Financial Returns on R&D: Looking Back at History, Looking Forward to Adaptive Licensing

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Abstract: Investment in R&D for drugs launched in the late 1970s to early 1990s generated good returns for investors. R&D was inexpensive. Clinical trial success rates were high. Consumption was increasing. Drug prices were outstripping inflation, which raised profit margins. Tax rates were falling. However, returns on R&D have been falling since the early 1990s given rising clinical trial costs, rising failure rates, and lower consumption growth in developed markets. Many investors believe that average financial returns on today’s R&D will be below the cost of capital, particularly if US drug price inflation moderates. Thus R&D investment by major drug companies is flat or perhaps falling in real terms. Various regulatory initiatives have tried to streamline clinical development and approval. The latest is Adaptive Licensing (AL). The near-term effect of AL on industry-level financial returns will be modest. AL will, however, be salient for decisions to invest in specific trials and may make it easier for smaller companies to fund development. AL could become more important in the long run if it helps shift industry, regulators, and payers from what has been an increasingly linear model of innovation; predicated on the ideas that basic science predicts, trials test predictions, and trial results form a complete description of a drug’s attributes. History shows that many drugs become important because doctors and patients discover utility that was not initially apparent to regulators, payers, or investors. One hope for AL, therefore, is that it will bring more acceptably safe chemical diversity into real world use at lower R&D cost.

Keywords: Adaptive Licensing, AMR, Antimicrobial resistance, Clinical trial costs, Drug development, Drug discovery, R&D productivity

1. INTRODUCTION

Most funds for biomedical R&D come from the commercial sector [1-4]. In the US, for example, from 2003 to 2008, nearly 60% of domestic investment came from drug, biotechnology, and medical device companies, with a little over 40% coming from Federal and State governments and from charities [4]. All new drugs approved by the FDA in recent years have been dependent on at least some private sector investment.

Private sector investors, while perhaps not completely indifferent to the wider benefits of advances in medicine, are usually indifferent to such benefits on a professional basis. They place an overwhelming priority on financial returns. Every dollar that is invested in R&D by a drug company whose stock they hold could have had another use. For example, it could be used to pay a bigger dividend which could pay pension fund holders, or be reinvested in a different industry with a more attractive risk or return profile; tobacco, fast food or alcoholic drinks perhaps?

Shareholders will only be enthusiastic about drug firms’ R&D investment if they believe that the financial returns are at least as high as the returns that could be achieved elsewhere with the same level of risk. This level of return is what shareholders regard as the “cost of equity”. Today, the nominal cost of equity for most major drug companies is around 9.5%. This figure varies over time, as, for example, government bond yields, stock market volatility, and risk perceptions change. In general, and in the long run, one should expect a withdrawal of investment from R&D by firms if returns are believed by their shareholders to be below the cost of equity, and an increase in R&D investment if the returns are believed by shareholders to be above the cost of equity.

Some investors believe that financial returns on current R&D investment in the biopharmaceutical industry as a whole are below the cost of equity [5-8]. Financial markets have started to signal that some, though certainly not all, drug companies become more attractive investments when they cut R&D spending and fire scientists [9, 10]. This is presumably because investors believe that the money that is saved will generate higher financial returns when deployed elsewhere. Thus, after roughly six decades in which drug industry R&D spending grew by an average of 7% to 8% a year in real terms [11, 12], R&D spending has fallen by 1% to 2% a year in real terms since 2010. R&D investment is likely to remain flat to slightly declining in real terms for some time [13]. Some of this change is probably causally related to investors’ concerns over the financial returns on R&D.

Financial returns on private sector R&D investment have been constrained by rapid growth in the costs of clinical development. When comparing drug cohorts launched in the
1970s vs. the early 1990s, total real-terms capitalized R&D costs per new molecule approved grew ~ 5.8 fold, pre-clinical costs per molecule approved grew ~3.9 fold and clinical development costs grew ~8.6 fold (corresponding to annualized real-terms growth rates of ~10%, ~8% and ~12%) [14-17]. Given differential growth rates, clinical development now consumes around twice as much R&D resource² as discovery and pre-clinical development, reversing the situation that existed in the 1970s [18, 19] (Fig. 1).

For a discussion of the factors that have caused the increase in clinical trial costs over time, see the following references: [20-23]. In short, however, factors include: The ‘regulatory ratchet’, or the tendency to add regulatory requirements without reducing them, often in response to past drug withdrawals or safety concerns; smaller incremental effect sizes in areas with good established treatments, which thus require larger and more powerful clinical trials to maintain statistical power; a shift towards R&D investment in areas of specialty medicine with high treatment complexity and cost (e.g., oncology); a growth in the number of required procedures (e.g., laboratory tests, imaging studies, etc.) per patient per trial protocol; more investment in therapy areas where combination therapy has become important, which patient per trial protocol; more investment in therapy areas that have aimed to increase the speed and efficiency with which new medicines (or new indications for existing medicines) can be introduced, particularly for patients with serious conditions for which there are few good treatment options [24, 25]. In the US, for example, the FDA has adopted mechanisms that include Prescription Drug User Fees, Fast Track, Breakthrough Therapy designation, Accelerated Approval, and Priority Review [25]. Some of these changes have increased regulatory capacity and provided a formal timetable for review (e.g., the Prescription Drug User Fee Act of 1992). Some mechanisms expedite regulatory scrutiny whose parameters are otherwise unchanged (e.g., Priority Review). Some may reduce the pre-launch clinical trial requirements (e.g., Accelerated Approval³ may provide for initial approval on the basis of surrogate endpoints, while longer trials are conducted to confirm that there are real benefits. Approval can be withdrawn if real benefits fail to materialize). Others (e.g., Fast Track and Breakthrough Therapy designation) increase the degree of collaboration between the FDA and the sponsoring drug company with respect to the design and conduct of the clinical programme.

There are also schemes in the US that recognize that R&D costs deter the investment required to discover and develop drugs for small numbers of patients. The Orphan Drug Act, passed in 1983, provides 7 years of market exclusivity following approval by the FDA, a 50% tax credit on clinical trial costs, and the possibility of Federal funding to perform clinical trials [26-28]. More recently, under the FDA Safety and Innovation Act of 2012, the US has applied “orphan-like” incentives to new antimicrobial drugs. The Act also required the FDA to revise its guidance for industry on the development of antimicrobial drugs. Before the Act, some elements of FDA guidance were regarded by many in the drug industry and in professional medical bodies as largely unworkable⁴.

Partly in response to concerns about the cost and duration of drug R&D projects, there have been a variety of regulatory changes that have aimed to increase the speed and efficiency with which new medicines (or new indications for

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² Not adjusting for the time cost of money, see later.

³ Under Section 506(c) of the Federal Food, Drug and Cosmetic Act (FD&C Act), accelerated approval is reserved for products intended to treat or cure a "serious or life-threatening condition" based on surrogate endpoints that are "reasonably likely to predict clinical benefit."

⁴ For example, it may have been impractical to conduct trials that were both ethical and compliant with the FDA’s requirements in patients with hospital-acquired or ventilator-associated bacterial pneumonia [75, 76]. One of the
Several of the FDA developments find parallels at the EMA, the European drug regulator. Europe has orphan drug regulations that are similar to those in the US [29]. The EMA has revised its guidance on the development of antimicrobials [30], and the FDA and EMA are now broadly in line with one another. The EMA’s Conditional Approval process is broadly equivalent to the FDA’s Accelerated Approval process. In 1995 the EU also introduced the Centralized Procedure for the approval of medicinal products. This provides a single centralized regulatory pathway that leads to marketing authorisation in all EU member states plus Iceland, Lichtenstein, and Norway. This is regarded by investors a major advance.

1.1. Adaptive Licensing (AL)

One regulatory innovation that is generating excitement today is “Adaptive Licensing” (AL) [24, 31-34], which is also sometimes called “Medicines Adaptive Pathways for Patients” (MAPPS). The EMA has recently started an AL pilot project with drug candidates selected from 26 that were put forward by the drug industry [35, 34].

The AL approach is based on the idea that a better compromise could be reached between the often competing demands of patient access, evidence on a drug’s risks and benefits and cost effectiveness, and returns on financial investment. AL structures clinical development around a graded, but prospectively planned, introduction of a new drug as evidence on its risk-benefit profile accumulates by a variety of means [24, 33, 34]. Perhaps, for example, commercial sales in a high-need subset of patients can be permitted on the basis of the results of Phase II trials, while further evidence is collected that eventually allows a broader label and wider use in a larger patient population. The emphasis shifts away from large pre-approval trials and towards more diverse and perhaps more “ecologically valid” evidence of real-world utility (e.g., patient registries for safety data). AL differs from Accelerated Approval in that the graded introduction and evidence collection is prospectively planned. It does not simply follow, for example, from unexpectedly good results in Phase II trials or from impressive interim results on surrogate endpoints (e.g., progression free survival with first-line use in metastatic breast cancer) in a Phase III trial that is designed to measure hard outcomes (e.g., overall survival with first-line use in metastatic breast cancer).

In this review, we consider AL from the shareholders’ perspective. Does it matter? Should it make drug companies’ shareholders more or less optimistic? What would investors need to know to take a view?

2. FINANCIAL RETURNS ON R&D

Before we consider the investment implications of AL, we review historical trends in financial returns on R&D and the factors to which financial returns are most sensitive. This will put the subsequent AL analyses in context. Readers should also see a thorough review published in 2012 by Di-Masi and Grabowski [14].

In what follows, we will generally express returns on investment in terms of Internal Rate of Return or IRR. The IRR of an investment can be thought of as the rate of interest at which cash outflows and cash inflows, when both time-discounted at that rate of interest, are equal to one another. So, for example, if one invested a dollar today, and received a dollar and ten cents in exactly one year’s time, the IRR would be 10%. If one invested a dollar today and received $1.21 in exactly 2 years’ time, the IRR would also be 10%. IRR can cope with more complicated cash flows, of the kind that occur in drug R&D, and collapse them to a single measure of financial reward. For any given level of investment risk, investors prefer opportunities with a higher IRR. Company activities that yield a post-tax IRR that is below the cost of equity appear to shareholders to be wasting money.

Sometimes we will express financial figures in “real” (inflation adjusted) terms. At other times, we will use “nominal” figures (not adjusting for inflation). In general, we will use real figures for backward looking analyses. We will typically use nominal figures for forward looking analyses because we know the nominal cost of equity (which already reflects, to an extent, investors’ inflation expectations) but we do not know what future inflation rates are going to be.

While it should, in principle, be relatively easy to work out the IRR on historical drug R&D it is surprisingly difficult in practice. This is for several reasons. First, most data on the cost of drug discovery and development are held by commercial organizations. Second, these companies do not disclose the profitability of individual drugs. These two factors make it hard to match investments with returns at a product level. Third, there is often a very long delay between the costs of R&D and the subsequent profits. Fourth, both costs and profits are smeared over long periods of time; several decades in some cases. Fifth, many drug companies have other lines of business. These three factors tend to make conventional accounting measures of financial returns on drug R&D hard to calculate and/or somewhat irrelevant. Sixth, most of the cost of R&D is associated with things that fail. There is no perfectly objective way of allocating the cost of failure to the individual projects that succeed. Furthermore, successes tend to be visible, while failures are more private. Seventh, companies have a lot of general costs (e.g., the cost of maintaining the laboratory drains) which are hard to allocate in an objective way to specific R&D projects. Eighth, financial returns on R&D are highly skewed, with a small number of successful drugs (perhaps 10% of those that are approved) generating around half of the net value of all branded drug profits [36]. This means that IRR is highly variable between companies and over time in a stochastic manner, independent of any underlying differences or trends which may also be present. Therefore returns estimates will be sensitive to the sample of drugs, or set of companies, chosen for analysis. Ninth, the economics of R&D vary substantially between therapy areas and between indications within each therapy area.

Finally, and importantly, R&D costs and drug company profits are politically and commercially contentious and are
drawn into debates on drug pricing, access, and regulation [2, 33, 37-43]. So, for example, companies tend to signal to their shareholders that financial returns on today’s R&D are good (otherwise they would be admitting to shareholders that they were failing in their duty to allocate capital effectively) while simultaneously signaling to governments and payers that R&D returns are poor and that the R&D enterprise is precarious (otherwise governments might feel able to demand lower prices and/or higher regulatory barriers without a negative effect on the level of R&D investment).

The various analytic and data challenges have been most thoroughly addressed in several papers published by Grabowski, Vernon, and DiMasi [14, 36, 44, 45] and in a paper by Joglekar and Patterson [46]. These studies have taken a “lifecycle” approach to R&D investment (Fig. 2). They consider the cash flows associated with specific drugs that are discovered, developed, approved, and launched (illustrated in Fig. 2). The studies have used a cohort of drugs launched during a particular time period, and tried to build representative samples of R&D investment, using costs derived from industry surveys (e.g., [15-17, 47, 48]), and making adjustments and corrections for failures (whose costs are allocated to those drugs that succeed) and for portfolio mix [16]. Furthermore, these analyses have been performed far enough into the commercial lives of the drug cohort to make reasonably robust estimates of sales and profits.

Perhaps the main limitation of the academic life cycle-based studies is that they are backward looking, and that the most recently published work on financial returns relates to drug cohorts launched in the 1990s, based on R&D activity stretching back to the 1970s [36]. Conceptually similar analyses, though generally methodologically opaque and making bolder assumptions about future sales in order to take a forward looking view, are periodically produced by consulting firms and by investment analysts, and sometimes make it into the public domain. See, for example: [7].

It is also possible to estimate “P&L-based” R&D returns from standard accounting statements (i.e., income statement or P&L, balance sheet, cash flow statement) which are published by all publicly traded companies (see, for example, [5, 6, 49-52]). The approach here is to calculate returns on R&D by comparing the historic company- or industry-level R&D investment with profits that are generated after some suitable time period and perhaps with some suitable time course. This approach has the advantage of completeness since R&D costs at any time will reflect all on-going R&D activity. It is also relatively simple, once one adjusts for mergers and acquisitions. However, the approach cannot resolve the time course of specific investments. There are difficulties in allocating later profits to R&D investment if companies have a mix of non-drug businesses that contribute to the overall profit figure but which are much less R&D intensive (e.g., chemicals, medical devices, etc.).

Estimates of financial returns at an industry level, derived from both lifecycle-based and P&L-based approaches are summarized in Fig. (3A). Fig. (3) also illustrates some of the factors that have influenced returns. Some of the measures in Fig. (3) are rather US-centric. However, it is possible to get good long-term time-series data for the US. The US also provides around 50% of profits for major drug companies. Fig. (3A) shows estimates of real (i.e., inflation adjusted) IRR based on drugs launched through several time periods (solid lines) based on lifecycle analyses [36, 44, 45]. The Figure also shows P&L-based estimates of real IRR derived from work by SSR Health [5] (dotted line).
Fig. (3). Panel A. Estimates of real IRR derived from lifecycle based analyses (solid lines) for drug cohorts launched from 1970-74 and 1975-79 [44], 1980-84 [45], and 1990-94 [36]. These estimates were adjusted upwards slightly (around one percentage point or less) from the originals to reflect our calculation of the effect of declining tax rates during the lifecycles of the products. The dotted line shows estimates of real IRR from a P&L based analysis [5] assuming a 16 year lag between R&D costs and profits. The horizontal axis shows drug launch year. For a discussion of why the lifecycle based and P&L based methods yield different estimates see the main text. Panel B. Real (i.e. CPI adjusted) drug sales in the US indexed vs. 1960. This is based on OECD data. The R&D index is drug industry R&D as a % of sales multiplied by US drug sales. Panel C. Indexed real-terms drug prices in the US. PPI reflects the prices received by domestic U.S. drug producers for their output. CPI reflects drug prices paid by consumers. PPI is a more appropriate measure, but was not computed prior to 1981. Pharmaceutical CPI and Pharmaceutical PPI are both indexed vs. the general consumer price index in the graph. The graph is based on data from the U.S. Bureau of Labor Statistics. Note that both Pharmaceutical PPI and Pharmaceutical CPI under-estimate branded drug price rises in recent decades, because both indices include generic drugs, whose share of each index has grown. We estimate that from 2006 to 2013, like-for-like price inflation for branded drugs in the US ran close to a nominal 10% per year (~8% real), while the pharmaceutical PPI rose by a nominal 5.5% (~3.5% real) per year. Panel D. The graph shows a variety of estimates of the probability that a drug entering Phase I trials is ultimately approved by the FDA. Each line represents a different study or a major subgroup within a study. The horizontal axis shows the approval years for each cohort. For details see: [53-58]. Panel E. Margin structure for sample of major US-listed drug companies. The sample is corrected for mergers and acquisitions. Margins are shown cumulatively, building to 100% of sales. Operating profit is profit before tax and interest expenses. COGS are selling, general, and administrative expenses. COGS are the manufacturer’s production costs of goods sold. Note how the operating profit margin parallels real-terms drug prices (panel C) while COGS (see the spread between the COGS and SG&A lines) mirrors real-terms drug prices. Panel F. Median corporation tax rate for a sample of major publicly-traded drug companies. The cash available to pay shareholders comes from post-tax earnings, while R&D expenses depress current profits and so provide a partial shield against tax. Thus declining tax rates tend to increase IRR on R&D.
The early 1970s’ lifecycle-based cohort yielded relatively low returns. The real IRR was below the real cost of equity at the time (around 9%). The early 1970s drugs were launched into a sluggish market (Fig. 3B) with declining real-terms drug prices (Fig. 3C) and falling operating profit margins for drug companies (Fig. 3E). Real financial returns were higher for the late 1970s, early 1980s, and early 1990s cohorts. For these cohorts, real IRR was a little higher than the real cost of equity (which was in the 10% to 11% range). These cohorts of drugs were launched when clinical trial success rates were relatively high (Fig. 3D) which offset rising R&D costs (Fig. 3B). Drugs were also launched into a market in which there was real-terms drug price inflation (Fig. 3C) and in which profit margins were rising (Fig. 3E). It might be interesting to speculate on the direction of causality here. Did better drugs allow for higher prices which in turn encouraged more R&D investment, or did the pricing power come first?

The P&L-based method shown here (Fig. 3A, dotted line) estimates real IRR by assuming that the cash investment in R&D one year is solely and entirely responsible for the cash returns on R&D exactly 16 years later. This time delay is a reasonable point-estimate of the timings of R&D investment and profits in a typical lifecycle analysis (Fig. 2).

The P&L-based method (and other P&L-based methods which are not shown on the graph, but see for example [49] and [52]) gives a higher IRR estimates than the life-cycle based method. The most likely reasons for the difference are: (a) the misallocation of R&D independent profits (e.g., from chemicals, medical devices, or consumer healthcare) to drug R&D costs; and (b) persistent profits from old drugs, particularly in the years before efficient generic substitution, being misallocated to later R&D. Bailey [49] suggested that financial returns on R&D were extremely good before major regulatory changes in 1962. However, efficient generic substitution methods were not implemented until the mid-1980s. Thus P&L-based methods for estimating the IRR on R&D would capture the persistent profits from the earlier drug cohorts and misallocate them to the R&D spend on drugs that were launched later. This may explain the high IRR estimates from the P&L based method, particularly before the mid-1970s.

Setting aside the methodological differences, the P&L-based method suggests that the real IRR on R&D probably started to fall for launch cohorts from the early 1990s (Fig. 3A). Despite continued real-terms drug price inflation (Fig. 3C) and profit margin expansion (Fig. 3E), clinical trial success rates tended to fall (Fig. 3D), R&D spending as a percentage of sales continued to rise (Fig. 3B), and drug market growth slowed (Fig. 3B).

Tax rates have also been in long-term decline for drug companies (Fig. 3F). R&D expenses provide a shield from tax by reducing taxable profits at the time they are spent. Shareholders’ dividends, on the other hand, are paid from post-tax earnings. Thus falling tax rates have tended to boost the post-tax value of lagged profits to shareholders versus the post-tax cost to shareholders of the prior R&D investment that generated those profits. We estimate that the decline in tax rates will have raised the real IRR of the average drug lifecycle investment by between 0.75 and 1 percentage points.

2.1. Sensitivity of Financial Returns to Model Parameters

While it may be difficult to calculate the IRR on historic R&D investment, it is easier to calculate the factors to which R&D returns are most sensitive for any given model or analytical framework. In general, things that reduce or delay tax-adjusted R&D costs or any other costs will increase IRR, while things that reduce or delay post-tax profits will tend to reduce IRR. The main challenge is not the calculation. Rather, it is to judge the ranges through which the models’ parameters could plausibly vary, as a result of changes in regulatory policy, management action, or payer behaviour. However, several factors have been recurrent themes in published sensitivity analyses over the last ~30 years. These include regulatory timetables, the length commercial product life in the face of generics, R&D costs, profitability (which is closely related to pricing) and tax rates. See, for example: [36, 44-46, 59].

The results of more recent sensitivity analyses by SSR Health are illustrated in Fig. (4) [5]. The underlying analyses are lifecycle based, and are similar in principle to those of [36]. However, SSR Health re-create an “average” large drug company portfolio of projects; a portfolio of lifecycles, which are at different stages of the R&D process, some of which are small molecule projects and some of which are biologics projects, and some of which reflect in-licensed drugs and some of which represent in-house discoveries. The analysis shows that the duration and cost of R&D remain important. The analysis also shows that returns are particularly sensitive to US drug price inflation.

Drug price inflation is important because it has compounding effect over time, and because the time course of drug R&D and drug life cycles are long. Suppose, for example, an R&D project is initiated into a world with 3.5% real terms of drug price inflation. Around 20 years later, when the drug that the project yielded might be approaching its peak level of sales, drug prices will have doubled in real terms, and profit contributions will have roughly tripled (assuming production and selling costs track general inflation). Note how drug industry profit margins track US drug prices in Fig. (3E) vs. Fig. (3C).

2.2. Variability of Financial Returns with Drug Profits and R&D Investment

Another important feature of R&D investment, which appears consistent over time, is that financial returns vary hugely between R&D projects; even between the ~10% of clinical development projects that yield an approved drug [14, 36, 44, 45]. Around 10% of approved drugs probably account for around half of all the net present value of all post

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Less likely reasons, given the way the analyses were conducted, include: Failures in the attempt to turn accounting measures into cash flows (e.g., adjustments for acquisition related in-process R&D), R&D-specific depreciation and amortisation, changes in working capital, etc.; survivor bias in accounting based methods (i.e., only companies that do well end up in the data set); and non-representative sampling of R&D projects or random sampling error by the life-cycle methods.
R&D cash-flows. Conversely, around 60% of approved drugs generate profits whose net present value is less than the average R&D investment per new approved drug (Fig. 5). In this respect, drug R&D projects resemble high-risk technology projects [60].

R&D costs also vary hugely between projects, even setting aside for a moment the cost of failure. The coefficient of variation of cost across Phase III programmes is high (0.7 for a cohort of drugs launched between 1983 and 1994) [48]. The average Phase III programme in community acquired bacterial pneumonia appears to cost just over one third as much as the average Phase III programme in hospital-acquired and ventilator-associated bacterial pneumonia [44]. Some recent oncology approvals have been based on trials involving only a few hundred patients or less (e.g., crizotinib, vismodegib) while other oncology drugs have seen waves of Phase III trials across different indications with a cumulative enrolment of over 10,000 patients (waves of Phase III trials across different indications with a cumulative enrolment of over 10,000 patients (e.g., trametinib, crizotinib)).

Such a high degree of variability in costs and profits has several practical implications for investors. First, their experiences - even if they are relatively diversified within the drug and biotechnology sector - will tend to depend on their level of exposure to a small number of drugs with extreme economics. Second, underlying industry productivity trends will likely be obscured by random variations in both the number and value of approved drugs in the short to medium term (Fig. 6). If productivity seems unusually bad for a year or two, it will probably get better. If productivity seems unusually good for a year or two, it will probably get worse. Third, some particular niches may continue to look attractive and receive substantial investment even if R&D investment returns are poor for the industry as a whole.

2.3. Financial Returns Change Through the R&D Process

For investors who are exposed to the full R&D cycle, either because they invest in early-stage companies, or because they invest in large drug companies that undertake drug discovery and/or use their profits to acquire early-stage companies or rights to their drug candidates, the lifecycle based returns and sensitivity analyses are an appropriate way to view the world.

However, specific investment decisions through the R&D process, by company management for example, should be...
regarded differently. Drug candidates tend to become more valuable later in the R&D process. By the time the decision comes to initiate Phase III trials, most of the costs of R&D have already been sunk. Thus a profit stream that might have looked pathetic when viewed from the start of the drug discovery process, might still justify a Phase III trial programme once positive Phase II data are in.

This is illustrated in Table 1 in which average R&D project costs per molecule approved (including the cost of failure) are based on data from [19]. In this example, the subsequent profits (not shown) are set to give an IRR of 11%, when viewed from the start of the process, more than 13 years before a drug launch. However, at the end of a positive Phase II programme for the same project, perhaps less than 5 years from launch, the prospective IRR appears to be 27.5%. This is one reason why companies have to pay higher prices when they acquire later-stage drugs [62].

Table 1 also shows that the salience of changes in clinical trial costs or in regulation is different at different points in the R&D process. Suppose, for example, we could somehow reduce Phase III trial costs by 50% while keeping all other things the same (scenario (b) in Table 1). Such a change would increase the expected IRR from 11% to 11.9% when viewed from the start of the process. However, provided there were positive Phase II results, the change would increase the expected IRR of incremental investment from the start of Phase III trials onwards from 27.5% to 34%. Thus a major change in the conduct or cost of Phase III trials is more salient for investment in development projects than it is for investment in drug discovery.

### Table 1

<table>
<thead>
<tr>
<th>R&amp;D stage</th>
<th>Target to hit</th>
<th>Hit to lead</th>
<th>Lead opt.</th>
<th>Preclin.</th>
<th>PI</th>
<th>PII</th>
<th>PIII</th>
<th>Sub’n to launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard pre-tax R&amp;D costs and attrition (after Paul et al., 2010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of launch at start of stage</td>
<td>4%</td>
<td>5%</td>
<td>7%</td>
<td>8%</td>
<td>12%</td>
<td>22%</td>
<td>63%</td>
<td>91%</td>
</tr>
<tr>
<td>Out of pocket R&amp;D cost per stage of the one successful molecule ($m)</td>
<td>1</td>
<td>3</td>
<td>10</td>
<td>5</td>
<td>15</td>
<td>40</td>
<td>147</td>
<td>40</td>
</tr>
<tr>
<td>Out of pocket R&amp;D cost per stage for all failed molecules ($m)</td>
<td>23</td>
<td>46</td>
<td>136</td>
<td>57</td>
<td>113</td>
<td>145</td>
<td>88</td>
<td>4</td>
</tr>
<tr>
<td>Total out of pocket R&amp;D cost per stage ($m)</td>
<td>24</td>
<td>49</td>
<td>146</td>
<td>62</td>
<td>128</td>
<td>185</td>
<td>235</td>
<td>44</td>
</tr>
<tr>
<td>Capitalized R&amp;D cost per stage including failures ($m)</td>
<td>96</td>
<td>166</td>
<td>414</td>
<td>150</td>
<td>273</td>
<td>319</td>
<td>314</td>
<td>48</td>
</tr>
<tr>
<td>Cumulative capitalized R&amp;D cost ($m)</td>
<td>96</td>
<td>262</td>
<td>676</td>
<td>826</td>
<td>1,099</td>
<td>1,418</td>
<td>1,732</td>
<td>1,780</td>
</tr>
<tr>
<td>Time vs. launch (years)</td>
<td>-13.3</td>
<td>-11.7</td>
<td>-10.0</td>
<td>-8.5</td>
<td>-7.3</td>
<td>-5.2</td>
<td>-2.8</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

(a) IRR on incremental investment rises through R&D process
- Nominal IRR on incremental R&D investment at start of stage
  - 11.0% 11.5% 12.6% 15.7% 17.2% 20.7% 27.5% 52.0%
- Nominal IRR on incremental R&D investment after successful completion
  - 11.5% 12.6% 15.7% 17.2% 20.7% 27.5% 52.0% NA

(b) Salience of lower PIII costs increases through R&D process
- Base case - Nominal IRR on incremental R&D investment at start of stage
  - 11.0% 11.5% 12.6% 15.7% 17.2% 20.7% 27.5% 52.0%
- Nominal IRR with 50% reduction in PIII cost
  - 11.9% 12.5% 13.6% 17.3% 19.0% 23.5% 34.0% 52.0%

3. WHAT SHOULD INVESTORS MAKE OF ADAPTIVE LICENSING (AL)?

Adaptive licensing (AL) has generated considerable interest in some health policy circles [24, 33], within parts of the drug industry, among some with huge FDA expertise [31], and at the EMA, which has initiated a pilot project with a handful of drug candidates [35, 34]. Given all the other factors that influence the IRR on today’s R&D investment, should investors share this enthusiasm for AL?

Clearly there may be benefits for investors. For example, Baird et al. [33] have applied several AL scenarios to the development, approval, and post-market monitoring of three drugs: Vemurafenib (Zelboraf, a melanoma drug); fingolimod (Gilenya, a multiple sclerosis (MS) drug) and rimonabant (Acomplia, a weight-loss drug). They argued that financial returns to the sponsoring drug company tended to rise when the scenario was more “adaptive” [33]. Furthermore, 26 drug candidates were recently put forward by drug companies for the EMA’s AL pilot [34]. One presumes the companies could have chosen the conventional route to market for each of these drugs had the conventional route looked preferable.

However, the fact that companies are taking part in an EMA pilot does not guarantee that all think it is positive. Perhaps companies are involved because they believe that the regulator will impose AL on them at some stage, and they want to influence the process and learn how to navigate it. Perhaps they need to demonstrate corporate responsibility. For example, it would be difficult to lobby European governments to improve access to expensive new drugs while simultaneously declining to support a regulatory model that might provide earlier access.

7
3.1. Impact of AL Scenarios on Returns of Individual R&D Projects

We have explored the influence of various AL scenarios on the IRR of an “average” project (Table 2, Fig. 7). Given the huge variability value of projects (Fig. 5) and huge variations in project R&D costs, we would not give the precise values too much emphasis. However, the differences in returns between the scenarios may be interesting. The scenarios are deliberately extreme, but if extreme cases don’t substantially shift the IRR, then shareholders are unlikely to be particularly concerned about less extreme ones. The scenarios are as follows:

**Scenario 1:** A base-case project lifecycle with a nominal IRR of 9% (as in Fig. 2). 40% of R&D costs are allocable to Europe and 60% of R&D costs are allocable to the US and the rest of the world. Europe generates 25% of drug profits, with the US generating 50%, and the rest of the world ex-US generating 25% of profits. R&D costs and phasing are based on Paul *et al.* [19]. Commercial costs and profits follow a standard time course and are scaled so that the lifecycle nominal IRR is 9%, close to the nominal cost of equity for large drug companies at the time of writing (Fig. 7).
Scenario 2: A positive European AL scenario. We assume that successful AL in Europe has a negligible impact on R&D costs and sales in the rest of the world, where costs and profits are identical to the base case. As a result of AL, European Phase III costs fall by 50%, and the drug is launched in Europe 2 years earlier than otherwise. Furthermore, the sales trajectory is as brisk as it would be under conventional approval. Under this scenario, nominal IRR rises to 9.6% for the lifecycle (Fig. 7, Table 2).

Scenario 3: European AL works as in the previous scenario, but it has negative effects on US trial costs and timing. Less formal Phase III requirements in Europe mean more investment in the US to satisfy the FDA. Thus the 50% reduction in European Phase III cost is accompanied by a 20% increase in Phase III cost in the US. Furthermore, the need to recruit more patients into US Phase III trials delays launch in the US and the rest of the world by 1 year. The nominal IRR is 8.9% (Fig. 7, Table 2).

Scenario 4. A positive global AL scenario. Here, global Phase III costs fall by 50% and drug launch occurs 2 years earlier than in the base case. The nominal IRR in this scenario is 11% (Fig. 7, Table 2).

Scenario 5. This provides some calibration to illustrate the effect of drug price inflation. We assume base case figures, but reduce drug price inflation in the US from its historic (i.e., 1981 to the present) ~3% over general CPI to a mere 1% over general CPI. We estimate that a decline in real-terms drug price inflation from 3% to 1%, would depress US profit growth by around 3% a year. The nominal lifecycle IRR in this scenario is 7%. Thus, in this analysis, the absolute effect of a permanent two percentage point reduction in real-terms annual US drug price inflation has about the same absolute effect on IRR as halving global Phase III costs while simultaneously reducing by 2 years the time it takes to bring drugs to market, as per Scenario 4.

We think the implications of the scenario analysis are as follows. First, even successful implementation of AL in Europe will have a relatively modest impact on the lifecycle returns of a project that follows the AL route, in the absence of similar changes in the US. The size of the effect on IRR (IRR rising from 9% in the base-case to 9.6% with European AL) is smaller, for example, than the historic effect of a falling tax rate (Fig. 3F). Second, there is often a high degree of
coherence between the requirements of the FDA and EMA with respect to the Phase III trials on which current drug approval is based. R&D is globally integrated. The same two Phase III trials are typically designed to satisfy both the FDA and the EMA. Under European AL, two Phase III trials may still be required by the FDA. Therefore, without regulatory convergence, some dis-synergies are likely. Third, AL would have a much bigger impact on the project’s returns if the EMA and FDA were able to agree on AL requirements.

Fourth, and importantly, the salience of AL for R&D investment increases later in the project (Tables 1 and 2). Therefore, AL may have a substantial influence on decisions on which drugs to move into Phase II trials and beyond, on how to conduct clinical development, on early access to medicines in some patient groups, and on the ability of some small or mid-sized companies to fund trials or to raise capital, without having a major influence on lifecycle returns on R&D investment. It may become much more important to specialist investors who fund certain parts of clinical development than to the major shareholders of large drug companies.

### 3.2. Scope of AL Probably Limited in the Near to Medium Term

Turning from returns for the “average” project, to returns for the population of projects run by the drug industry, it seems likely that the scope of AL will be narrow in the near to medium term. We expect that AL will be applied to therapy areas where approval is already quasi-adaptive. The typical progression of some oncology drugs from approval in later to earlier lines of therapy, and from approval for use in fewer to use in more combinations, is reminiscent of AL; albeit usually based on randomized controlled trials rather than other sources of evidence (see, for example, the vemurafenib example in Baird et al. [33]). Outside of oncology, one can see that AL models could apply to antimicrobial drugs. Many drug companies already use a strategy in various niches, to prove utility in a narrow indication in man before risking investment to develop a broader label and exploit larger markets [12]. The near- to medium-term effect of AL will be formalize and enhance development strategies and regulatory options that are already being used.

In the longer-term, AL could have a larger impact on financial returns across the drug industry in two ways. The first applies if there still exist a reasonable number of relatively common diseases where one could generate data on safety and efficacy in a narrow population (high medical need, and high risk tolerance) which would be sufficiently relevant to a wider population (lower medical need and lower risk tolerance). In other words, the same underlying pathophysiology must be present in patients across the spectrum of disease severity. In this case, AL improves financial returns by streamlining the clinical development and approval process. The second way is if AL makes it easier for drug candidates to find real-world niches in which they have utility. In this case, AL improves financial returns by increasing the proportion of drugs that find markets.

Turning to the former possibility, it is not immediately obvious to us that many such diseases exist. In fact, the practical challenges of drug and disease choice may have been illustrated in a recent paper by Baird et al. [33]. We applaud the authors for publishing explicit and quantitative AL scenarios. However, we are not sure that investors would be convinced of the realism of the analyses applied to rimonabant (Acomplia) in obesity and fingolimod (Gilenya) in multiple sclerosis. We consider these examples in some detail, to illustrate the kind of investor skepticism that certain AL claims may face.

#### 3.2.1. Rimonabant AL Scenario

In June 2006, rimonabant was approved by the EMA “as an adjunct to diet and exercise for the treatment of obese patients or overweight patients with associated risk factors such as type 2 diabetes mellitus or dyslipidaemia.” The major trials on which approval was based recruited patients with a BMI of over 30 (obese) or over 27 (overweight) but with additional risk factors.

In October 2008, the EMA ruled that the drug’s risks outweighed its benefits. Marketing approval was formally withdrawn in early 2009 [63]. The drug was never approved by the FDA. The commercial failure of rimonabant was a major disappointment to Sanofi Aventis shareholders.

Baird et al. [33] appear to suggest that the failure of rimonabant was largely due to “inappropriate use.” They suggest that 50% of use was off-label, presumably in patients who were insufficiently obese or lacked co-morbidities (for those with a BMI of under 27), or in patients who had a history of psychiatric illness. Baird et al. [33] explored AL scenarios which had “closely managed post-marketing controls” to reduce “inappropriate use.” In their AL scenarios, these controls sometimes kept the drug on the market in Europe and allowed approval in the US. This was more lucrative for the drug company than the withdrawal that actually occurred.

However, the AL scenarios all appear to be based on the assumption that rimonabant had a positive risk-benefit profile in the absence of “inappropriate use.” It is not clear to us that this was the case.

First, the EMA’s justification for withdrawal focused on the possibility that the absolute magnitude of the risks from some psychiatric disorders (e.g., aggression, suicide) had been under-estimated in the clinical trial data that formed the basis of European approval, and that real-world weight loss was less than in the clinical trials, probably because real-world patients tended to continue to the drug for only a relatively short period of time [63]. Thus the EMA’s justification for the withdrawal of the drug did not primarily focus on
inappropriate use, although it was a concern\textsuperscript{11} [63].

Second, the EMA did not appear to believe that there were reasonable steps that could be taken to match the drug to the right patients. According to the EMA [63]: “It is unlikely that additional measures to reduce exposure of patients most at risk of psychiatric reactions would lead to a favourable balance of risk and benefit because the patients at highest risk of these reactions, and those that might benefit most from the product, cannot reliably be identified.” [our emphasis]. This EMA statement seems to contradict the assumption of the AL scenarios; namely, that the benefit/risk trade-off would have been positive in an identifiable group of “appropriate” patients who had there been more stringent post-marketing controls\textsuperscript{2}.

3.2.2. Fingolimod AL Scenario

Fingolimod [64] was approved in 2010 for use in relapsing forms of multiple sclerosis. Baird et al. [33] remind us that the 5 Phase II and Phase III trials plus long-term extension studies took around 7 years and enrolled 3900 patients. Approval was then based on safety and efficacy data from 2800 patients, “with post-approval commitments to submit safety data from the remaining 1100 patients and to conduct an observational study comparing the frequency of specific safety signals in patients treated with Gilenya or another disease-modifying drug”. The authors suggest that an AL-based approach could have enrolled 2800 patients in 4 Phase II and III trials, and would have led to limited approval after only 5 years based on initial safety and efficacy data from 1100 patients. The initial approval would have been for a narrow label in patients with “moderate to severe MS only”. Around 30 months later, sufficient data would have been available from the on-going trials and from registries of patients with “moderate to severe MS” treated outside of the formal trials, to permit treatment of “patients with MS of any severity”. Thus the author’s AL scenario resulted in more patients treated sooner, and was more valuable to the sponsoring company.

We agree with the authors [33] that diseases like MS may be the kinds of conditions in which AL is likely to find use. However, investors might wonder if the AL scenario fairly captures the situation for fingolimod as it would have existed at the time. This is for several reasons which include:

First, it is not clear what “moderate to severe MS” is. The term is not used to describe, for example, the approved indications of the current set of drugs that are used for MS. Thus the scenario itself is unclear.

Second, fingolimod was known to have a “hairy” side effect and adverse event profile even before major trials in MS. Its first trial use was as an immunosuppressant in renal transplantation [65]. Development was stopped because the risk-benefit profile did not look attractive. The major Phase III trials for fingolimod in MS started in June 2006 (fingolimod vs. placebo, clinical trials identifier number NCT00355134) and May 2006 (fingolimod vs. beta-interferon, clinical trials identifier number NCT00340834). In 2008, a recently approved MS drug, also with a “hairy” side effect and adverse event profile (natalizumab / Tysabri) was temporarily withdrawn from the market because of cases of a rare but frequently fatal side effect\textsuperscript{12}. It seems reasonable to wonder if this conjunction of factors might have undermined regulatory support for fingolimod as an AL project\textsuperscript{12}, forcing a switch to a more conventional strategy during the Phase III programme. Such a switch would have negative economic consequences for the trial sponsor. However, this outcome was not included among the AL scenarios.

Third, it is not clear that the proposed AL approach would have been seen as attractive by the drug sponsor or, perhaps more precisely, it might have added costs which are not captured in the Baird et al. scenario [33].

The fingolimod trials that actually occurred would appear to have provided rather little data on the safety and efficacy of fingolimod in the subset patients with “moderate to severe MS.” The Phase III trials for fingolimod, like most other commercially sponsored MS trials in recent years, recruited patients with less aggressive or advanced MS\textsuperscript{15}.

If the regulator asked for AL trials to recruit more patients with “moderate to severe MS” to provide evidence to support early access in this group, the sponsor may have been concerned that the trials would be less convincing when trying to sell the drug into the larger and more lucrative population of patients with early-stage disease. This competitive concern could have been serious, given the large number of drug candidates from other firms that were in late-
state development for MS at the time of the fingolimod trials. The problem could perhaps have been solved by recruiting more patients with less severe MS to support some kind of subset analyses in these patients, but that would have increased trial costs in the AL scenario.

Again, we applaud Baird et al. [33] for providing concrete AL scenarios expressed in quantitative terms. However, our observations on the fingolimod and rimonabant scenarios suggest that choices on an AL vs conventional approval route will depend on technical and commercial details of each drug. It will be difficult for investors to take a view on the wider implications of AL until there are more real-world precedents.

3.3. Other AL Questions

Investors will have a range of other questions on the practicalities of AL, some of which will be answered over the next few years by the EMA pilot programme. For example, will higher levels of regulatory risk tolerance survive safety problems, whether real or imagined? Are the new post-marketing data going to be made available for public scrutiny? Technical risk-benefit discussions between regulators and drug companies can be difficult to conduct in public. What of the new demands that AL will place on national drug pricing and health technology assessment (HTA) agencies? Will payers be able to move quickly enough? Might AL become an excuse for foot-dragging by national pricing agencies who fear that the initial price for limited use become an anchor when access is broadened beyond the initial patient group? Will HTA agencies such as NICE in the UK be prepared for a partial abandonment of some central tenets of “evidence-based medicine”?

Another important uncertainty is what AL will mean for international reference pricing. Investors may be more aware than most others the extent to which prices in one country influence prices in another, and the extent to which drug prices determine the financial returns on R&D investment. International reference pricing happens via a variety of formal and informal means. It is one reason why drug prices net of rebates and discounts remain obscure. As one drug industry investor told us recently, “Do European governments understand the global nature of reference pricing? If you accept a low price in Germany, you can lose all over the world.”, or as another told us, “Drug companies fear a political backlash in the US unless they narrow the US - Europe price differential. This does not necessarily mean US prices go down.” The UK’s recent cancer drug experience suggests that the drug industry prefers to abandon individual European markets rather than to set risky pricing precedents [66]. Shareholders overwhelmingly support this behaviour because it protects financial returns.

4. CONCLUDING REMARKS

The drug industry’s economic history makes it hard to be particularly optimistic about the future of industry-wide financial returns on R&D. We are struck by the definitive lifecycle analyses (Fig. 3A) for drug cohorts launched in the late 1970s, early 1980s, and early 1990s [44, 45, 36]. If taken at face value, the best method for calculating R&D returns suggests that IRR was only moderately higher than drug companies’ cost of equity for cohorts launched after inexpensive R&D (Fig. 3B) that was likely to result in drug approval (Fig. 3D) into a rapidly growing market (Fig. 3B) seeing strong real-terms drug price inflation in the US (Fig. 3C), increasing profitability (Fig. 3E), and a falling tax rate (Fig. 3F). R&D costs are now much higher, market growth is slower, there are risks to drug price inflation in the US, and tax rates appear unlikely to decline much further.

So why does the industry keep spending so much money on R&D? Here, the huge variability in returns may be the friend of the sick, but the foe of the shareholder. Negative financial returns at the company level have “plausible deniability” of the kind that can be important in international diplomacy. The uncertainty is such that the directors of any drug companies can claim that the returns on their current R&D investment are above the cost of capital, without being demonstrably wrong at the time they make the claim. Sometimes they will be proved right. Furthermore, there are probably managerial actions that could be taken to improve the returns on R&D among the major drug companies. For example, various patent citation-derived metrics appear to be valid (if noisy) measures of the value of innovation that companies generate [67]. If we take 22 of the largest publicly traded drug companies, the average member of this group generates - using a patent-citation derived metric - 1.2% of global biopharmaceutical “innovation”. However, the average member of the group then derives 70% of its clinical development projects from internally-generated discoveries [6]. It seems unlikely, therefore, that the industry is putting the best ideas into clinical trials.

Turning to AL, we think it will probably be applied conservatively, to drug candidates in therapy areas where approaches are already quasi-adaptive. It will influence decisions on which drugs to move into Phase II trials and beyond. It will influence trial conduct. It should provide early access to medicines in some patient groups. It may improve the ability of some small or mid-sized companies to fund development. It may become important for specialist investors who fund clinical development (e.g., via biotechnology IPOs / stock market floatations). However, the implications for the shareholders of most drug companies will be small.

More importantly perhaps, and shifting from a narrow fi-
financial view, history suggests that R&D was much more productive when there was more emphasis on clinical observation of the effects of drugs on man, and a short feedback loop between such observations and medicinal chemistry and animal models. We are also struck that no-one really seems to know which drugs will be important [68] and lucrative [69] until they have been used by real patients in the real world. There is evidence that “field-based discovery” remains more important than generally thought [70] but that it faces major financial and evidential constraints [71]. The dominant R&D, regulatory, and health technology assessment models seem insufficiently sensitive to evidence that a drug’s usefulness often emerges as a consequence of real world experience [71-74]. They are based more on a linear model of innovation: Basic science predicts, clinical trials test the predictions, and clinical trial results form a complete description of the drug’s attributes.

Set this linear view against an example of real-world innovation; the case of propofol [68], an anaesthetic that a panel of expert physicians recently identified as one of the most transformative drugs of the last 25 years. In some respects, propofol looked like some other anaesthetics already available when it came to market. It sent patients to sleep. They usually woke up again. There would not appear to be much to excite a national drug pricing agency or HTA organisation. However, propofol has a very short plasma half-life, and patients awake feeling relatively well. Also, roughly contemporaneous with the advent of propofol was the advent of the laryngeal mask, a safe and easy route for ventilating anaesthetized patients. Surgeons took the combination of propofol and the laryngeal mask and used them to facilitate the switch to modern day-case or ambulatory surgery. Ambulatory surgery is a huge benefit to patients and health systems. That is why propofol is on the list of transformative drugs [68]. It illustrates the point that important drugs often become important because they allow doctors to create utility for patients; utility that was never anticipated by the regulator, by an HTA agency, or by investors. Propofol is not unusual in this respect [70].

AL is not setting out with such bold ambitions. However, the infrastructure that is required for AL and the experience that it generates may provide an environment under which more acceptably safe chemical diversity is released into the real world. It may also provide evidential tools that make it easier for doctors and patients to decide which of the diversity is useful in important and surprising ways. This would be good for therapeutic innovation. It would also nudge financial returns in the right direction.

CONFLICT OF INTEREST

J. W. Scannell is a director of JW Scannell Analytics Ltd., which sells consulting services related to drug R&D.

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PATIENT CONSENT

Declared none.

LIST OF ABBREVIATIONS

AL = Adaptive Licensing
COGs = Cost of goods sold
CPI = Consumer price index
EMA = European Medicines Agency
EU = European Union
FDA = Food and Drug Administration
HTA = Health technology assessment
IPO = Initial public offering (or stock market floatation)
IRR = Internal rate of return
MS = Multiple sclerosis
NME = New molecular entity
NPV = Net present value
PML = Progressive multifocal leukoencephalopathy
PPI = Producer price index
P&L = Profit and loss account, also known as the Income Statement
R&D = Research and development
SG&A = Selling, general, and administrative expenses

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