible for CF, ΔF508 in the gene that codes cystic fibrosis transmembrane conductance regulator (CFTR) [13]. CFTR normally transports sodium and chloride ions together with their waters of hydration. At least 1000 mutations to the CFTR are known to be part of the disease, and all affect the CFTR ability for ion transport. Vertex's recent drug registration for Kalydeco (ivacaftor), which improves function of mutant G551D CFTR, found in just 4% of patients, shows the success that can be achieved when the molecular basis of the disease is understood.

Crizotinib, an ALK kinase inhibitor, targets lung cancer patients with ALK mutations; likewise, AstraZeneca's gefitinib is most effective in mutated EGFR in non-small-cell lung cancers, although this was reportedly only discovered through subset analysis of clinical trial data rather than designed in during its discovery. The clinical use of these drugs is facilitated by the use of diagnostic tests to identify patients carrying the appropriate mutations [14, 15].

In most other diseases, where a genetic basis of disease has not been identified so far, patient selection is focusing at the level of biomarkers for disease classification, but you have to pick the right biomarker. A biomarker is defined by the FDA as [16] "measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic toxicologic pharmacologic or clinical significance of the test results." The FDA and European Medicines Agency (EMA) recognize "qualified biomarkers," which can be used for regulatory decision making, while the pharmaceutical industry will work with exploratory biomarkers, which they may use for internal decision making and for which they may seek to achieve qualification.

For example, subsets of asthmatics can be defined as eosinophilic, with high blood/sputum eosinophil counts, or with a high Th2 cell count phenotype. A working hypothesis is that these are biomarkers of a disease phenotype and that therapies targeting Th2 cells or eosinophils in these eosinophilic/Th2 high patient subsets would be expected to show increased efficacy over asthmatics with low eosinophil/Th2 cell counts. Lebrikizumab is a humanized IL-13 antibody; IL-13 is secreted by Th2 cells and apparently involved in eosinophil cell recruitment. In a phase II clinical study of lebrikizumab, the efficacy of lebrikizumab was compared in asthmatic patients segmented by high/low blood eosinophil counts and high/low Th2 cell phenotypes. But just prior to unblinding the study, a further subset was defined based on another biomarker, periostin. Periostin is also controlled by IL-13. The high/low eosinophil and high/low Th2 subsets did not produce any significant separation in clinical effect; similar effects were observed in high Th2 and low Th2 groups, but the periostin separation did show a significant difference with increased efficacy in the high periostin class [17].

In the absence of anything else, patient selection can be based on the lack of response to another drug, if preclinical evidence suggests the mechanism under question may be particularly efficacious. Through these steps of patient selection, we are aspiring to reduce phase II/III efficacy attrition for future programs, by how much we will succeed is difficult to say.

1.3.1 Target Engagement

Pfizer, through a systematic retrospective analysis of 44 of their phase II programs (with an overall success rate in achieving positive phase II readout of 33%), were able to define three pillars of survival success to reaching positive phase II decisions and phase III progression. The three fundamental elements that needed to be demonstrated early in development were:

- Exposure at the target site of action over a desired period of time
- Binding to the pharmacological target as expected for its mode of action
- Expression of pharmacological activity commensurate with the demonstrated target exposure and target binding

Only when they had confidence in both pharmacology and exposure were they confident of phase II success. Out of the 44 phase III projects studied, only 14 had experimental data providing confidence in both the pharmacology and exposure, and all 14 of these achieved a positive phase II decision, and 8 progressed to phase III. In comparison, 12 projects had no data demonstrating confidence in exposure and pharmacology, and all 12 were phase II failures [18].

Phase II is also the start of the investigation of the properties of the drug on wider groups of individuals and the context of its future uses as a drug, for example, in the presence of comedications. At this stage, the potential for drug–drug interactions is investigated in clinical pharmacology studies. Adverse findings can have an impact on the contents of the drug label, which might ultimately limit the scope for use of the drug and have an effect on market size. Such considerations must be weighed in the decision to progress to phase III and ultimately to the regulatory submission. Increasingly, multiple complications with the properties of a drug can undermine the commercial case, even if the drug demonstrates efficacy. Again, such trends will reduce the number of new drugs reaching the market, limiting the choice within a class for physician and patients.

1.3.2 Clinical Trial Design

As in other areas of biology dealing with populations, the clinical phases of drug discovery and development present the problem of signal to noise. Signals for efficacy and safety have to be detected against the noise from interindividual variability. The clinical development phase is by far the most expensive stage of the process of drug innovation such that decision making on the funding of studies is a significant source of attrition. Frequently, it is not possible to power early studies to deliver a statistical endpoint for a relatively weak signal, often leading to equivocal outcomes in phase II. Complex designs to compare subgroups of patients in phase II, which might be very beneficial in investigating the scope of a new target in disease, can be unattractive when viewed against the eroding patent life of a project. Furthermore, complex studies can be difficult to implement in practice, as clinical centers might not be available to deliver a biomarker, for example. Nevertheless, there are some encouraging trends in the design of phase I and II trials, which offer opportunities to reduce attrition or allow earlier decision points.

For a number of years, regulators have attempted to stimulate flexibility in phase I studies and in fact do seem to be open to novel and scientifically well-based study concepts. The

exploratory IND is a clear example. The advantages are that it is possible to generate initial human data somewhat faster, requiring less preclinical data. Pharmacokinetics can be examined, and multiple compounds compared. However, the dose used needs to be sub-pharmacological for the target (less than 100 μg in most cases), and further progression requires a second stage with completion of a full IND.

More recently, microdosing studies using accelerator mass spectrometry are increasingly popular. The very low doses used (nanograms in most cases) are readily justifiable in terms of predicted biological effects. However, there are risks around nonlinearity of pharmacokinetics especially as this is a tool more likely to be used in cases where there is increased uncertainty over the prediction of human pharmacokinetics from preclinical studies. On balance, in many cases, a well-designed and rapidly executed normal phase I program probably takes less time and allows continuity into phase II. Most experienced project teams have good ideas how to reduce attrition at this stage, by thorough evaluation of dose to man predictions. For example, much time and cost can be saved by careful design of the toxicology program to attempt to avoid heroic doses in preclinical species, thus limiting the need for expensive drug substance at this stage.

Phase Ib studies where there is an attempt to demonstrate proof of mechanism or proof of principle in a small number of patients are increasingly popular, supported most commonly by biomarkers or less often by surrogate markers (simply as there are fewer of those well validated). Perhaps an overemphasis on the phase Ib aspect of a trial could become a source of attrition in itself—the purpose of phase I is to investigate clinical safety and set doses for phase II. Without a firm foundation at this stage, phase II can easily be compromised.

Adaptive designs for clinical trials (phase I, but possibly also phase II) where the dose selection and escalation are not fixed at the start of the trial but are modified during the trials in response to the results at the earlier stages (sometimes using Bayesian statistical methods) can be economical on subjects and drugs. However, such trials may be more complex and lengthy to conduct—there might be practical issues in the preparation of dose sizes, for example, or the rotation of subjects in the clinical pharmacology units. Specialist CROs and consultancies are experienced in these issues, so further progress can be expected.

Clinical trial simulation [30] is a powerful tool in the design of phase II trials—arguably the stage of clinical development responsible for most attrition. Computationally intensive stochastic simulations are now done relatively easily, so that the predictive power of different trial designs can be estimated before the trial design is finalized. For example, with a set budget for a trial, the number of subjects split between a number of doses or groups could be varied in the simulations. The signal to noise of a biomarker might be examined to assess its value in the trial, with the level of powering or measurement accuracy and precision available.

1.4 PHASE III ATTRITION

But what about failure in phase III? Historically, greater than 66% of phase III projects would be expected to reach the market. With the potentially large numbers of patients, and possibly long trials involved, failures here can be financially disastrous. While not all phase III trials are huge (patients can be around 100 per group in some indications), the commercial value of a company is based on the strength of its phase III pipeline. To a

large pharmaceutical company, phase III failure can result in major share price fluctuations, and to small biotechs, it can be catastrophic. In 2012, the failure of Abbott's bardoxolone partnered with Reata wiped 3.5% off its share price in one day [19]. In 2011, AntiSoma closed in dramatic fashion after the failure of its phase III program for AS1413 and discontinuation of its phase IIb program for A1411 [20]. In 2008, it had already sold off its FDA-approved fludarabine to back its own development portfolio, with the loss of AS1413 there was little value left in the company.

So why do drugs fail in phase III, when efficacy failures appear to have been weeded out at such expense in phase II? In 2013, Eli Lilly's ramucirumab failed to meet its primary endpoint on progression-free survival among women with metastatic breast cancer (although it was successful in its phase III trial in advanced gastric cancer) [21]. Eli Lilly also stopped enzastaurin, a kinase inhibitor that failed to meet the main goal for boosting disease-free survival in a phase III study in patients with diffuse large B-cell lymphoma [22]. AstraZeneca's fostamatinib, an SYK kinase inhibitor, was stopped after 2 phase III trials as results did not "measure up to the promising results we saw earlier in development" [23]. GlaxoSmithKline and Prosensa announced that phase III clinical study of drisapersen, an investigational antisense oligonucleotide, for the treatment of Duchenne muscular dystrophy (DMD) patients with an amenable mutation, did not meet the primary endpoint of a statistically significant improvement in the six minute walking distance (6MWD) test compared to placebo [24]. Roche's PPARα/γ agonist aleglitazar was halted prior to the completion of its phase III program due to safety signals and lack of efficacy [25]. Roche was working in a high-risk area that has seen the failure of more than 50 other PPAR agonists in clinical development.

All of these drugs had positive clinical signals in phase II patient studies, which did not translate into phase III success. We appear to be failing on efficacy badly in both phase II and phase III. An analysis for 2011–2012 phase III failures found 56% of them failed for efficacy reasons (59/105 failures which reported reason for failure) [26], and most of these failed to demonstrate efficacy versus placebo. The mechanistic hypothesis was supposed to have been tested in phase II trials, and attrition in this phase was already the highest of any phase, at 66%. These phase II trials are conducted in 10s to 100s of patients and designed to give statistically significant, clinically meaningful indication of efficacy, and differentiation where there are preexisting therapies, on which to base decisions on the huge investments required in the phase III trials.

Phase III are the pivotal efficacy trials, which will be used to make the registerable claims for the drug. Phase III endpoints may be different from phase II trials. Phase II endpoints may be surrogate endpoints, biomarkers of clinical efficacy, or recognized endpoints that are thought to be indicative of clinically meaningful benefit such as blood pressure, cholesterol levels, bone density, or composite endpoints scoring systems, for example, ACR20, ACQ, and SLEDII, but phase III endpoints will generally be primary endpoints. They will be endpoints that directly measure how a patient feels, benefits, or survives [27]. Drugs granted accelerated approval may be registerable based on surrogate endpoints for life-threatening diseases with no treatment option. The lack of translation of positive phase II results into phase III trials may be the failure of the surrogates to translate to patient benefit, or a problem of sample size, or a problem of control over studies executed necessarily in many multiple centers across many countries. Phase III expectations from regulators are becoming more demanding, and not necessarily consistent across jurisdictions, and may

also change during the conduct of phase III trials, and be applied retrospectively to the outcome. While Pfizer's JAK inhibitor tofacitinib met its primary phase III endpoints, and was approved by the FDA,[1] the EMA has so far refused registration [28]. The EMA Committee for Medicinal Products for Human Use had major concerns about the overall safety profile of tofacitinib relative to its efficacy, and while acknowledging tofacitinib resulted in a reduction in disease activity and physical function of patients, there was no consistent reduction in structural joint damage in the target patient population, who had failed at least two other disease-modifying antirheumatic drugs [29].

1.4.1 Safety Attrition in Phase III

In 2011–2012, 28% of phase III programs were stopped due to clinical safety/safety margin issues. Even after the extensive safety evaluation that drugs have undertaken before the final phase III trials, toxicity is still a source of late-stage attrition. For example, Takeda recently announced the termination of its phase III program for fasiglifam (TAK-875) due to concerns over liver safety [31]. Abbott and Reata's NRF2 activator bardoxolone trial in stage 3/4 chronic renal disease patients was stopped in 2012 due to "excess mortality" in the dosed groups [32]. Merck's withdrawn cholesterol drug Tredaptive, a combination of niacin and an experimental drug laropiprant, showed that one-quarter of patients in a new trial withdrew because of side effects including itching, rashes, and muscle problems. Bristol-Myers Squibb halted development of the hepatitis C nucleotide polymerase inhibitor BMS-986094 after 9 trial patients were hospitalized and one trial participant died of heart failure following drug administration [33].

Comprehensive safety packages are designed around our clinical programs to avoid harm to patients in clinical trials. *In vitro* and *in vivo* safety studies are valuable, have undoubtedly contributed to the avoidance of safety catastrophes, and have a critical place in our development framework. But rare or infrequent events are statistically unlikely to show up in any study in small numbers of patients, and it is only in late-stage studies, or even postmarketing where large numbers of patients are treated, that these events become significant. A safety finding of a single drug molecule in a unique mechanism may never be fully explainable, particularly if the finding is serious as further human studies would not be supported. But when multiple drug molecules exhibit common toxicologies, common patterns may be observed upon which hypotheses can be drawn and investigated. The identification that rare potentially fatal torsades de pointes were related to the use of certain marketed antihistamine drugs and that these drugs blocked the hERG cardiac ion channel enabled a life-threatening toxicology to be reduced to selective pharmacology [34]. We were then able to screen for hERG liabilities very early in the drug discovery. On a more positive note, observations of side effects of drugs are a common feature of new medical innovation. Viagra was originally trialed as an antiangina treatment, before its true value arose. The recently registered Tecfidera is rapidly becoming a blockbuster treatment for multiple sclerosis and is in fact a formulation of dimethyl fumarate, which had been used for many years as an antipsoriatic treatment. Drug reprofiling is becoming big business.

[1] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm327152.htm

There are three particularly important points made in the previous paragraph that are not often stated overtly:

1. Safety issues, once you get past the obvious ones that appear in preclinical studies, are nearly impossible to predict with any useful degree of accuracy.
2. Basic mechanisms of an adverse event sometimes require not only many thousands of patients to be exposed but also that more than one drug in the class be developed such that a specific common mechanism can be identified or at least a "class effect" can be postulated.
3. An enormous amount of resource must be spent on characterizing a drug's therapeutic and side effects before other possible uses can be identified.

In the context of safety-related drug attrition, let us look at these three aspects in a little more detail.

1.4.1.1 Safety Issues are Nearly Impossible to Predict with any Useful Accuracy With this statement, one's mind automatically goes to the ability of preclinical species to reflect side effects in humans, which by some estimations is quite reasonable. Therefore, it should be reasonably easy to at least perform an adequate risk assessment for humans from preclinical species. This may be expecting too much and may in fact represent an experiment that is impossible to actually perform correctly. Expecting a readout in a preclinical species (or several) to translate to humans at the right exposure for the right duration in a vastly differing phenotypic background is asking quite a bit of studies consisting of the minimum number of fairly homogeneous animals as possible. But another aspect of our expectations of preclinical findings translating to the clinical setting is that the data used to determine whether preclinical studies actually do predict clinical outcomes are skewed by the fact that many drug candidates are abandoned after findings in preclinical species are deemed "unmanageable" or "unmonitorable" in the clinic and thus never make it to humans to test whether this relationship holds or not. While this is, in most cases, prudent, it must be acknowledged that our knowledge of how these examples would actually perform in the human population is poor. In some cases, judging a finding to be unmanageable or unmonitorable in the clinical setting is down to technical reasons, for example, no biomarker or imaging technique is available. However, in some cases, it comes down to a templated approach to clinical development in many organizations that does not accommodate research into side effects, either for resource reasons or for lack of early clinical investigators who are interested in the relatively unglamorous and complicated world of side effects. The consequence of this situation is that safety-related attrition in human trials will continue because the preclinical safety assessment of drugs is an oversimplification of the real human response to a drug and that some very useful therapies will be abandoned because we cannot adequately risk-assess their effects in humans due to an underdeveloped approach to research into human side effects.

1.4.1.2 Basic Mechanisms of an Adverse Event Sometimes Require not only Many Thousands of Patients to be Exposed, but also that more than One Drug in the Class be Developed such that a Specific Common Mechanism can be Identified or at least a 'Class Effect' can be Postulated With this statement, one must acknowledge the complexity of biological systems in general and these same systems under the influence of a

pharmacological intervention in particular. The basic ambition of most therapies under development is that they are specific in two ways: first, that the intervention (small molecule, antibody, etc.) is specific to its target and, second, that the role of the target in the given disease is specific to the hypothesized disease mechanism. In the vast majority of cases, neither of these conditions is fulfilled and one is left managing the cornucopia of effects and carefully recording observable changes in the patient and, as discussed earlier, usually neglecting to thoroughly explain the mechanisms of these effects. However, as several projects attempt to target a specific biological mechanism and clinical (or preclinical) safety observations are accumulated, patterns oftentimes do emerge that can give indications whether side effects are related to the specific intervention or are a result of alterations in the target biology brought about by the intervention. This important learning exercise involving many clinical trials performed with many drug candidates in many patients becomes extremely expensive but is the only way to separate effects specific to a particular drug candidate and effects related to the alterations in the biological makeup of the patient. This situation, after we acknowledge it, may help to set expectations for future drug discovery/development projects. We have to resign ourselves to working with a "black box" and that understanding mechanisms will not happen until massive amounts of data from several attempts at therapies against a specific target are made. While this may be a rather pessimistic approach, it also points to the need to strengthen the research environment within regulatory bodies who will in the end be the only group to have a complete overview of all of the positive and negative effects of a group of drug candidates. One can speculate that a more open, balanced reporting environment may have spotted the relationship between hERG inhibition and torsade de points earlier, as this was neither a protein target class (on pharmacology) nor a chemical structural class safety problem, but rather a shared off-target pharmacology of diverse structural classes driven largely by bulk physical properties.

1.4.1.3 An Enormous Amount of Resource must be Spent on Characterizing a Drug's Therapeutic and Side Effects before other Possible Uses can be Identified The discovery and development of a safe and pharmacologically active substance is unquestionably a challenge. Once the drug candidate is given to human subjects, opportunities begin to appear, but without the previously mentioned "research-minded" clinical development, many projects are simply abandoned when they either show unacceptable side effects at the "therapeutic" dose for which they are being developed or simply show too little efficacy in the patient population chosen. At this point, the project is shelved and often quickly forgotten as other priorities take over. With a success rate in clinical development of less than 5%, one cannot help thinking that this "lost 95%" is a neglected resource. Of course, the issue is that it is essentially invisible, including the safety data, from which trends, patterns, and sometimes mechanisms could be derived. There is no current solution to this situation, partially because of the confidentiality (both patient and commercial), but perhaps more importantly because of the internal resources required to find, summarize, anonymize, and analyze the data. Hence, many opportunities are probably being lost to cursory data analysis and the inability to access these data for further analysis and merging with other relevant datasets. It is often said that many drugs have been discovered by serendipity. Serendipity can only occur when the right eyes view the right data. At the moment, this potential is severely handicapped by shelving this lost 95%.

The assessment of significance of an observed safety concern and the assessment of the relative safety risk patients are exposed to by a new treatment relative to the efficacy benefit a patient could potentially gain are the core discussions between pharmaceutical companies and regulatory bodies. When all the trials are completed, these discussions can lead to attrition, market opportunity, or delay. What is acceptable in one disease or patient population may not be acceptable in another and likewise with different regulatory authorities.

1.5 REGULATION AND ATTRITION

Earlier in 2013, the FDA rejected Novo Nordisk's Tresiba (long-acting insulin degludec), against the advice of its own advisory panel, as it asked for a further dedicated cardiovascular outcome trial to investigate potential cardiovascular risks associated with the treatment. A requirement for a cardiovascular safety study after the completion of phase III can torpedo many projects outright. The FDA as the tollgate to the largest pharmaceutical market in the world has been, and continues to be, a major source of controversy. The FDA is often accused of both hindering access of patients to potential lifesaving therapies and, at the same time, allowing harmful drugs to reach patients. The history of the FDA highlights that its regulatory framework was built on heart-breaking real-world experience of the harmful effects of inappropriate or unregulated drug use [35]. The 1912 Sherley Amendment to the Drugs Act prohibited not just false labeling of ingredients but also false claims and was in part a response to the widespread sale of dubious and outright dangerous tinctures, ointments, and treatments, like Mrs. Winslow's Soothing Syrup for teething and colicky babies, unlabeled yet laced with morphine, and thought to have been the cause of many infant deaths. The Federal Food, Drug, and Cosmetic (FDC) Act of 1938 contained many new provisions, not least in response to the marketing of Elixir of Sulfanilamide, which contained the poisonous solvent diethylene glycol, which it is claimed killed 107 persons, many of whom were children. In 1962, the Kefauver-Harris Drug Amendments were passed, in response to the public outcry caused by birth defects observed in many countries due to use of thalidomide, even though it was never approved for use in the United States. For the first time, drug manufacturers were required to prove to the FDA the effectiveness of their products before marketing them as well as safety. The FDA's mission then, and today, is to protect public health, and in increasing its vigilance, it protects patients from treatments whose risks outweigh their benefits but in doing so also delays useful medicines from reaching patients rapidly. Prior to 1962, the approval process in the United States on average took just 7 months but by 1998, with the impact of the Kefauver-Harris amendments, took almost 7 years [36].

During the HIV epidemic of the 1980s, organizations such as ACT-UP accused the FDA of unnecessarily delaying the registration of new HIV medications. In 1990, the then chairman of the presidential advisory panel on drug approval, Louis Lasagna, estimated that thousands of lives were lost each year due to delays in approval and marketing of drugs for cancer and AIDS. Partly in response to these criticisms, the FDA introduced expedited approval of drugs for life-threatening diseases and expanded preapproval access to drugs for patients with limited treatment options.

In 1992, the FDA instituted the *accelerated approval* regulations. When studying a new drug, it can sometimes take many years to learn whether a drug actually provides

a real effect on how a patient survives, feels, or functions. Mindful of the fact that it may take an extended period of time to measure a drug's intended clinical benefit, the regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint. Use of a surrogate endpoint enabled the FDA to approve these drugs faster. A surrogate endpoint is a measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit, such as blood pressure or cholesterol levels in cardiovascular disease.

Accelerated approval does carry an obligation that the sponsoring company continues postmarketing clinical studies to show clinical effectiveness of the treatment, which the surrogate endpoint was predictive of clinical effectiveness. Genentech's Avastin, a monoclonal antibody that inhibits angiogenesis by blocking vascular endothelial growth factor A, was approved for a breast cancer indication in February 2008 under the FDA accelerated approval process. But in 2011, on the basis of two additional clinical studies that showed only a small effect on tumor growth without evidence of an impact on mortality or improved quality of life, the FDA withdrew marketing authorization for this indication [37]. The drug remains on the market in the United States for other cancer indications and remains approved for breast cancer in other countries.

The FDA continues to evolve its processes to ensure beneficial drugs reach patients as rapidly as possible. In 2012, congress passed an amendment that allowed the FDA to base accelerated approval for drugs on a surrogate or an intermediate clinical endpoint. An intermediate clinical endpoint is an endpoint that is reasonably likely to predict clinical benefit (based on available data), even if it has not achieved such widespread acceptance, but following registration the company is required to conduct trials to demonstrate the clinical benefit, if it cannot be subsequently demonstrated, or if the company does not show due diligence in conducting such a trial, the drug may be removed from the market. The FDA recently approved a multiple sclerosis treatment on the basis of a large clinical effect on relapse rates after 13 months but with uncertainty of the durability of the effect. The sponsor was required to continue the trials to show durability of the clinical effect for a further 2 years [38]. In the oncology field [38], objective response rate was historically acceptable endpoint for drug registration, but in the 1980s, there was a move toward clinical endpoints of survival and patient reported quality of life outcomes. For accelerated approval, the FDA will accept progression-free survival, objective response rate, and complete response.

The year 2013 saw the introduction of a new breakthrough review status for drugs and biologics for serious life-threatening diseases, which brings the number of expedited programs to four: fast-track, breakthrough therapy, accelerated approval, and priority review. A drug may be accepted under one or more of these programs.

Fast-track review is granted upon request to facilitate development and speed review of compounds for life-threatening diseases. A fast-track designation allows the drugs to receive some or all of the following:

- More frequent meetings with the FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval
- More frequent written correspondence from the FDA about such things as the design of the proposed clinical trials and use of biomarkers
- Eligibility for *accelerated approval and priority review, if relevant criteria are met*

- *Rolling review*, which means that a drug company can submit completed sections of its biologics license application (BLA) or new drug application (NDA) for review by the FDA, rather than waiting until every section of the application is completed before the entire application can be reviewed (BLA or NDA review usually does not begin until the drug company has submitted the entire application to the FDA)

Breakthrough status is granted upon request for drugs for life-threatening diseases where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint and includes the benefits of fast-track review and in addition intensive guidance on an efficient drug development program, beginning as early as phase I, as well as organizational commitment involving senior managers.

Under the Prescription Drug User Fee Act (PDUFA), the FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times: *standard review* and *priority review*. A *priority review* designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).

A *priority review* designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions, documented evidence of patient compliance expected to lead to improvement in serious outcome or evidence of safety and effectiveness in a new subpopulation, when compared to standard applications.

One certainly feels that the FDA places science at the center of its decision making. In many areas, the required science does not exist, and the FDA has been a leading force in investment in the necessary research, for example, in the areas of pharmacovigilance and pharmacoepidemiology, clinical trial design, and integration of population pharmacokinetics, pharmacodynamics, and toxicokinetics in drug development. The regulatory bodies' role is to ensure patients benefit from treatments with an acceptable level of risk. They are independent and their decisions are driven by data, they are not in themselves sources of attrition, but they do implement it through their decisions both in premarketing and in postmarketing.

1.6 ATTRITION IN PHASE IV

Even after all development hurdles have been passed, and the drug reaches the market, the problems may not be over. The pharmaceutical company still has to be able to sell the drug and make a profit to return to shareholders. In 2011, Savient Pharma obtained marketing approval for its gout treatment Krystexxa (pegloticase). Savient was reputedly for sale after marketing approval was gained from the FDA, but due to a lack of suitors, the company took the drug to market itself. Sales remained stubbornly low, and with production problems, the challenge to increase sales to cover its rising debts proved too great and Savient was forced to file for bankruptcy in 2013. Too many marketed drugs fail to recoup their developments costs, but clearly the worst outcome of all is the withdrawal of a drug when it is on the market. This can have serious consequences for the manufacturer but also for patients—both for those who might experience adverse effects and for other patients (the vast majority) who lose the benefit of an efficacious medicine that they might have tolerated well (Table 1.1).

TABLE 1.1 Drug withdrawals By Year

Drug	Year	Country	Indication	Reason
Drotrecogin alfa (Xigris)	2011	Worldwide	Severe sepsis	Lack of efficacy as shown by PROWESS-SHOCK study
Propoxyphene (Darvocet/ Darvon)	2010	Worldwide	Mild to moderate pain	Increased risk of heart attacks and stroke
Gemtuzumab ozogamicin (Mylotarg)	2010	United States	Acute myelogenous leukemia	No improvement in clinical benefit; risk for death
Ozogamicin	2010	United States		No improvement in clinical benefit; risk for death; veno-occlusive disease
Sibutramine (Reductil/ Meridia)	2010	Australia, Canada, China, the European Union (EU), Hong Kong, India, Mexico, New Zealand, the Philippines, Thailand, the United Kingdom, and the United States	Weight loss	Increased risk of heart attack and stroke
Sitaxentan	2010	Germany	Pulmonary arterial hypertension	Hepatotoxicity
Efalizumab (Raptiva)	2009	Germany	Psoriasis	Withdrawn because of increased risk of progressive multifocal leukoencephalopathy
Aprotinin (Trasylol)	2008	United States	Inhibit bleeding in complex surgery	Increased risk of death
Rimonabant (Acomplia)	2008	Worldwide	Weight loss	Risk of severe depression and suicide
Lumiracoxib (Prexige)	2007–2008	Worldwide	Pain	Liver damage
Clobutinol	2007	Germany	Cough suppressant	Ventricular arrhythmia, QT-prolongation
Nefazodone	2007	United States, Canada, others	Antidepressant	Branded version withdrawn by originator in several countries in 2007 for hepatotoxicity. Generic versions available

Pergolide (Permax)	2007	United States	Parkinson's disease	Risk for heart valve damage
Tegaserod (Zelnorm)	2007	United States	Irritable bowel syndrome	Risk for heart attack, stroke, and unstable angina. Ref. 2 was available through a restricted access program until April 2008
Alatrofloxacin	2006	United States	Broad-spectrum antibiotic	Liver toxicity; serious liver injury leading to liver transplant; death
Gatifloxacin	2006	United States	Respiratory tract infections	Increased risk of dysglycemia
Ximelagatran (Exanta)	2006	Germany	Anticoagulant	Hepatotoxicity
Natalizumab (Tysabri)	2005–2006	United States	multiple sclerosis and Crohn's disease	Voluntarily withdrawn from US market because of risk of Progressive multifocal leukoencephalopathy (PML). Returned to market in July 2006
Adderall XR	2005	Canada	Attention deficit hyperactivity disorder	Risk of stroke. The ban was later lifted because the death rate among those taking Adderall XR was determined to be no greater than those not taking Adderall
Hydromorphone (Palladone)]	2005		Opioid analgesic	High risk of accidental overdose when administered with alcohol
Thioridazine (Melleril)	2005	Germany, United Kingdom	Schizophrenia and psychosis	Withdrawn from UK market because of cardiotoxicity
Bezitramide	2004	Netherlands	Analgesic	Fatal overdose
Co-proxamol (Distalgesic)	2004	United Kingdom	Back pain	Overdose dangers
Dofetilide	2004	Germany	Maintenance of sinus rhythm	Drug interactions, prolonged QT
Rofecoxib (Vioxx)	2004	United States	Pain in osteoarthritis and rheumatoid arthritis	Risk of myocardial infarction and stroke
Valdecoxib (Bextra)	2004	United States	Pain in osteoarthritis and rheumatoid arthritis	Risk of heart attack and stroke

(*Continued*)

TABLE 1.1 (*Cont'd*)

Drug	Year	Country	Indication	Reason
Levomethadyl acetate	2003	United States	Opioid dependence	Cardiac arrhythmias and cardiac arrest
Kava Kava	2002	Germany	Social anxiety	Hepatotoxicity
Ardeparin (Normiflo)	2001	United States	Deep vein thrombosis	Not for reasons of safety or efficacy
Cerivastatin (Baycol, Lipobay)	2001	United States	Cardiovascular disease	Risk of rhabdomyolysis
Rapacuronium (Raplon)	2001	US multiple markets	Anesthesia	Withdrawn in many countries because of risk of fatal bronchospasm
Sparfloxacin	2001	United States	Antibacterial	QT prolongation and phototoxicity
Alosetron (Lotronex)	2000	United States	Irritable bowel syndrome	Serious gastrointestinal adverse events; ischemic colitis; severe constipation. Reintroduced 2002 on a restricted basis
Cisapride (Propulsid)	2000	United States	Gastrointestinal dysmotility	Risk of fatal cardiac arrhythmias
Phenylpropanolamine (Propagest, Dexatrim)	2000	Canada, United States	Decongestant	Hemorrhagic stroke
Troglitazone (Rezulin)	2000	United States, Germany	Antidiabetic	Hepatotoxicity
Trovafloxacin (Trovan)	1999–2001	European Union, United States	Broad-spectrum antibiotic	Withdrawn because of risk of liver failure
Amineptine (Survector)	1999	France, United States	Antidepressant	Hepatotoxicity, dermatological side effects, and abuse potential
Aminopyrine	1999	France, Thailand	Anti-inflammatory	Abuse; dependence; severe acne
Astemizole (Hismanal)	1999	United States, Malaysia, Multiple Nonspecified Markets	Antihistamine	Fatal arrhythmia
Grepafloxacin (Raxar)	1999	Withdrawn Germany, United Kingdom, United States, others	Broad-spectrum antibiotic	Cardiac repolarization; QT interval prolongation
Levamisole (Ergamisol)	1999		Antihelminthic	Still used as veterinary drug; in humans was used to treat melanoma before it was withdrawn for agranulocytosis

Temazepam (Restoril, Euhypnos, Normison, Remestan, Tenox, Norkotral)	1999	Sweden, Norway	Insomnia	Diversion, abuse, and a relatively high rate of overdose deaths in comparison to other drugs of its group. This drug continues to be available in most of the world including the United States, but under strict controls
Bromfenac	1998	United States	Ocular inflammation and pain	Severe hepatitis and liver failure (some requiring transplantation)
Ebrotidine	1998	Spain	Antiulcer	Hepatotoxicity
Mibefradil	1998	European Union, Malaysia, United States, others	Hypertension	Fatal arrhythmia, drug interactions
Mibefradil (Posicor)	1998		Hypertension	Withdrawn because of dangerous interactions with other drugs
Proxibarbal	1998	Spain, France, Italy, Portugal, Turkey	Antianxiety	Immunoallergic, thrombocytopenia
Sertindole	1998	European Union	Antipsychotic	Arrhythmia and sudden cardiac death
Tolcapone (Tasmar)	1998	European Union, Canada, Australia	Parkinson's disease	Hepatotoxicity
Terfenadine (Seldane, Triludan)	1997–1998	France, South Africa, Oman, others, United States	Allergy	Prolonged QT interval; ventricular tachycardia
Dexfenfluramine	1997	European Union, United Kingdom, United States	Appetite suppressant	Cardiac valvular disease
Fen-phen (popular combination of fenfluramine and phentermine)	1997		Appetite suppressant	Cardiotoxicity
Pemoline (Cylert)	1997	Canada, United Kingdom	Attention deficit hyperactivity disorder	Withdrawn from United States in 2005. Hepatotoxicity Reason: hepatotoxicity
Phenolphthalein	1997	United States	Laxative	Carcinogenicity

(*Continued*)

TABLE 1.1 (*Cont'd*)

Drug	Year	Country	Indication	Reason
Chlormezanone (Trancopal)	1996	European Union, United States, South Africa, Japan	Anxiolytic and muscle relaxant	Hepatotoxicity; Stevens–Johnson Syndrome; Toxic Epidermal Necrolysis
Minaprine	1996	France	Antidepressant	Convulsions
Tolrestat (Alredase)	1996	Argentina, Canada, Italy, others	Diabetic complications	Severe hepatotoxicity
Alpidem (Ananxyl)	1995	Worldwide	Anxiolytic	Not approved in the United States, withdrawn in France in 1994 and the rest of the market in 1995 because of rare but serious hepatotoxicity
Bendazac	1993	Spain	Anti-inflammatory	Hepatotoxicity
Flosequinan (Manoplax)	1993	United Kingdom, United States, others	Congestive heart failure	Increased mortality at higher doses; increased hospitalizations
Ketorolac	1993	France, Germany, others	Anti-inflammatory analgesic	Hemorrhage, renal failure
Moxisylyte	1993	France	Benign prostatic hypertrophy	Necrotic hepatitis
Remoxipride	1993	United Kingdom, others	Antipsychotic	Aplastic anemia
Sorivudine	1993	Japan	Antiviral	Drug interaction and deaths. [citation needed]
Thiobutabarbitone	1993	Germany	Anesthetic	Renal insufficiency
Benzarone	1992	Germany	Peripheral venous disorders	Hepatitis
Temafloxacin	1992	Germany, United Kingdom, United States, others	Antibiotic	Low blood sugar; hemolytic anemia; kidney, liver dysfunction; allergic reactions
Temafloxacin	1992	United States	Antibiotic	Allergic reactions and cases of hemolytic anemia, leading to three patient deaths

Encainide	1991	United Kingdom, United States	Antiarrhythmic	Ventricular arrhythmias
Fipexide	1991	France	Senile dementia	Hepatotoxicity
Flunitrazepam	1991	France	Hypnotic	Abuse
Terodiline (Micturin)	1991	Germany, United Kingdom, Spain, others	Antispasmodic in urology	Prolonged QT interval, ventricular tachycardia and arrhythmia
Triazolam	1991	France, Netherlands, Finland, Argentina, United Kingdom, others	Severe insomnia	Psychiatric adverse drug reactions, amnesia
Dilevalol	1990	United Kingdom	Hypertension	Hepatotoxicity
Dinoprostone	1990	United Kingdom	Induction labor	Uterine hypotonus, fetal distress
Fenoterol	1990	New Zealand	Bronchodilator	Asthma mortality
Metipranolol	1990	United Kingdom, others	Glaucoma	Uveitis
Pirprofen	1990	France, Germany, Spain	Anti-inflammatory	Gastrointestinal toxicity
Broazolam	1989	United Kingdom	Hypnotic	Animal carcinogenicity
Etretinate	1989	France	Severe psoriasis	Withdrawn United States (1999). Risk for birth defects
Exifone	1989	France	Senile dementia	Hepatotoxicity
L-Tryptophan	1989	Germany, United Kingdom	Cognitive disorders	Eosinophilic myalgia syndrome
Proglumide	1989	Germany	Antiulcer	Respiratory reaction
Prenylamine	1988	Canada, France, Germany, United Kingdom, United States, others	Angina pectoris	Cardiac arrhythmia and death
a	1988	Germany	Anti-infective	Dermatologic, hematologic and hepatic reactions
Sulfamethoxydiazine	1988	Germany	Anti-infective	Unknown
Suprofen	1986–1987	United Kingdom, Spain, United States	Anti-inflammatory/ mitosis	Flank pain, decreased kidney function
Nikethamide	1988	multiple markets	Stimulant/tranquilizer overdose	CNS Stimulation
Cinepazide	1987	Spain	Vasodilator	Agranulocytosis

(*Continued*)

TABLE 1.1 (*Cont'd*)

Drug	Year	Country	Indication	Reason
Clometacin	1987	France	Anti-inflammatory	Hepatotoxicity
Cyclofenil	1987	France	Scleroderma/Raynaud's disease	Hepatotoxicity
Muzolimine	1987	France, Germany, European Union	Hypertension	Polyneuropathy
Vincamine	1987	Germany	Vasodilator/nootropic	Hematologic toxicity
Beta-ethoxy-lacetanilanide	1986	Germany		Renal toxicity, animal carcinogenicity
Bucetin	1986	Germany	Pain, fever	Renal toxicity
Canrenone	1986	Germany	Diuretic	Animal carcinogenicity
Difemerine	1986	Germany	Antispasmodic	Multiorgan toxicities
Sulfamethoxypyridazine	1986	United Kingdom	Antibacterial	Dermatologic and hematologic reactions
Cianidanol	1985	France, Germany, Spain, Sweden	Liver disorders	Hemolytic anemia
Indalpine	1985	France	Depression	Agranulocytosis
Perhexilene	1985	United Kingdom, Spain	Angina pectoris	Neurologic and hepatic toxicity
Phenylbutazone	1985	Germany	Pain, fever	Off-label abuse, hematologic toxicity
Suloctidyl	1985	Germany, France, Spain	Dementia thrombotic disorders	Hepatotoxicity
Oxyphenbutazone	1984–1985	United Kingdom, United States, Germany, France, Canada	Pain, fever	Bone marrow suppression, Stevens–Johnson syndrome
Nitrefazole	1984	Germany	Alcohol deterrent	Hepatic and hematologic toxicity
Althesin (=Alphaxolone amineptine + Alphadolone)	1984	France, Germany, United Kingdom	Anesthetic induction	Anaphylaxis
Antrafenine	1984	France	Pain, fever	Unspecific experimental toxicity
Fenclofenac	1984	United Kingdom	Rheumatoid arthritis	Cutaneous reactions; animal carcinogenicity
Feprazone	1984	Germany, United Kingdom	Pain	Cutaneous reaction, multiorgan toxicity
Glafenine	1984	France, Germany	Pain, fever	Anaphylaxis

Isaxonine phosphate	1984	France	Lesions on peripheral nerves	Hepatotoxicity
Methaqualone	1984	South Africa (1971), India (1984), United Nations (1971–1988)	Insomnia	Withdrawn because of risk of addiction and overdose
Dimethylamylamine (DMAA)	1983	United States	Nasal decongestant dietary supplement	Voluntarily withdrawn from market by Lily. Reintroduced as a dietary supplement in 2006;[13]:13 and in 2013 the FDA started work to ban it due to cardiovascular problems [14]
Indoprofen	1983	Germany, Spain, United Kingdom	Pain, fever	Animal carcinogenicity, gastrointestinal toxicity
Isoxicam	1983	France, Germany, Spain, others	Pain, fever	Stevens–Johnson syndrome
Propanidid	1983	United Kingdom	Short-acting anesthetic	Allergy
Zimelidine	1983	Worldwide	Depression	Risk of Guillain–Barré syndrome, hypersensitivity reaction, hepatotoxicity [3, 45, 46] banned worldwide
Zomepirac	1983	United Kingdom, Germany, Spain, United States	Pain, fever	Anaphylactic reactions and nonfatal allergic reactions, renal failure
Benoxaprofen	1982	Germany, Spain, United Kingdom, United States	Pain, fever	Liver and kidney failure; gastrointestinal bleeding; ulcers
Clomacron	1982	United Kingdom		Hepatotoxicity
Methandrostenolone	1982	France, Germany, United Kingdom, United States, others	Female tonic	Off-label abuse
Pentylenetetrazol	1982		Convulsant therapy	Withdrawn for inability to produce effective convulsive therapy, and for causing seizures

(*Continued*)

TABLE 1.1 (*Cont'd*)

Drug	Year	Country	Indication	Reason
Nomifensine	1981–1986	France, Germany, Spain, United Kingdom, United States, others	Depression	Hemolytic anemia, hepatotoxicity, serious hypersensitive reactions
Amobarbital	1980	Norway	Hypnotic	Self-poisoning
Cyclobarbital	1980	Norway	Insomnia	Self-poisoning
Pentobarbital	1980	Norway	Sedative hypnotic	Self-poisoning
Ticrynafen (Tienilic acid)	1980	Germany, France, United Kingdom, United States, others	Hypertension	Liver toxicity and death
Alclofenac	1979	United Kingdom	Pain, fever	Vasculitis, rash
Methapyrilene	1979	Germany, United Kingdom, United States	Allergy insomnia	Animal carcinogenicity
Pyrovalerone	1979	France	Lethargy	Abuse
Buformin	1978	Germany	Diabetes	Metabolic toxicity
Phenformin and Buformin	1977	France, Germany, United States	Diabetes	Severe lactic acidosis
Azaribine	1976	United States	Psoriasis	Thromboembolism
Oxeladin	1976	Canada, United Kingdom, United States (1976)	Antitussive	Carcinogenicity
Pifoxime (=Pixifenide)	1976	France	Anti-inflammatory	Neuropsychiatric reaction
Dipyrone(Metamizole)	1975	United Kingdom, United States, others	Analgesic, antispasmodic, and antipyretic	Agranulocytosis, anaphylactic reactions
Diethylstilbestrol	1970s		Gonorrheal vaginitis, atrophic vaginitis, menopausal symptoms, and postpartum lactation suppression	Risk of teratogenicity
Mebanazine	1975	United Kingdom	Antidepressant	Hepatotoxicity, drug interaction

Phenacetin	1975	Canada	Analgesic	An ingredient in "A.P.C." tablet; withdrawn because of risk of cancer and kidney disease [24] Germany Denmark, United Kingdom, United States, others Reason: nephropathy
Nialamide	1974	United Kingdom, United States	Antidepressant	Hepatotoxicity, drug interaction
Clioquinol	1973	France, Germany, United Kingdom, United States	Antifungal, antiprotozoal	Neurotoxicity
Dimazol (Diamthazole)	1972	France, United States	Antifungal	Neuropsychiatric reaction
Diacetoxydiphenolisatin	1971	Australia	Laxative	Hepatotoxicity
Triacetyldiphenolisatin	1971	Australia	Laxative	Hepatotoxicity
Amoproxan	1970	France	Antiarrhythmic, antianginal	Dermatologic and ophthalmic toxicity
Chlormadinone (Chlormenadione)	1970	United Kingdom, United States	Contraceptive	Animal carcinogenicity
Dihydrostreptomycin	1970	United States	Anti-infective	Neuropsychiatric reaction
Fenclozic acid	1970	United Kingdom, United States	Anti-inflammatory	Jaundice, elevated hepatic enzymes
Anagestone acetate	1969	Germany	Contraceptive	Animal carcinogenicity
Chlorphentermine	1969	Germany	Appetite suppressant	Cardiovascular toxicity
Cloforex	1969	Germany	Appetite suppressant	Cardiovascular toxicity
Ibufenac	1968	United Kingdom	Anti-inflammatory	Hepatotoxicity, jaundice
Bithionol	1967	United States	Antihelminthic	Dermatologic toxicity
Phenoxypropazine	1966	United Kingdom	Antidepressant	Hepatotoxicity, drug interaction
Metofoline	1965	United States	Analgesic	Unspecific experimental toxicity
Pronethalol	1965	United Kingdom	Hypertension	Animal carcinogenicity
Xenazoic acid	1965	France	Antiviral	Hepatotoxicity
Benziodarone	1964	France, United Kingdom	Hypertension	Jaundice
Butamben (Efocaine) (Butoforme)	1964	United States	Local anesthetic	Dermatologic toxicity; psychiatric reactions

(*Continued*)

TABLE 1.1 (*Cont'd*)

Drug	Year	Country	Indication	Reason
Dithiazanine iodide	1964	France, United States	Antihelminthic	Cardiovascular and metabolic reaction
Iodinated casein strophanthin	1964	United States	Appetite suppressant	Metabolic reaction
Iproniazid	1964	Canada rest of world	Antidepressant	Interactions with food products containing tyrosine
Bunamiodyl	1963	Canada, United Kingdom, United States	Contrast agent	Nephropathy
Ethyl carbamate	1963	Canada, United Kingdom, United States	Antineoplastic	Carcinogenicity
Triparanol	1962	France, United States	Cardiovascular disease	Cataracts, alopecia, ichthyosis
Thalidomide	1961	Germany	Sedative hypnotic antisickness	Withdrawn because of risk of teratogenicity; returned to market for use in leprosy and multiple myeloma under FDA orphan drug rules
Thenalidine	1960	Canada, United Kingdom, United States	Antipruritic	Neutropenia
Lysergic acid diethylamide (LSD)	1950s–1960s		Psychedelic therapy	Marketed as a psychiatric drug; withdrawn after it became widely used recreationally
Oxyphenisatin (Phenisatin)		Australia, France, Germany, United Kingdom, United States	Laxative	Hepatotoxicity
Secobarbital		France, Norway, others	Anesthetic, anticonvulsant, anxiolytic, sedative, and hypnotic	Self-poisoning

Adapted from http://en.wikipedia.org/wiki/List_of_withdrawn_drugs

In recent years, there have been several high-profile examples including Bayer's Baycol, GlaxoSmithKline's Avandia, and Merck's Vioxx Baycol (cerivastatin), a cholesterol-lowering statin that was approved in 1997 and voluntarily withdrawn by Bayer in 2001 after 31 deaths were reported due to severe rhabdomyolysis in patients taking the drug [39]. Vioxx, the cyclooxygenase 2 inhibitor, also approved by the FDA in 1999, was withdrawn by Merck in 2004, after concerns of increased risk of heart attack and stroke after long-term use. It was widely used to treat rheumatoid arthritis and other diseases involving chronic pain, and it was estimated it had been used in over 50 million patients before withdrawal but also associated with between 88,000 and 140,000 cases of severe heart disease [40].

As the safety–efficacy balance has become increasingly driven in the direction of safety, these cases will probably increase. Perhaps what is most worrying about some of these instances is that they have been driven not by overt observation of toxicity in controlled trials but by retrospective meta-analysis of trials outside of the formal regulatory process. In some cases, this had led to rounds of challenge and counterchallenge between regulatory agencies and their critics, as exemplified by the controversy surrounding GSK's diabetes drug Avandia. Rosiglitazone is the active ingredient in Avandia, and it is a PPAR agonist used in monotherapy and combination treatment for diabetes. Avandia could control a patient's blood sugar levels for longer than traditional oral antidiabetic drugs and therefore was an important option to help patients control their sugar levels. It was approved in United States in 1999 and achieved peak sales of over $2.5B per year by 2006. However, its label was amended in 2001, as concerns surfaced over hepatic risks and its cardiovascular safety when used in combination therapy with insulin compared to insulin therapy alone [41]. In 2001, along with the label change, the FDA also requested GSK embark on the 6-year "RECORD" study comparing cardiovascular outcomes of Avandia to other commonly prescribed antidiabetic drugs.

Meanwhile, in 2004, in a settlement after a lawsuit concerning the withholding of negative clinical trial data on another of GSK's drugs, Paxil, the company agreed to publish all its clinical trial data on its own website. However, this step caused GSK more controversy over Avandia. A meta-analysis published in *New England Journal of Medicine* (NEJM) in 2007 across 42 clinical trials published on GSK's own website linked the drug's use to an increased risk of heart attacks [42]. To counter the NEJM article, GSK published an interim analysis of the RECORD study and showed the cardiovascular risk of Avandia was not significantly different from the control groups in the key outcomes of hospitalization of death through cardiovascular outcomes. The FDA issued a prescriber safety update in 2007 [43] highlighting the contradictory evidence and later that year amended the box label for Avandia. The label stated:

> "A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive".

There were calls for the drug to be withdrawn, but in 2010, the FDA did not agree and it remained on sale in the United States, although in September of that year the EMA

suspended marketing authorization of rosiglitazone-containing medications. In February 2011, the FDA recommended label changes that imposed severe restrictions on its use, limited prescribing to patients already taking rosiglitazone, to patients whose blood sugar could not be controlled with other antidiabetic medicines and who, after consulting with their healthcare professional, did not wish to use pioglitazone-containing medicines. The FDA also required a Risk Evaluation and Mitigation Strategy, which would severely limit the availability of rosiglitazone-containing medicines [44]. The FDA also called on GSK to convene a panel of independent scientists to readjudicate the results of the RECORD study, which compared the cardiovascular safety of AVANDIA to standard type II diabetes drugs. In 2010, from their peak in 2006, sales had crashed. In 2011, sales were just $205M, and as a final blow, its patent expired in 2012.

In 2013, the independent re-review of the results of the 2009 RECORD study confirmed the original conclusions and failed to show an increased risk of heart attack linked to the drug over standard of care diabetes drugs, and the FDA withdrew all restrictions on the use of Avandia [45]. This came perhaps somewhat late for GSK and many patients who might have benefitted from its use. The Avandia story certainly provides a cautionary tale, but it is common for high-profile drugs to be targets for controversy, and the debate over safety and efficacy can rage throughout the drug's patent life.

1.7 FIRST IN CLASS, BEST IN CLASS, AND THE ROLE OF THE PAYER

The pharmaceutical industry has been very successful in delivering valuable drugs that have changed the course of medical treatment. The introduction of antibiotics; cardiovascular drugs; steroids, both topical and inhaled; statins; anti-TNF biologics; antiulcer drugs; histamine antagonists; analgesics; antidepressants; immunosuppressants; and even contraceptives, to make an incomplete list, has changed the course of patients' lives. As a striking example, between 1995 and 1997, deaths from HIV/AIDS fell from 16.2/100,000 of the population to 6/100,000 of the population due to the widespread introduction of indinavir to HIV combination therapy, and with further drug introductions, by 2011, deaths had fallen even further to 2/100,000 of the population [46–48].

But drug companies only have the life of the intellectual property, and its regulatory market exclusivity, to reap a return on investment. After the expiry of these, generic competition reduces the ability of the innovating company to continue to make a financial return. A survey found that only 2/10 drugs discovered between 1990 and 1994 had lifetime sales that exceeded the average cost of development [49].

A natural next step for companies with a franchise in a particular disease area, or seeking a place within the market dominated by competitor companies, was to develop follow-on compounds, which address identified weaknesses in the earlier compounds. Pfizer's amlodipine became the best-in-class calcium channel antagonist and largely took the market from the earlier compounds such as felodipine. Likewise, AstraZeneca's proton pump inhibitor Nexium became a replacement for its own Losec, and GSK's histamine antagonist ranitidine became the best-selling follow-on to SKB's cimetidine, which in their respective heydays were both the world's biggest selling drugs. The oral neuraminidase inhibitor oseltamivir for influenza became a success at the expense of GSK's first-in-class inhaled zanamivir. While in the past there were many followers, nowadays, the follow-on drugs apparently cannot be economically further followed.

The market is rather satisfied with what it has, and hence, the hurdles to show differentiated profile have become significantly higher. In the last 5 years, it could be argued that the impact of payers' decisions (or probable decisions) have had an even bigger impact on drug development projects than regulatory concerns. The effect of national advisory bodies in those countries with government health systems (e.g., National Institute for Clinical Excellence (NICE) in the United Kingdom) on strategic thinking in project teams is now driving the introduction of "real-world evidence" early in project planning. The introduction of hard cutoffs on price might render certain therapeutic areas simply commercially nonviable in the countries where it is applied. Is the quality-adjusted life year (QALY) even index-linked to inflation by those users?

If this trend continues, many projects in exciting areas of emerging biology will probably be strangled at birth on the basis of commercial analysis. It has been argued that pricing agreements in Europe might transfer the full burden of development costs to those markets where higher prices can be obtained [50]. A move to a situation where the first-in-class drug takes the vast majority of the available market might not be desirable for patients since accumulated experience shows different patients may do better on different drugs within a class. In fact, doctors have been operating personalized healthcare for many years by matching superficially similar drugs to patients based on a patient-by-patient assessment of efficacy versus side effects. Probably, the best known example is in control of hypertension [51]. Can we afford the same range of drugs to work with in the future in other disease areas?

While some companies are still trying to innovate in these tight spaces, because of the success of the industry, the opportunity for innovation in follow-on compounds appears diminished (unless a niche for the new compound can be found through a personalized healthcare approach). Small biotechnology companies may thrive in this space, but for multinational pharmaceutical companies, the likely returns may be too small, with the need for blockbuster drugs expected to earn >1$B/year to sustain multinational profitability.

Even new targets in old areas are difficult territory, as AstraZeneca has found with the phase III failure of it's first-in-class SYK inhibitor fostamatinib for rheumatoid arthritis. Pfizer succeeded with it's also first-in-class JAK inhibitor tofacitinib, but not in Europe [52], at least so far. A number of CRTh2 antagonists from different companies have failed to show meaningful differentiated efficacy in asthma compared to inhaled steroids and β_2 agonists often with FEV1 as a clinical endpoint. GSK's recent FLAP inhibitor, GSK2190915 also failed to demonstrate meaningful clinical differentiation from the now generic cysteine leukotriene receptor 1 antagonist montelukast, even though montelukast is only partly effective in mild asthmatics. Commercial pressures are so high that even whole therapy areas have been sources of attrition as we shall see later.

As follow-on compounds are no longer rich picking grounds for blockbusters, and even new mechanism modulators in old diseases are challenging, the hunt is on for new targets in new diseases, where medical need is high. These are areas where both regulators and payers would welcome new innovation. But the focus on new targets that failed to translate into clinical efficacy has been a major source of attrition in modern portfolios. Indeed, in a review of sources of attrition by the management consultancy firm McKinsey's, novel mechanisms were twice as likely to suffer attrition in clinical development than known mechanisms [53]. Selecting which biological mechanisms we choose, in most disease areas, remains the primary challenge.

1.8 PORTFOLIO ATTRITION

While we struggle with our understanding of attrition due to biology and chemistry, we should not fail to mention human decision making as a major source of attrition in drug discovery and development pipelines. Projects can be stopped on the whims of new management or a management change of heart over the projected future value of a drug target, family of drug targets, or even disease areas. Even whole company portfolios can be at stake.

R&D is seen as an expense on the bottom line with little value being ascribed to an early portfolio. In business, it can be financially more attractive to acquire a company with its on-brand products and late-stage development opportunities than to develop your own. Even very large companies can be takeover targets to capitalize on the quirky tax regimens across global economies. Mergers, acquisitions, takeovers, and the closure of R&D pipelines can be financially viable propositions.

In 2014, Allergan announced it was to cut 1500 jobs, in a preemptive measure to cut costs as it attempted to defend itself from a $53 billion hostile bid from Valeant pharmaceuticals. It was a clash of corporate ideologies. Allergan with arguably a more traditional belief in sustainable growth driven through R&D innovation, versus Valeant and it's acquisition-based growth model and a focus on strong financial discipline. Throughout 2014, it was a battle fought in the boardroom, the courtroom, and in the press-room. However a final showdown was avoided, when a more welcome suitor emerged for Allergan. Activis, a company with corporate values apparently more closely aligned to Allergan's own, came forward with an acceptable $66 billion offer.

For US company AbbVie, the takeover of the Irish pharmaceutical company Shire for $53 billion ticked all the boxes. Shire provided AbbVie with products, late-stage development candidates, and a new tax domicile in Ireland with a lower rate of corporation tax from 22 to 13%. But following the international furor over the profit versus patients battle between Pfizer and AstraZeneca, the AbbVie–Shire deal was reputedly scuppered by changes in the tax regulations in the United States, which made the "tax inversion" much less attractive for US-based companies seeking to avoid US taxation on worldwide profits.

Neuroscience R&D has been hit hard in recent years, as pharmaceutical companies come under pressure to deliver value from their R&D investments, and the unpredictability and cost of clinical trials that seem particularly apparent in neuroscience. In 2010, GSK ended neuroscience R&D in England and Italy, and Novartis closed neuroscience R&D in Basel in 2011. Likewise, AstraZeneca closed its neuroscience R&D units in Wilmington, United States; Montreal, Canada; and Södertälje, Sweden, and replaced these with a small virtual neuroscience R&D group, following a largely opportunistic and completely outsourced R&D model.

Anti-infectives are another disease area that has been receiving lower investment from major pharmaceutical companies. Anti-infective research has its own challenges, and over the past 30 years, only two new classes of antibiotics have been introduced (in 2000 the oxazolidinones and in 2003 the lipopeptides) and only three antibiotic NMEs in this decade [54]. The requirement to kill rapidly growing (and mutating) bacteria requires high plasma levels relative to other drugs and to be safe at these higher levels [55]. Unfortunately, anti-infectives when effective are given for only a short time to cure their disease or maybe are reserved only for second-line therapy. They can have a limited market life due to emerging resistance, all limiting the commercial opportunity relative to

chronic therapies in other disease areas [56]. Many pharmaceutical companies have withdrawn from anti-infective R&D, while paradoxically the need for new antibiotics has never been higher. Governments are waking up to the fact that the supply of new antibiotics has dried up, as recognized in a recent World Health Organization (WHO) report [57]. Perhaps indicating a change of view, or at least a gap in the market, is the recent re-entrance of companies like Roche and Merck into antibacterial R&D. Since 2013 Roche has acquired rights to a number of new antibiotic development programs while in January 2015 Merck spent an estimated $9.5B in it's aquisition of anti-infectives specialist Cubust Pharmaceuticals.

Lagging behind the opposition can cause the termination of otherwise interesting projects: there is a strong current perception that first in class is dominant. That would be supported to date in the case of DPP-IV inhibitors, where Januvia has maintained leadership over later market entrants in the class. However, there are clear examples of the reverse, especially when the fast follower can benefit from experience acquired by the leader: two examples could be Tarceva and Iressa in oncology, or more strikingly, Sovaldi and Incivek in hepatitis virus C therapy. Maybe Aesop's tortoise can indeed beat the hare.

While pharmaceutical companies may avoid certain disease areas where the risk/financial reward balance appears unfavorable, new models of drug discovery are emerging. Charity-funded R&D is now becoming a major player. The Cystic Fibrosis Foundation provided $75million dollars for Vertex to develop their CFTR channel modulator Kalydeco [58]. In December 2013, the Dementia Consortium launched a £3M fund to bolster dementia drug discovery. In 2009, members of the Association of Medical Research Charities funded $1.1B of research in the United Kingdom alone. In 2012, the Bill and Melinda Gates Foundation alone made grants of $892M for global health projects. To stimulate R&D into new anti-infectives, and following a European Parliament resolution to establish an European Union-wide plan to combat antimicrobial resistance, the Innovative Medicines Initiative in partnership with five pharmaceutical companies has launched a $280M program to spur new anti-infective R&D [59] and will fund a phase III program for GSK's peptide formylase inhibitor for community-acquired pneumonia. However, one wonders whether this really is a solution to the problem. While the discovery and development of Vertex's Kalydeco is a triumph for CF treatment and an undoubted success for charity–industry partnerships, patient groups who raised and donated the $75M toward the costs of discovery of Kalydeco are now possibly consider they required to pay again, albeit more likely through their medical insurances, this time in excess of $311,000 per year per patient to receive it [60]. It is no wonder with examples such as this that even organizations as eminent as the WHO are questioning the value of relying on a commercial pharmaceutical industry, to meet the needs of the world's sick. They are looking to open innovation and a fully funded "idea to market R&D" model, in the interests of world health. As an example, the Indian government, recognizing the healthcare needs of its growing population, has embraced and is investing in open innovation. India would rather consider fully funding pharmaceutical R&D without industrial property protection and allow generic pharmaceutical manufacturing companies to sell the discovered drug with market competition to restrict pricing as a more economical healthcare model than the one currently operating with pharmaceutical companies. With an investment of $35 million so far committed, it is leading a global open innovation initiative called Open Source Drug Discovery, with the vision to provide affordable healthcare to the developing world [61].

Although it feels like the major pharmaceutical company model of drug discovery is broken, and the pharmaceutical industry is in decline, global pharmaceutical companies

still spent an estimated $135B in 2011 of R&D. So it is probably fairer to say that it is changing. Large and significant grants are being made by the government and charity sectors, and they are liable to increase. New models of pharmaceutical R&D are being explored, such as open innovation. Taken together, these ventures can only be seen as a good thing.

1.9 "AVOIDING" ATTRITION

If new drugs at new targets are proving too tough a challenge, pharmaceutical companies seek other opportunities to bring drugs to the market that meet unmet patient need, at lower overall risk. These opportunities include new formulations, new drug combinations, new indications for existing drugs, and even new drug modalities, among others.

1.9.1 Drug Combinations and New Formulations

New formulations have always been a source of innovation, intellectual property, and therefore profits. Many diseases require polypharmacology, and as patient compliance to any one drug is already a major source of efficacy variability, polypharmacology increases the problem. Thus, fixed-dose combinations for oral topical or inhaled formulations have been a major interest and major commercial and clinical success. The combination of amoxicillin and the β-lactamase inhibitor clavulanic acid has been a longtime success for the treatment of penicillin-resistant bacteria. The fixed-dose combinations of a β_2 agonist and a steroid, such as Symbicort (budesonide and formoterol) and Advair (fluticasone and salmeterol), are world's leading therapies for asthma and COPD. Gilead in combination with various pharmaceutical partners has a portfolio of fixed-dose combinations for HIV/AIDS treatment including Stribild, approved in 2012, a quad combination of elvitegravir/cobicistat/emtricitabine/tenofovir; Complera, a triple combination of rilpivirine + emtricitabine + tenofovir approved in 2011; as well as Atripla, a triple combination of efavirenz + emtricitabine + tenofovir approved in 2006, and Truvada, a double combination of emtricitabine + tenofovir approved in 2004.

The regulators, patent authorities, and payers all wish to see that combinations should show significant advantages over dosing the drugs individually, as the monotherapies could be used in combination, often at lower cost, as they may now be generic. The FDA [62], EMA [63], and WHO [64] have all issued guidance on fixed-dose combinations and indicate the likely situations where fixed-dose combinations are more and less likely to be approved.

The regulatory approval itself provides drugs with market protection through a period of data exclusivity. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman amendments) provided a more streamlined pathway for generic drugs to be brought to market, whereby some or all of the efficacy and safety data relied upon for approval were not conducted by the applicant or for which the applicant did not have a right of reference. But to still provide incentives for pharmaceutical innovation, the Act also authorized a period of NCE data exclusivity, preventing generic drug applications citing the original data for a period of 5 years. In Europe, the data exclusivity can be 10 years, and this protection can exceed the protection provided by the patent. But in the United States, where one part of the fixed dose combination has been previously registered, data exclusivity was only 3 years. After petitions from

companies such as Gilead and Bayer, the FDA has recently amended this to 5 years for future drug applications [65].

But the path to success with drug combinations is not an easy one. In 2012, the FDA rejected Merck's application for their lipid-lowering combination product Liptruzet, a combination of ezetimibe with atorvastatin (a generic version of Pfizer's Lipitor), indicating a requirement for more data. This drug was seen as a replacement for Merck's existing drug combination of ezetimibe with the generic statin, simvastatin. This was almost the end of the road for this particular combination. The FDA had previously rejected the application in 2009, but it was third time lucky for Merck, as in May 2013 the FDA finally approved the combination.

Intellectual property challenges to drug combinations are also causing problems for the industry. Patent challenges have led to the revocation of some high-profile combination patents, opening the door to generic competition. In 2004, the United Kingdom combination patent for GSK's Advair, a fixed-dose combination of salmeterol and fluticasone proprionate, was revoked on the basis of obviousness over GSK's existing combination of salbutamol and beclomethasone dipropionate sold in a metered dose inhaler device before the relevant priority date, after challenge from four generic companies. In 2007, the European Patent Office revoked AstraZeneca's combination patent for Symbicort, its fixed-dose combination of formoterol and budesonide.

In 2013, the UK patents court revoked the patent for GSK's malaria combination Malarone, a 5:2 mixture of atovaquone and proguanil, due to the presence of prior art found in a presentation and an abstract to a lecture [66]. In June 2013, the US federal court handed down a decision in Novo Nordisk A/S versus Caraco Pharmaceutical Laboratories Ltd. revoking a patent covering Novo's diabetes treatment involving a combination of drugs metformin and repaglinide as an obvious combination of known diabetes treatments [67]. The case highlights the difficulties in establishing nonobviousness when claim elements are individually known even where there is evidence of synergistic benefits of the combination. Novo has petitioned for a rehearing, and this was granted, partly on the recognition of the industry-wide implications of the decision.

The Indian patent authority in particular is currently taking a strict approach on patents for new formulations, salts, and other improvements. It has recently revoked a patent granted to GSK for a new salt for its dual tyrosine kinase inhibitor lapatinib, concluding that improved efficacy should be interpreted strictly on a therapeutic basis, taking no account of pharmaceutical properties such as flow, stability, or hygroscopicity [68]. Drug combinations are clearly a complicated area for pharmaceutical companies.

1.9.2 Biologics versus Small Molecules

Biologic drugs have been a major clinical and commercial success. Fifteen years ago, there were only small molecules in the world's top 10 selling drugs list. In 2012, the top 3 selling drugs were all biologics targeting TNF-alpha, that is, Humira, Remicade, and Embrel, with combined sales of $25.3 billion. Pharmaceutical companies have been rapidly trying to buy up or strike deals with the biologics companies. Biologic drugs are attractive due to the high levels of efficacy and specificity and have achieved rapid development times with lower levels of attrition than with small-molecule drugs. A cross-industry analysis found that between 2006 and 2010 25% of large molecules in phase II reached the market compared to only 10% for small molecules the 13 contributing pharmaceutical companies [69]. An analysis by Tufts University covering top 50 pharmaceutical

companies for drugs entering development from 1999–2004 up to 2009 found similar results and found the clinical success rate for large molecules was 32% compared to 13% for small molecules [70]. Biologic drugs have also been less susceptible to generic competition. Apart from the difficulty in the production of biologic drugs, which in itself gives a drug protection from competition, a process for biologic generic registration was only clarified in 2010 in the United States with the Biosimilars Act. The act itself provides a market exclusivity advantage to the innovator biologic of 12 years relative to a small molecule, which is granted only 5 years. Generic biologics have to wait longer. Even then the first generic to market is itself granted between 12 and 42 months of exclusivity, relative to only 180 days for small-molecule generic drug. The costs of biologic drug production are also high, and with the high efficacy, biologic drugs have been able to command high prices. It has been seen as a potential advantage for small-molecule drugs to undercut biologics on price due to the lower production costs. But this may also change. There is a global production overcapacity for biologic drugs, and some estimates suggest that the production cost is only 5% of the total price of the biologic drug [71]. It is therefore likely that any production cost differential could disappear, meaning small-molecule drugs have to meet biologics head-on on efficacy differentiation, safety, and compliance. It all sounds like bad news for small-molecule drugs. But small molecules also have advantages over biologics, for example, they can target both intracellular and extracellular mechanisms and have wider options for administration. They also can demonstrate a pleiotropic effect through targeting more than one pharmacology, or by modulating divergent signaling pathways, which has been shown to be a key contributor to the efficacy of a number of small-molecule drugs [72]. There is room and opportunity for both small- and large-molecule therapeutics.

1.9.3 Small-Molecule Compound Quality

From Hansch [73] to Lipinski [74], we've been aware of the controlling influence of bulk physical properties on the key pharmacokinetic properties of drug molecules. It is not too surprising that lipophilicity, molecular size, charge type, and hydrogen bond donor counts in particular have important controlling influences on the pharmacokinetic and toxicological profile of drugs. Lipophilic compounds tend to be less water soluble, distribute into fat, are more highly metabolized, and, as many receptors tend to have hydrophobic active sites, may be more promiscuous with respect to off-target pharmacology [75]. Database studies indicate that more lipophilic compounds also have a higher chance of attrition in clinical development [76]. Molecular size can be understood to have a direct impact on permeability, as molecular diffusion is dependent upon molecular size as described by the Stokes–Einstein equation. Where the lipophilicity scale is described by *n*-octanol-water partitioning, hydrogen bond donor counts need to be considered separately, because *n*-octanol likely overestimates the partitioning ability of donors into a hydrophobic phase [77]. Charge type is apparently an independent contributor to promiscuity, as a number of database analyses have shown bases are more promiscuous than similarly lipophilic acids or neutrals, that is, are more frequent hitters in broad selectivity screens. Certain chemical motifs are also disfavored in drugs, most often due to their chemical or metabolic reactivity with the potential to lead to *in vivo* covalent adducts or highly reactive genotoxic intermediates. Many companies maintain lists of "ugly" functionality to eliminate compounds containing these features from screening collections and discourage their inclusion in designed drug molecules [78, 79].

Other descriptors have also been variously implicated as playing a role, including sp2/sp3 count and numbers of aromatic rings. The statistical validity of some of the claims has recently been questioned [80] as have the overall conclusions [81]. Different companies place different degrees of emphasis on these compound quality indicators, which may suggest a lack of acceptance or a different "organizational culture" over how compound quality optimization can lead to development success [82]. There is a continuing debate over compound quality considerations, which are variously viewed as either focusing innovation in areas of property space more likely to give success or overly limiting the opportunity for chemical innovation [83]. Whichever camp you are in, it is certain that there is an opportunity for innovation at the edges of "drug-like space." Of the drugs that are Lipinski violations, many are cyclic/macrocyclic drugs, or drugs known to be subject to active transport. Large molecules have advantages in affinity, and this may be particularly important where the drug is required to antagonize a protein–protein interaction. Protein–protein molecular recognition interfaces often yield high binding energies, as the interacting proteins may be present at low concentrations in cells. It therefore may require a high-affinity small-molecule ligand to be able to compete. But the protein–protein interaction interface is often spread over a large surface area, adding to the difficulty for small-molecule low molecular weight antagonists. Lipinski-compliant small molecules just don't have the affinity capacity required, but the larger and more complex macrocycles and linear or cyclic peptides do, and hence, these are an exciting new area for drug discovery innovation. A number of biotech companies offer screening and drug discovery services based on libraries of cyclic and linear peptides of macrocycles. But while nature and evolution, with a little help from formulation science, has helped molecules such as cyclosporine and FK-506 to become successful oral drugs, the edges of Lipinski space carry with them the attendant problems of solubility and permeability as might be expected, and these will need some pharmaceutical ingenuity to overcome them. But with some ingenuity and determination progress can be made. Roche and Abbvie's BCL-2 inhibitor Venetoclax may be classified as an "ugly" molecule by compound quality measures (Mwt = 839.4, ACDlogP = 10.9), it has recently been granted FDA breakthrough status after successful phase II results in chronic lymphocytic leukaemia patients with a 17p gene deletion.

1.10 GOOD ATTRITION VERSUS BAD ATTRITION

It is desirable to stop projects that are likely to fail as early as possible and instead invest in projects that have a better chance to succeed. Certainly, finding out at the end of a phase IIb clinical study that the biological hypothesis that linked a target to disease is not valid is not good attrition. We want to be masters of attrition and not the victims of it. Attrition through the informed scientific decisions we make is good attrition. The earlier we can make that good scientific stop/go decision for a project, the better. Pharmaceutical companies have been developing guidelines, such as AstraZeneca's 5 Rs [84, 85], which are used to ask questions of R&D projects throughout their lifetime, to ensure projects are on track to delivering medicines that meet patient's needs and that payers will pay for (5 Rs = right target, right patients, right safety, right tissue/exposure, right commercial). AstraZeneca's 5 "rights" were based on a detailed retrospective analysis of the successes and failures of 142 small-molecule R&D projects from 2005 to 2011, and with only a 15% success rate in phase II compared with an industry average in that period of 33%, there was

a justifiable reason to ask searching questions. The outcome was a framework for five determinants of technical success in projects and portfolio quality, along with a sixth determinant, which was a culture for truth-seeking and rigorous decision making based on these determinants. The framework encourages those involved in the projects to question themselves against the 5 Rs at every stage of project progression.

Right target

- Strong link between target and disease
- Differentiating efficacy from existing therapies
- Available and predictive biomarkers
- Right tissue exposure
- Adequate bioavailability and tissue exposure
- Human pharmacokinetics/pharmacodynamics (PD) prediction
- PD biomarkers
- Drug–drug interaction
- Right safety
- Clear assessment of safety risks
- Clear understanding of risk/benefit
- Availability of predictive biomarkers

Right patients

- Scientific evidence in lead indication
- Risk/benefit stratification of patient population
- Personalized healthcare strategy including diagnostic/biomarkers
- Right commercial
- Differentiated value proposition versus future standard of care
- Priority geographies
- Market access/payer/provider focus
- Personalized healthcare strategy including diagnostic/biomarkers

AstraZeneca (and other companies) hope the aspiration to reduce attrition in R&D, and particularly late-phase attrition will be met.

1.11 SUMMARY

For the beleaguered drug project team battling these challenges, what hope can be offered? One major disadvantage of the decreasing size of major pharmaceutical company model is the decreasing opportunity for R&D scientists to gain experience over many projects. Drug discovery is still an empirical science; we continue to learn by our successes and failures. The experience if properly applied can have a major impact in reducing attrition as previous mistakes are avoided. As the industry becomes more and more fragmented, the chances of mistakes being repeated, or inappropriate R&D strategies being followed, increase.

Attrition can be summarized in three stages. At the initiation of drug research, there is strategic attrition in deciding to exit or not pursue certain therapeutic areas on the basis of low likelihood of technical success or failure to envisage a return on investment. We have discussed the withdrawals from CNS and antibiotic research, but other areas such as critical care, stroke, and septic shock are areas of major unmet need that are now less attractive. Clearly, regulators and payers have a role to play here in changing the landscape. In the middle stage of drug discovery and development, the major form of attrition is technical, for example, unpredicted toxicity, lack of target engagement, poor translation of effect, and patent competition. This phase is at the same time the most challenging and the stage where our understanding is improving most rapidly. Finally, there is late-stage attrition. Short of outright therapeutic or safety failure, attrition is often the result of a combination of technical complexity and commercial uncertainty. As the patent clock is ticking, reducing the potential time to make a return on investment, research companies can be unwilling to risk further resources in new trials to investigate effects seen in the first clinical evaluations. This creates a "one strike and you are out" approach, which seems potentially wasteful. Again, this is an area where a new framework for commercial viability is needed. The breakthrough status designation from the FDA is a promising step in this direction.

This book can suggest many tools and strategies to maximize the chance of success. It is an opportunity to distill that empirical understanding into something of real value for the way we will do drug discovery over the next few years. Great progress has been made in the last 20 years in the basic science of producing both small- and large-molecule drugs. As discussed in detail previously, the drive to understanding the translational link from target to disease is still a major difficulty, but here the impact of genetics of disease (and likely soon the epigenetic basis of disease) will make a rapidly accelerating contribution. The understanding of the major players in drug metabolism and drug transporters now allows reasonable prediction (and hence the opportunity to design out) drug–drug interactions or nonlinear kinetics. The benefits of investments in clinical pharmacology in phase II for better dose ranging are now being seen in many development programs. Investments in personalized healthcare, genetics of disease, patient segmentation, and biomarkers are helping to direct the right drug to the patients who would benefit most. Lastly, chemists have progressed in their understanding of what compound quality means. It is now up to the reader to implement these ideas in selecting the target and through the chemical structures you design, synthesize, and test.

Perhaps ultimately, there will need to be (further) discussion about the benefit of medicines to society, in an era of aging populations and rising expectations for healthcare. The whole commercial basis of drug development might need to be revaluated, as it has been in the past, with patent term extensions being increased to encourage even more thorough investigations of drugs in phase III. But bolder steps could be taken. We can see the commercial model failing in areas of still high unmet medical need, and pharmaceutical companies turn to withdraw from unprofitable or high-risk areas such as anti-infectives, third world diseases, and neuroscience. It is reassuring to see charities and governments stepping in and becoming themselves new and growing players in the global R&D. This is a fascinating time to be in the industry, and we look forward to monitoring the progress of alternative funding models, such as open innovation. The current system is far from perfect, and any attempt to provide additional ways of meeting areas of unmet medical need is to be welcomed the goose that laid the golden eggs.

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