VIEWPOINT

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.1653 Published online 22 October 2014 in Wiley Online Library

# R&D productivity rides again?

**Dennis Lendrem,[a]* Stephen J. Senn,[b] B. Clare Lendrem,[a] and John D. Isaacs[a]**

**A recent analysis of R&D productivity suggests that there are grounds for 'cautious optimism' that the industry 'turned the corner' in 2008 and is 'on the comeback trail'. We believe that this analysis is flawed and most probably wrong. We present an alternative analysis of these same data to suggest that the industry is not yet 'out of the woods' and suggest that many of the systemic issues affecting pharmaceutical R&D productivity are still being resolved.** 

**Keywords:** R&D productivity; R&D costs; pharmaceutical industry; strategy; development; costs; pharmaceutical innovation crisis

## 1. INTRODUCTION

There has been considerable speculation regarding the continued fall in R&D productivity within the pharmaceutical industry [1–6]. Once again, the fall in new drugs approved by the FDA from 39 in 2012 to just 27 in 2013 has raised the issue of pharmaceutical R&D productivity. Recently, Schulze *et al.* presented an assessment suggesting that R&D productivity is in a state of recovery [7]. They present data suggesting that the number and aggregate peak sales value of new therapeutic drugs (NTDs) are on the increase. While describing their analysis as grounds for cautious optimism, they conclude that R&D productivity 'turned the corner' in 2008 and describe recent data as evidence that the industry is 'on the comeback trail'.

We believe the evidence for such a 'recovery' is at best weak and most probably wrong.

In particular, the analysis relies heavily on expected peak sales of NTDs. Although peak sales for earlier approvals (pre-2002) are actual peak sales achieved, those for later approvals are progressively forecast-based using analyst projections of peak sales. Because peak sales typically show a 10-year lag from product launch, this means that estimates of peak sales for later years are increasingly uncertain. Estimates of peak sales for 2013, for example, are based upon expected future sales in 2023. Such estimates are likely to be subject to optimism bias [8–10].

Although analyst projections may have improved in recent years, and the authors express confidence that these projections are likely to underestimate subsequent actual peak sales, they present no evidence to support this—despite other analyses reporting the remarkable unreliability of pharmaceutical analyst projections [11].

Instead, we focus on R&D productivity measured as the number of NTDs per $US billion R&D spent per annum. This analysis supports a rather different, and more sober, interpretation of pharmaceutical R&D productivity.

## 2. REANALYSIS

R&D output in terms of the numbers of NTDs has remained relatively constant throughout the period 1990–2013. The exception was 1996 when there was a marked increase in the number of NTDs following changes to the FDA review process relating to the introduction of the Prescription Drug User Fee Act. Upon excluding this year, all the data points fall within statistical control limits: the variation in the number of NTDs is no greater than expected given the annual variability in R&D output [12], (See Figure 1).

Indeed, excluding this year, the mean number of registrations is 30.7 and the variance is 29.5, which is entirely consistent with Poisson variability. We believe that R&D output has been disappointing, but relatively constant, during this period.

In contrast, R&D spending has increased significantly over this same period [7]. Using the R&D costs data in Schulze *et al. Supplementary Information S2 (Aggregate industry spending on research and development)* [7], we calculated the annual number of NTD per $US billion R&D spent (see Figure 2).

Figure 2 shows a marked decline in R&D productivity as measured by the number of NTDs per $US billion R&D spent per annum. Although the industry has taken steps to curb annual R&D spending—currently around $US140bn per annum—this fall in productivity is largely attributable to the *tenfold* increase in inflation-adjusted R&D costs during this period [7].

## 3. COMMENT

Escalating pharmaceutical R&D costs are the dominant feature of R&D productivity during the period 1990–2013. This rise in pharmaceutical R&D costs may be attributable to a number of factors. These include increased societal risk aversion with its attendant regulatory burden and strategic changes in pursuit of high risk projects as the pharmaceutical industry seeks high value indications to recover increasing pharmaceutical R&D costs. However, these rising costs may be attributable, at least in part, to an increase late-stage attrition costs arising from historical changes to the drug development process [13–16].

In the wake of the re-engineering movement of the 1990s, the pharmaceutical industry focused (almost exclusively) on maximizing development speed to increase R&D productivity [17].

[a] *Institute of Cellular Medicine, Newcastle University, UK*

[b] *CRP-Santé, Strassen, Luxembourg*

**Correspondence to: Dennis W. Lendrem, Institute of Cellular Medicine, Framlington Place, Newcastle University NE2 4HH, UK.*
*E-mail: dennis.lendrem@newcastle.ac.uk*

 

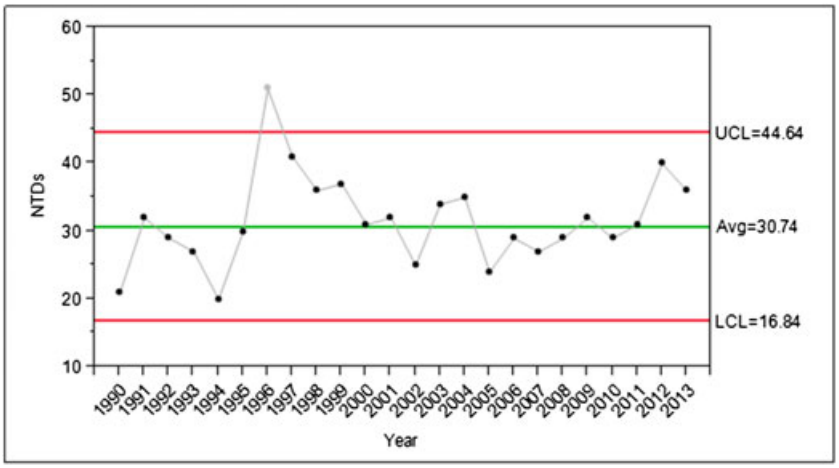


**Figure 1.** Individual statistical process control charts for the number of NTDs from 1990 to 2013. Values within the upper and lower statistical control limits (UCL and LCL) suggest that R&D output was in a state of control. With the exception of the sharp increase in approvals in 1996—assignable to FDA regulatory process changes following the introduction of the Prescription Drug User Fee Act—the number of NTDs remains within control. Upon excluding the 1996 value, all values fall within the revised control limits. In fact, the mean (30.7) is almost identical to the variance (29.5) as we might expect for a random process with Poisson variability.

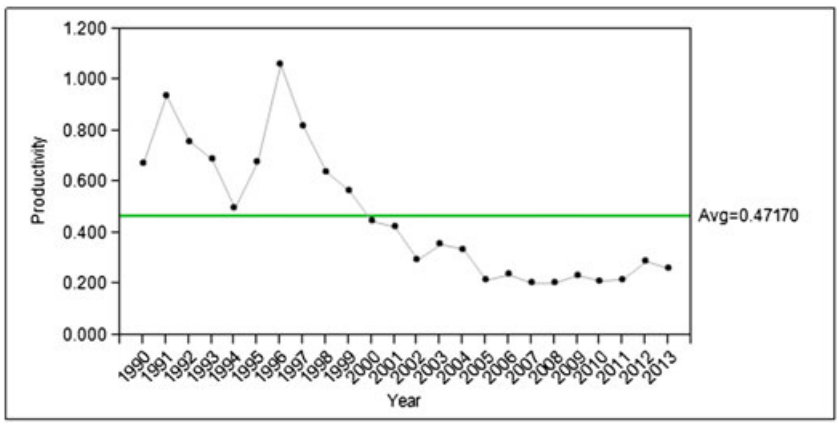


**Figure 2.** Pharmaceutical R&D Productivity 1990–2013. R&D Productivity is expressed as the number of NTDs per $US billion R&D spent per annum. Although R&D output, measured as NTDs, remained relatively constant during this period, inflation adjusted R&D costs increased tenfold giving rise to the marked decline in the overall R&D Productivity during the period 1990–2013.

Although such development speed initiatives led to a significant reduction in the time taken to get *successful* molecules to market—halving cycle times for successful molecules in the period from 1990 to 2001—this may have been at the expense of increasing the cost of terminating unmarketable molecules. The misguided pursuit of maximum possible development speed may have harmed the entire drug development process.

At the time, some observers [18,19] commented that placing development activities in parallel in order to reduce the cycle time of successful molecules, risked increasing R&D burn rates, increasing late-stage attrition, reducing R&D productivity, precipitating a pharmaceutical R&D productivity crisis [18–22]. As a result of these changes, the pharmaceutical industry simply became really slick at delivering late-stage failures to the market place. By turning the development process from a largely serial process to a highly parallelized process, the industry lost opportunities for early termination of unsuccessful molecules before they incurred substantial late-stage development costs. Losing this, the options value, was a disaster for the pharmaceutical industry leading to an inevitable increase in late-stage attrition and increased R&D costs [20].

Counter-intuitively, such development speed initiatives may even have *reduced* R&D productivity. Minimizing the cycle time of successful molecules may lead to an increase in the expected time to marketing authorization approval and a fall in R&D productivity—the Development Speed Paradox [18,22].

The realization that it is more important to do the right science than to do the wrong science quickly has prompted a complete re-think of the discovery and development process [1,2,15,16]. Ultimately, development strategies directed at (a) preventing marginal or failing projects from entering development (b) building more opportunities to terminate unsuccessful molecules earlier in the development process are likely to restore the option value, reducing R&D costs and driving future improvements to pharmaceutical R&D productivity.

## Acknowledgements

DWL and JDI were supported by the National Institute for Health Research (NIHR) Newcastle Biomedical Research Centre based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University. SJS was supported by European Union FP7 grant

602552 for the IDEAL project. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, CRP-Santé or the Department of Health.

## REFERENCES

[1] Bunnage ME. Getting pharmaceutical R&D back on target. *Nature Chemical Biology* 2011; **7**(6):335–339.
[2] Garnier J-P. Rebuilding the R&D engine in big pharma. *Harvard Business Review* 2008; **86**(5):68–70.
[3] Khanna I. Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discovery Today* 2012; **17**(19):1088–1102.
[4] Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery* 2004; **3**(8):711–716.
[5] Munos B. Lessons from 60 years of pharmaceutical innovation. *Nature Reviews Drug Discovery* 2009; **8**(12):959–968.
[6] Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. *Nature Reviews Drug Discovery* 2011; **10** (6): 428–438.
[7] Schulze U, Baedeker M, Chen YT, Greber D. R&D productivity: on the comeback trail. *Nature Reviews Drug Discovery 13* 2014:331–332, advance online publication.
[8] Kahneman D, Lovallo D. Timid choices bold forecasts: a cognitive perspective on risk taking. *Management Science* 1993; **39**(1):17–31.
[9] Lim T. Rationality and analysts' forecast bias. *The Journal of Finance* 2001; **56**(1):369–385.
[10] Tyebjee TT. Behavioral biases in new product forecasting. *International Journal of Forecasting* 1987; **3**(3):393–404.
[11] Cha M, Rifai B, Sarraf P. Pharmaceutical forecasting: throwing darts? *Nature Reviews Drug Discovery* 2013; **12**(10):737–738.
[12] Montgomery DC. *Introduction to statistical quality control*. John Wiley & Sons: New York, 2007.
[13] Arrowsmith J. Trial watch: phase III and submission failures: 2007–2010. *Nature Reviews Drug Discovery* 2011; **10**(2):87.
[14] Arrowsmith J, Miller P. Trial watch: phase II and phase III attrition rates 2011–2012. *Nature Reviews Drug Discovery* 2013; **12**(8):569.
[15] Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery* 2010; **9**(3):203–214.
[16] Peck RW. Driving earlier clinical attrition: if you want to find the needle, burn down the haystack. Considerations for biomarker development. *Drug Discovery Today* 2007; **12**:289–294.
[17] Hammer M, Champy J. Reengineering the corporation: a manifesto for business revolution. *Business Horizons* 1993; **36**(5):90–91.
[18] Lendrem DW. More haste, less development speed. *Scrip Magazine* Dec 1995:22–23.
[19] Senn S. Some statistical issues in project prioritization in the pharmaceutical industry. *Statistics in Medicine* 1996; **15**(24):2689–2702.
[20] Burman C-F, Senn S. Examples of option values in drug development. *Pharmaceutical Statistics* 2003; **2**:113–125.
[21] Lendrem DW, Lendrem BC. Torching the Haystack: modelling fast-fail strategies in drug development. *Drug Discovery Today* 2013; **18**(7–8):331–336.
[22] Lendrem DW, Lendrem BC. The development speed paradox: can increasing development speed reduce R&D productivity? *Drug Discovery Today* March 2014; **19**(3):209–214.