How to improve R&D productivity: the pharmaceutical industry's grand challenge

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Abstract | The pharmaceutical industry is under growing pressure from a range of environmental issues, including major losses of revenue owing to patent expirations, increasingly cost-constrained healthcare systems and more demanding regulatory requirements. In our view, the key to tackling the challenges such issues pose to both the future viability of the pharmaceutical industry and advances in healthcare is to substantially increase the number and quality of innovative, cost-effective new medicines, without incurring unsustainable R&D costs. However, it is widely acknowledged that trends in industry R&D productivity have been moving in the opposite direction for a number of years. Here, we present a detailed analysis based on comprehensive, recent, industry-wide data to identify the relative contributions of each of the steps in the drug discovery and development process to overall R&D productivity. We then propose specific strategies that could have the most substantial impact in improving R&D productivity.

New molecular entity (NME). A medication containing an active ingredient that has not been previously approved for marketing in any form in the United States. NME is conventionally used to refer only to small-molecule drugs, but in this article we use the term as a shorthand to refer to both new chemical entities and new biologic entities.

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The pharmaceutical industry is facing unprecedented challenges to its business model. Experienced observers and industry analysts have even predicted its imminent demise[1–3]. Over the past decade, serious concerns about the industry's integrity and transparency — for example, around drug safety and efficacy — have been raised, compromising the industry's image, and resulting in increased regulatory scrutiny[4,5]. This erosion in confidence in the industry and its products has resonated poorly with patients, health-care professionals, payers and shareholders. Indeed, the industry's price/earnings ratio, a measure of the current valuation of the industry, has decreased below that of the S&P 500 index and has remained more or less flat, as have share prices for the past 7 years.

The industry's profitability and growth prospects are also under pressure as healthcare budgets become increasingly strained. Generic drugs, although clearly helping to keep drug prices in check, are currently approaching 70% of all prescriptions written in the United States[6]. Moreover, key patent expirations between 2010–2014 have been estimated to put more than US$209 billion in annual drug sales at risk, resulting in $113 billion of sales being lost to generic substitution[7]. Indeed, for every dollar lost in declining product revenues due to patent expirations by 2012, it has been estimated that large-cap pharmaceutical companies will only be able to replace on average 26 cents with new product revenues[8].

Simply stated, without a dramatic increase in R&D productivity, today's pharmaceutical industry cannot sustain sufficient innovation to replace the loss of revenues due to patent expirations for successful products. A key aspect of this problem is the decreasing number of truly innovative new medicines approved by the US Food and Drug Administration (FDA) and other major regulatory bodies around the world over the past 5 years (in which 50% fewer new molecular entities (NMEs) were approved compared with the previous 5 years)[9]. In 2007, for example, only 19 NMEs (including biologics) were approved by the FDA, the fewest number of NMEs approved since 1983, and the number rose only slightly to 21 in 2008. Of the 21 new drugs approved by the FDA in 2008, only 6 were developed by the 15 largest pharmaceutical companies and only 29% would be considered 'first-in-class' medicines. In 2009, 24 new drugs were approved, 10 of which were developed by large pharmaceutical companies and only 17% of which could be considered first-in-class. Some have argued that the number of approved 'mechanistically

innovative' and first-in-class NMEs have remained stable at about 5–6 per year. However, the number of potential revenue-generating drugs (innovative or otherwise) as a percentage of R&D expenditures has undeniably fallen sharply.

With an estimated $50 billion in collective annual R&D spending by the large pharmaceutical companies, and appropriate allocation over time to the successful discovery and development of NMEs, the average cost for these companies to bring an NME to market is now estimated to be approximately $1.8 billion (see below for details underlying this estimate), and is rising rapidly. Moreover, there is little evidence that the average costs of successfully launching an NME vary significantly between large pharmaceutical or small biotechnology companies[10,11].

Although R&D productivity has been declining for a number of years[2], the unprecedented combination of reduced R&D output in the form of successfully launched truly innovative NMEs, coupled with diminishing market exclusivity for recently launched new medicines and the huge loss of revenues owing to generic competition over the next decade, suggest that we may be moving closer to a pharmaceutical 'ice age' and the potential extinction of the industry, at least as it exists today[12,13]. Although this might be welcomed by the industry's critics, the impact on the health and well-being of patients owing to delayed or even lost opportunities to introduce the next generation of innovative medicines could be devastating. In this regard, we underscore the findings of Lichtenberg[14] on the effects of medical innovation (including controls for the impact of obesity and income), which indicate that ~40% of the 2-year increase in life expectancy measured from 1986–2000 can be attributed to the introduction and use of new drugs. It took approximately 3 years for NME launches to have their maximal impact on longevity — this effect was not observed for non-NME (older) drugs. One can only speculate as to the impact on longevity and quality of life that new drugs now in clinical development for cancer and Alzheimer's disease might have. Without these new medicines, and given the rise in diseases such as diabetes and childhood obesity, it is possible that life expectancy may actually decrease over time[15].

Among all the challenges faced by the pharmaceutical industry, we argue that improving R&D productivity remains the most important. The environmental factors that are reducing the industry's profitability can only be mitigated by substantially and sustainably increasing the number and quality of innovative, as well as cost-effective, new medicines; but only if accomplished at reasonable R&D costs. So, the key questions are where, how and by how much can R&D productivity be improved? Here, we present a detailed analysis of R&D productivity by first defining and modelling the essential elements of contemporary drug discovery and development that account for the current cost of a new medicine, and discuss the rate-limiting steps of the R&D process that are contributing to reduced R&D productivity. We then propose, and illustrate, ways to improve these factors.

How do we define R&D productivity?

R&D productivity can be simply defined as the relationship between the value (medical and commercial) created by a new medicine (considered here to be an NME) and the investments required to generate that medicine. However, R&D productivity can in our view best be elaborated in two important dimensions: inputs leading to outputs, or R&D efficiency; and outputs leading to outcomes, or R&D effectiveness (FIG. 1).

R&D efficiency represents the ability of an R&D system to translate inputs (for example, ideas, investments, effort) into defined outputs (for example, internal milestones that represent resolved uncertainty for a given project or product launches), generally over a defined period of time. If launching (gaining regulatory approval and commercializing) an NME is the desired output, how can this be achieved with greater efficiency (that is, at a lower cost)?

R&D effectiveness can be defined as the ability of the R&D system to produce outputs with certain intended and desired qualities (for example, medical value to patients, physicians and payers, and substantial commercial value). Thus, R&D productivity can be viewed as an aggregate representation of both the efficiency and effectiveness of the drug discovery and development process; the goal of a highly productive R&D system is to efficiently translate inputs into the most desired and valuable outputs. For a more detailed description of these definitions, see Supplementary information S1 (box). With this definition of R&D productivity in mind, we have further adapted a productivity relationship or 'pharmaceutical value equation', which includes the key elements that determine both the efficiency and effectiveness of the drug discovery and development process for any given pipeline (see equation 1).

$$P \alpha \frac{WIP \times p(\mathrm{TS}) \times V}{CT \times C} \qquad (1)$$

R&D productivity (P) can be viewed as a function of the elements comprising the numerator — the amount of scientific and clinical research being conducted simultaneously, designated here as the work in process (WIP), the probability of technical success (p(TS)) and the value (V) — divided by the elements in the denominator, the cycle time (CT) and cost (C). Each of these parameters can be conceptualized and analyzed on a per project basis (for example, a single drug candidate or $WIP = 1$) or collectively as a larger portfolio or pipeline of projects or drug candidates. In general, increasing the numerator relative to the denominator will increase productivity and vice versa. Thus, if one could increase the p(TS) (that is, reduce attrition) for any given drug candidate or ideally for a portfolio of drug candidates at a given phase of development, P would increase accordingly. Similarly, for any given level of R&D investment, substantially reducing CT or lowering C (such as unit costs) would increase P.

However, most of the elements comprising equation 1 are inextricably linked to one another and changing one element can often adversely or beneficially affect

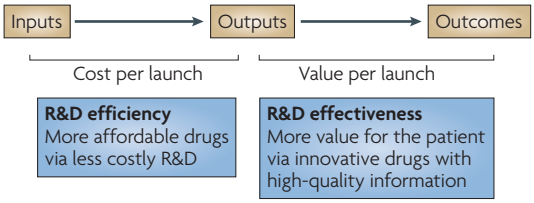

Figure 1 | **Dimensions of R&D productivity.** To improve R&D productivity, it is crucial to understand the interdependencies between inputs (for example, R&D investments), output (for example, new molecular entity launches) and outcomes (for example, valued outcomes for patients). This figure outlines the key dimensions of R&D productivity and the goals tied to R&D efficiency and effectiveness. An effective R&D productivity strategy must encompass both of these components. Value will be created by delivering innovative products with high-quality information.

another. For example, as discussed below, having sufficient pipeline *WIP* (by phase of development) is crucial given the substantial phase-specific attrition rates. However, increasing *WIP* (especially late-phase *WIP*) alone will undoubtedly increase *C* and may also increase *CT*, which could further reduce *P* and diminish productivity.

Finally, although carrying out definitive health outcome studies on late-stage compounds before approval is often highly desirable and increasingly necessary to unequivocally demonstrate value (*V*) for reimbursement purposes, such studies can substantially increase *CT* and *C*, thus also diminishing *P*. Nevertheless, such studies will also increase *V*, potentially offsetting any decrease, or even increasing, *P*.

A model of R&D productivity

To inform efforts to increase R&D productivity (*P*), the key questions include: which of the associated elements have the greatest impact; how might they be improved; and by what magnitude? To help address these questions, we have built an economic model of drug discovery and development which, using industry-appropriate assumptions, provides the basis for our estimate that the fully capitalized cost of an average NME developed by a typical large pharmaceutical company is currently ~$1.8 billion) (see Supplementary information S2 (box) for details). The model has been constructed using recently available R&D performance productivity data from a group of 13 large pharmaceutical companies, provided by the Pharmaceutical Benchmarking Forum (PBF)[16] (see Supplementary information S3 (box)), as well as our own internal data, to closely approximate the key elements of our productivity relationship that underlie R&D efficiency — *C*, *WIP*, *CT* and *p*(TS) — for each phase of discovery and development (FIG. 2).

We recognize that the estimated cost per NME is highly dependent on a number of economic or financial assumptions. Consequently, for our estimated cost of an NME we show both 'out of pocket' and 'capitalized' costs using a cost of capital of 11% (FIG. 2). Our estimate represents 'molecule only' costs and does not include the costs of exploratory discovery research (target identification and validation) or other 'non-molecule' costs (which include overheads, such as salaries for employees that are not engaged in research and development activities but that are otherwise necessary to support the R&D organization; these represent approximately 20–30% of total costs). We discuss comparisons of our estimates with other reported estimates in Supplementary information S2 (box). However, for modelling purposes, the exact cost per NME is not crucial as long as our assumptions for each parameter in our model are consistent and represent reasonable estimates. Each R&D organization can (and should) build a similar model based on their own data, which may vary from company to company.

The exact output of the model — the desired number of new launches (and the estimated commercial value per launch) — will depend on business aspirations, therapeutic focus and absolute level of R&D investments of a given company. Nonetheless, based on our model, a few key observations can be made.

First, clinical development (Phases I–III) accounts for approximately 63% of the costs for each NME launched (53% from Phase II to launch), and preclinical drug discovery accounts for 32%. However, this represents an underestimate of the costs for drug discovery, as we have excluded from our model the earliest phase of discovery research; that is, that prior to target selection. This is because the research required to identify and validate a given target is highly variable, making the underlying parameters difficult to quantify. However, target selection may well be one of the most important determinants of attrition (*p*(TS)) and thus overall R&D productivity (discussed below).

Second, based on realistic and current assumptions on *C*, *CT*, *p*(TS) and *WIP*, only 8% of NMEs will successfully make it from the point of candidate selection (preclinical stage) to launch (FIG. 2). It has been suggested that new biologic drugs have a higher probability of launch than small-molecule drugs[9,11]. For the purposes of our model, we have used 7% for small-molecule drugs and 11% for biologics.

Third, the process of discovering and developing an NME on average required approximately 13.5 years (*CT*) in 2007 (yearly averages ranged from 11.4 to 13.5 using the PBF study data across 2000–2007). This includes regulatory review but not the time it takes to fully identify and validate a drug target[16].

Fourth, based on our model, the number of molecules entering clinical development every year must be approximately 9 (or 11 if all small molecules) to yield a single NME launch per year. Most large companies aspire for 2–5 launches per year and therefore 18–45 Phase I starts (and resulting *WIP*) would be required annually. However, such numbers are rarely, if ever, achieved even in very large companies. If sustained over several years, this *WIP* deficit will result in a substantial pipeline gap. If it takes approximately 9 Phase I drug candidates annually to launch 1 NME per year and if these derive exclusively from a given company's internal discovery efforts, then the number of discovery projects (*WIP*) from target-to-hit, hit-to-lead and lead optimization is approximately 25,

Capitalized cost
This is the out-of-pocket cost corrected for cost of capital, and is the standard accounting treatment for long-term investments. It recognizes the fact that investors require a return on research investments that reflects alternative potential uses of their investment. So, the capitalized cost per drug launch increases out-of-pocket costs by the cost of capital for every year from expenditure to launch.

Out-of-pocket cost
This is the total cost required to expect one drug launch, taking into account attrition, but not the cost of capital.

Cost of capital
This is the annual rate of return expected by investors based on the level of risk of the investment.

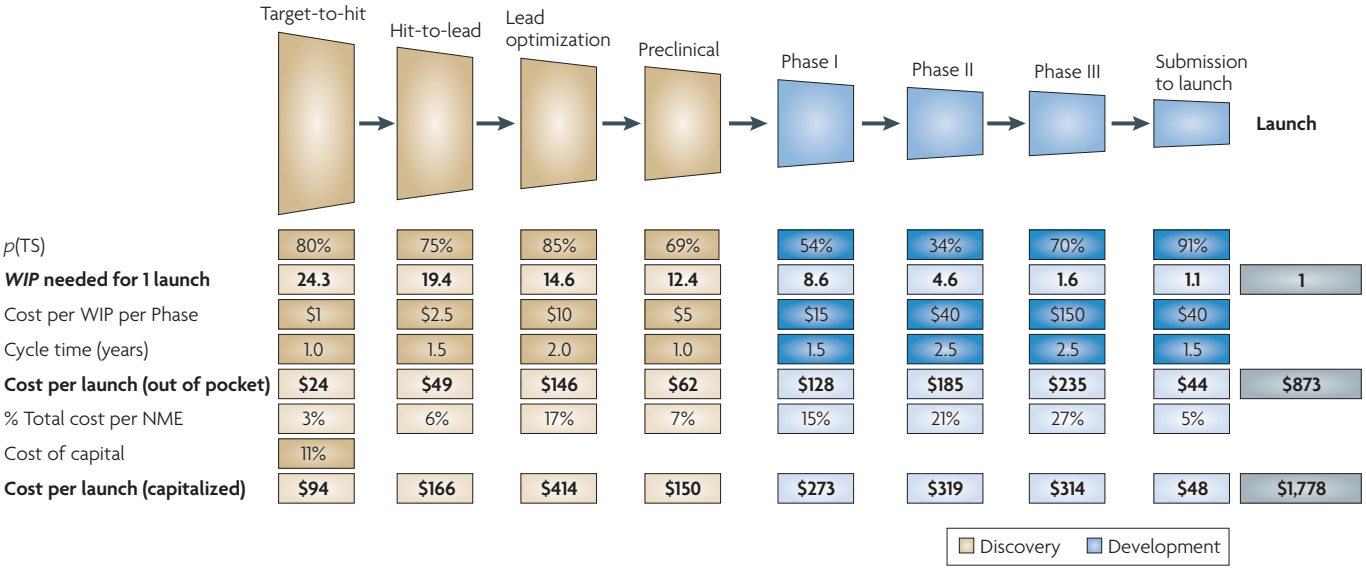

Figure 2 | **R&D model yielding costs to successfully discover and develop a single new molecular entity.** The model defines the distinct phases of drug discovery and development from the initial stage of target-to-hit to the final stage, launch. The model is based on a set of industry-appropriate R&D assumptions (industry benchmarks and data from Eli Lilly and Company) defining the performance of the R&D process at each stage of development (see Supplementary information S2 (box) for details). R&D parameters include: the probability of successful transition from one stage to the next (*p*(TS)), the phase cost for each project, the cycle time required to progress through each stage of development and the cost of capital, reflecting the returns required by shareholders to use their money during the lengthy R&D process. With these inputs (darker shaded boxes), the model calculates the number of assets (work in process, *WIP*) needed in each stage of development to achieve one new molecular entity (NME) launch. Based on the assumptions for success rate, cycle time and cost, the model further calculates the 'out of pocket' cost per phase as well as the total cost to achieve one NME launch per year (US$873 million). Lighter shaded boxes show calculated values based on assumed inputs. Capitalizing the cost, to account for the cost of capital during this period of over 13 years, yields a 'capitalized' cost of $1,778 million per NME launch. It is important to note that this model does not include investments for exploratory discovery research, post-launch expenses or overheads (that is, salaries for employees not engaged in R&D activities but necessary to support the organization).

20 and 15 respectively (FIG. 2). We will discuss the need for sufficient discovery investments and output (*WIP*) to achieve the level of drug candidates necessary below. In this model, in the absence of sufficient acquisition of drug candidates, especially late-phase compounds, achieved as one-off in-license deals or through mergers and acquisitions (M&A), most companies are simply unable to achieve (or afford) the numbers of compounds distributed across the phases of discovery and development they require to achieve their goals for new NMEs launched without a substantial increase in productivity.

Encouragingly, recent benchmark data on Phase I *WIP* across the industry indicate that most companies have begun to substantially increase investments in the earlier stages of drug discovery; this is reflected by the number of candidates entering Phase I trials, which has increased significantly[9,17,18]. However, based on the benchmark data, for most companies, the number of NMEs entering clinical development and progressing to Phase II and III are still insufficient to achieve 2–5 launches per year[9]; this reflects many years of operating at *WIP* levels below what would be required in the earlier stages of drug discovery and development. Thus, inevitable pipeline gaps will arise (as they have) and given the *CT* of the process (FIG. 2), such gaps cannot be filled quickly through traditional means.

Finally, we suggest that based on this model, many companies would find that their R&D operating expenses are not appropriately distributed across the various phases of drug discovery and development. Too many resources are often applied to late-stage development of drug candidates with relatively low *p*(TS) and/or post-launch support of marketed products. This may be the root cause of the current drought of new medicines and the business challenges most companies are experiencing.

Key areas for improving R&D productivity

Using our model (FIG. 2, Supplementary information S2 (box)) and starting from a baseline value for the estimated capitalized cost of a single NME of ~$1.78 billion, we can investigate which parameters contributing to this cost are the most important. To achieve this, we have varied the parameters *p*(TS), *CT* and *C* for different phases of the overall process across a realistic range of possibilities (reasonable estimates of industry highs and lows for each parameter) to identify parameters for which changes would have the greatest impact on R&D efficiency, and the extent of the impact in each case (FIG. 3).

As is evident from FIG. 3, attrition — defined as 1– *p*(TS) — in the clinical phases of development (especially Phase II and III) remains the most important

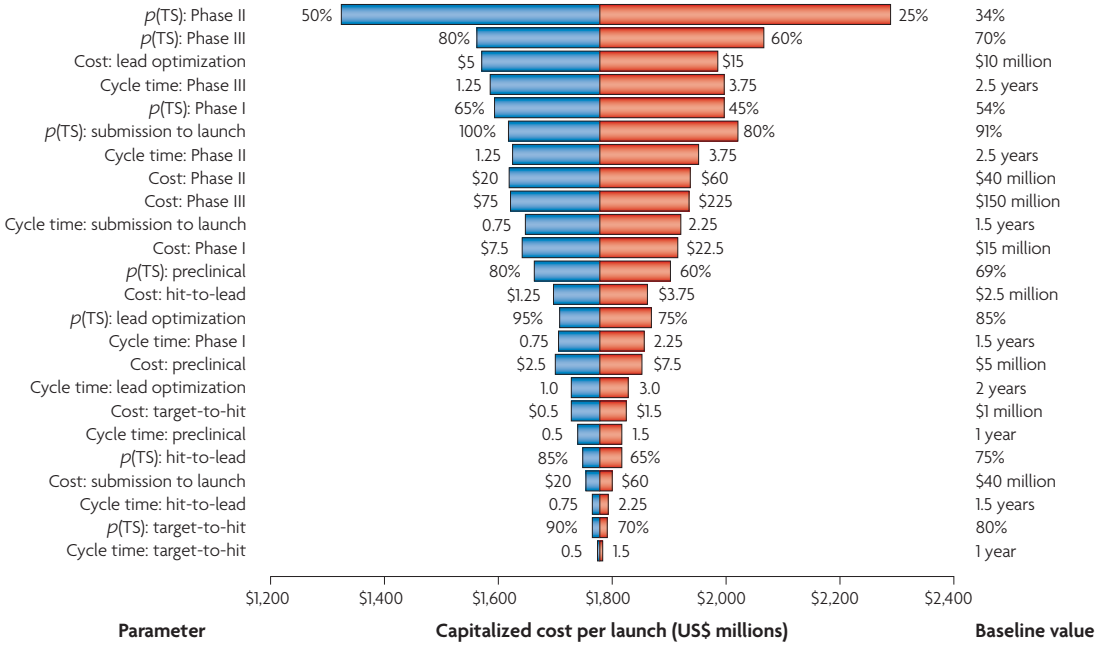

Figure 3 | **R&D productivity model: parametric sensitivity analysis.** This parametric sensitivity analysis is created from an R&D model that calculates the capitalized cost per launch based on assumptions for the model's parameters (the probability of technical success (*p*(TS)), cost and cycle time, all by phase). When baseline values for each of the parameters are applied, the model calculates a capitalized cost per launch of US$1,778 million (see Supplementary information S2 (box) for details). This forms the spine of the sensitivity analysis (tornado diagram). The analysis varies each of the parameters individually to a high and a low value (while holding all other parameters constant at their base value) and calculates a capitalized cost per launch based on those new values for that varied parameter. In this analysis, the values of the parameters are varied from 50% lower and 50% higher relative to the baseline value for cost and cycle time and approximately plus or minus 10 percentage points for *p*(TS). Once cost per launch is calculated for the high and low values of each parameter, the parameters are ordered from highest to lowest based on the relative magnitude of impact on the overall cost per launch, and the swings in cost per launch are plotted on the graph. At the top of the graph are the parameters that have the greatest effect on the cost per launch, with positive effect in blue (for example, reducing cost) and negative effect in red. Parameters shown lower on the graph have a smaller effect on cost per launch.

determinant of overall R&D efficiency. In our baseline model, Phase II *p*(TS) is 34% (that is, 66% of compounds entering Phase II fail prior to Phase III). If Phase II attrition increases to 75% (a *p*(TS) of only 25%), then the cost per NME increases to $2.3 billion, or an increase of 29%. Conversely, if Phase II attrition decreases from 66% to 50% (that is, a *p*(TS) of 50%), then the cost per NME decreases by 25% to $1.33 billion. Similarly, our baseline value of *p*(TS) for Phase III molecules is 70%; that is, an attrition rate of 30%. If Phase III attrition increases to 40%, then the cost per NME will increase by 16% to $2.07 billion. Conversely, if Phase III attrition can be reduced to 20% (80% *p*(TS)), then the cost per NME will be reduced by 12% to $1.56 billion (FIG. 3).

Combining the impact of these increases or decreases in Phase II and Phase III attrition illustrates the profound effect of late-stage attrition on R&D efficiency. At the higher end of the Phase II and III attrition rates discussed above, the cost of an NME increases from our baseline case by almost $0.9 billion to $2.7 billion, whereas at the lower end of the above attrition rates for Phase II and III, the cost per NME is reduced to $1.17 billion.

It is clear from our analyses that improving R&D efficiency and productivity will depend strongly on reducing Phase II and III attrition. Unfortunately, industry trends suggest that both Phase II and III attrition are increasing[9,19–21], given both the more unprecedented nature of the drug targets being pursued, as well as heightened scrutiny and concerns about drug safety and the necessity of demonstrating a highly desirable benefit-to-risk ratio and health outcome for new medicines. However, maintaining sufficient *WIP* while simultaneously reducing *CT* and *C* will also be necessary to improve R&D efficiency. We discuss these aspects first, before considering strategies to reduce attrition in depth.

Work in process (WIP). We have already emphasized the importance of having sufficient *WIP* at each phase of drug discovery and development, and have suggested that insufficient *WIP*, especially in discovery and the early phases of clinical development has contributed to the decline in NME approvals. To further illustrate this point and again demonstrate the impact of Phase II and Phase III attrition on Phase I *WIP* requirements, we have carried out another sensitivity analysis using these three parameters alone. FIG. 4 shows the impact of varying Phase II and III attrition on the number of Phase I entries per year required to launch a single NME annually. If the *p*(TS) in Phase II and Phase III are 25% and 50% respectively, approximately 16 compounds must enter Phase I

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