



ATTRITION *in the* PHARMACEUTICAL INDUSTRY

*Reasons, Implications,
and Pathways Forward*

Edited by

Alexander Alex

C. John Harris

Dennis A. Smith

WILEY

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EDITED BY

ALEXANDER ALEX

C. JOHN HARRIS

DENNIS A. SMITH

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INTRODUCTION

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Taking on this very complex and important topic and putting together a book seemed a large but rewarding task for individuals who have spent their careers discovering and developing drugs. Having completed the task, there is still the feeling of not quite answering the problem. What the book represents is a detailed analysis of what is largely failure and some important directions that can be followed. At the time of publication, the industry is moving from blockbuster drugs to patient-targeted entities. These have the potential to lower attrition and may change the commercial process. In assembling the volume, the editors felt more and more the massive importance and urgency to find solutions for the issue of attrition in the pharmaceutical industry, which has been an ever-growing threat to the entire industry for at least 20 years. The editors have themselves experienced significant changes designed to increase productivity, reduce cost, and tackle attrition in the sector. These range from the implementation of a “more is better” philosophy with compound library synthesis and high-throughput screening to the “genome revolution” through all the way to alliances, collaborations, mergers, and acquisitions. However, it seems that none of these approaches have really worked since drug discovery productivity, as measured by number of new chemical and biological entities (NCE and NBE), has essentially stayed flat since the 1980s, despite exponential increases in research spending throughout the industry until investment started to stagnate in the last few years. Many questions have been raised, and many attempts have been made to resolve this conundrum, but it appears that a long-term, sustainable solution has yet to be found and recent events with yet more reorganizations and takeovers on the horizon seem to confirm this.

A strong cohort of new drug approvals by the FDA toward the end of the year increased the total to 41 for 2014, the largest number in 18 years. Therefore, 2014 becomes the

second highest year on record for the approval of new chemical entities since the record of 53 new drug approvals in 1996. This is good news for the pharmaceutical industry but also for patients in need of new medicines. It is noticeable that the number of NCEs has been highly variable over the last 5 years with a total of only 29 new drug approvals in 2013, which followed 39 approvals in 2012, although, by any measure, 2014 approvals outstrip those of recent years (average of 24 per annum in the first decade of the new millennium and 31 per annum in the 1990s).

Despite these encouraging numbers, the total number of drugs approved for the last 5 years is most likely still below the ideal in terms of the needed return on investment, particularly for large pharmaceutical companies. The challenges facing the pharmaceutical industry in terms of compound attrition in discovery and clinical phases all the way to postmarket withdrawals will be outlined in this book.

It would be presumptuous in the extreme for any book to claim to provide all the answers to a given problem, never more so than when dealing with attrition in the pharmaceutical industry. However, this book is intended to provide a perspective from a number of industry and academia experts in the field and to stimulate discussion on the topic that may even help to point in the direction of potential solutions. It is not intended to review every aspect of attrition in the pharmaceutical industry over the last three decades, but rather to provide some context in order to enable a measured attempt to look forward. Although it is not possible to predict the future, we hope that this book will provide some useful information and insights for a productive, collaborative, and positive discussion on attrition in the pharmaceutical industry. We hope that it will make a small but useful contribution to the debate on reducing attrition and increasing productivity. Above all, we should never lose sight of the ultimate goal of our efforts, which is to provide new and urgently needed medicines for patients across the world.

Attrition in the pharmaceutical industry has been a topic of intense discussion for at least three decades. As with most debates, the underlying facts are often complex and difficult to agree on by experts. One of the unarguable facts that have emerged over the last 30 years is that the number of new drugs coming to market has remained effectively flat since the early 1980s despite increasing research and development (R&D) budgets [1]. To a large extent, budgets have been essentially flat over the last 5 years, but productivity is still not in line with even the stagnant investments. However, in reality, the productivity of a pharmaceutical company is not measured, at least not by investors, by the output of new drugs but instead in terms of costs, sales, and profits; the market valuation of a company; and particularly the ability to pay dividends to its investors at an expected level. Remarkably, while innovation has remained relatively flat, profits and dividends have not actually fallen for decades. So what has been going on? As with most measures of success, productivity is relative. Many pharmaceutical companies expanded in the late 1990s in line with double-digit growth predictions for the decade ahead, which never materialized due to unforeseen economical circumstances and overoptimism, particularly but not exclusively around overinflated expectations in increasingly volatile stock markets and the impact of competition from emerging economies and severe challenges in the international patent landscape. This was despite the ever-increasing demand for existing and new medicines from those countries as well as the more established sectors.

There have also been severe challenges from economists to the wide claims that research to discover and develop new medicines entails the high costs and high risks outlined and published, primarily by the pharmaceutical industry, in a paper by the London School of Economics in 2011 [2]. A widely used figure for the cost of a new NCE is that of \$802 million,

which originates from a study done in 2003 [3]. However, it appears that in these numbers, factors like taxpayer subsidies have not been included, and accordingly, a corrected estimate would be \$403 million per NCE [1]. Further adjustments as, for example, using a “cost of capital” rate called for by the US and Canadian governments in the calculations that is significantly lower than the one used in the 2003 study, leads to a further reduction of the actual cost to \$180–\$231 million [1]. In addition, it appears that one needs to be very careful when drawing firm conclusions about NCE costs from analysis of data, especially when it has been voluntarily submitted by the companies themselves and is confidential and therefore not verifiable [1]. Another way of calculating the cost of an NCE is by dividing the actual research budgets by the number of NCEs per company [4]. It turns out that from this analysis, the amount of money spent on a new NCE is simply staggering. For example, AstraZeneca would have spent \$12 billion in research for every new drug approved, as much as the top-selling medicine (Lipitor, Pfizer) has ever generated in annual sales, whereas Amgen would have spent just \$3.7 billion per new drug. It is probably fair to say that at around \$12 billion per drug, inventing medicines would be considered an unsustainable business and at around \$3.7 billion, companies might just about be able to make a profit [4].

Whatever the precise real costs for an NCE are and with the benefit of hindsight, the investments made in anticipation of overoptimistic growth rates led to a somewhat unsustainable economic situation across the entire pharmaceutical industry, especially in the R&D area. Indeed, companies had to adjust in an often drastic manner to the economic and social realities that pertained toward the end of the twentieth century, notably through a massive consolidation of the industry driven by both friendly and hostile takeovers and mergers on an unprecedented scale. The main objective for many of these acquisitions appeared to be either to access the revenue for already marketed drugs or to incorporate the most promising candidates from the respective R&D pipeline. It appeared that these actions were at least stabilizing for the profits of the remaining companies, although these measures could clearly only be a “fix” for a few years until the next wave of patent expiries were imminent. The first decade of the twenty-first century did not seem to help pharmaceutical companies to get back on track to achieve their desired profits and shareholders’ expectations, with the stock market and housing market crashing around the world during that time. The inevitable consequences of these global crises, that is, stagnation of incomes, austerity measures by governments, and the increase of poverty across even many of the wealthy countries in the so-called developed world, also had a profound impact on the healthcare market, with prices for medicines being a particularly prominent target for governments and healthcare providers. In order to avoid government regulations in particular countries, some companies may even have withdrawn their products from those markets, and one can only assume that this was done in order not to put their pricing strategies in other, more profitable countries at risk.

The financial cuts, staff reductions, and general consolidation in the pharmaceutical sector have come at an enormous price, both economically and socially, for the people who rely on this industry for their income and prosperity, but even more importantly for patients who are getting fewer and fewer novel medicines at a time when the need for new therapies, especially in chronic diseases and increasingly resistant infections, is growing greater than ever before.

Covering the extremely wide theme of attrition in the pharmaceutical industry is a challenging endeavor, and this book claims neither completeness nor the provision of comprehensive answers to the many questions one might ask in relation to this topic. It does however attempt to provide not only a historical account that may help to facilitate

learning but also, hopefully, to offer some stimulating and thought-provoking insights from a group of vastly experienced authors who have, despite the obvious challenges, kindly agreed to contribute. In order to make this book more forward looking, the editors strongly encouraged the authors to identify and incorporate new approaches and ways of thinking into their chapters and give their personal opinions and speculations about potential ways forward for reducing attrition. We hope that readers will find this approach appealing and useful and that this book will exert some positive influence through the vast expertise and considered opinions of their drug discovery research colleagues.

This book has been structured with the intention to guide the reader through the various stages of drug discovery and development in a systematic way, starting with an overview of attrition in drug discovery over the last 20 years in Chapter 1 and then focusing on more detailed analyses in Chapters 2–5 of the various stages from discovery through to phases I, II, and III and postlaunch. Following the chapters on the discovery and development pipeline, Chapter 6 investigates the influence of the regulatory environment, which has seen some major changes over the last 20 years. Chapter 7 then focuses on experimental screening strategies to reduce attrition, while Chapter 9 examines the influence of phenotypic and target-based screening strategies on compound attrition and project choice. Chapter 8 discusses the importance and evolution of medicinal strategies to reduce attrition in the early stages of the discovery process but also, as a consequence, reduce the risk of attrition later on in development. Chapter 10 focuses on *in silico* approaches to reduce attrition, highlighting the importance of the contribution of computational methods to modern drug discovery. Chapter 11 discusses current and future strategies for improving drug discovery efficiency, particularly on collaborations and interactions between industrial and academic drug research. Chapter 12 then looks at the impact of investment strategies, organizational structure and corporate environment on attrition, and future investment strategies to reduce attrition.

As might be expected, there is some overlapping content between chapters, primarily in the introductory parts but also on occasion in discussions and interpretations of the scientific literature. The editors have recognized this and considered it to be a very positive aspect of this book since it allows for diversity of views and opinions from all the authors.

The editors hope that this book will make a valuable contribution to not only the very intense ongoing discussion of attrition in the pharmaceutical industry but also to point out new approaches, productive critique and innovative thinking, as well as realistic and implementable ways forward to tackle this issue of such massive significance not only to the millions of people involved in the industry but also, most of all, to the billions of patients, who are still largely relying on the industry for the breakthrough medicines of the future.

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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 book 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.

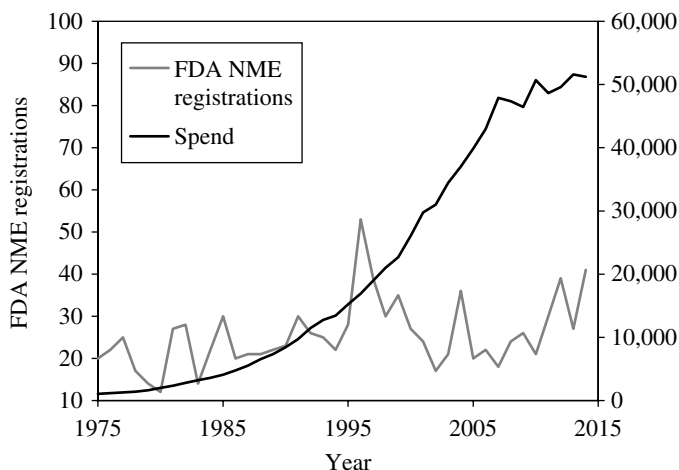


FIGURE 1.1 “The Graph”—Number FDA New medical entity registrations per year (gray curve) and total R&D expenditure/\$ millions (black curve) [2, 3].

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

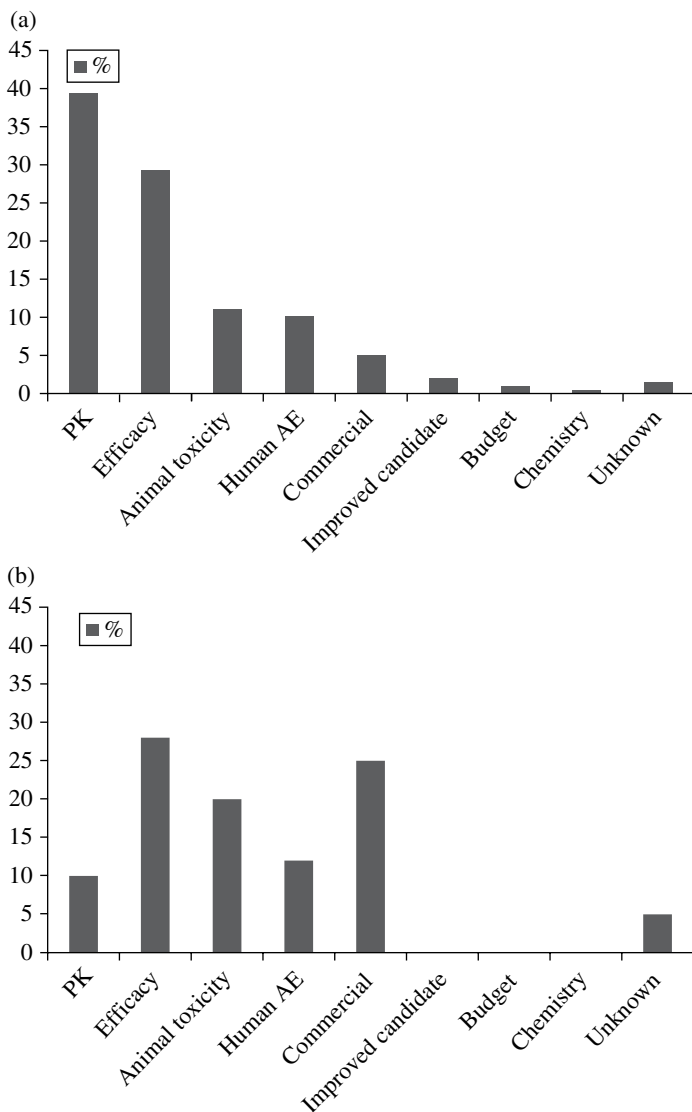


FIGURE 1.2 (a) Reasons for attrition. Data from Prentis and Walker [5]. (b) Reasons for attrition. Data from Kola and Landis [6].

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, $\Delta F508$ 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 μ g 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 PPAR α/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>