



# **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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Forward**

**EDITED BY**

**ALEXANDER ALEX**

**C. JOHN HARRIS**

**DENNIS A. SMITH**

**WILEY**

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# INTRODUCTION

ALEXANDER ALEX<sup>1</sup>, JOHN HARRIS<sup>2</sup> AND DENNIS A. SMITH<sup>3</sup>

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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.