TECHNOLOGY
bane or bonanza for the pharmaceutical industry?

Productivity in the pharmaceutical industry has long held well-documented concerns. While the adoption of new technologies into the drug discovery and development process has often been seen as a panacea this article argues that, without a true understanding of the complexities of introducing new technologies into the workplace and the ability to interpret the complex and massive data sets that are produced, then how can we expect it to be the bonanza to the pharmaceutical industry and the cure for all its woes?

By Dr Stephen Naylor, Adam W. Culbertson and Dr Stephen J. Valentine

The annual productivity of the pharmaceutical sector has invited comparison to the horse and buggy industry of yesteryear, as well as attracting descriptors such as the 'Wagon of Woe'[1,2]. This appears somewhat paradoxical given that global pharmaceutical sales for 2006 were $643 billion, up 85% from 1999 ($334 billion)[3]. However, there have been well-documented concerns about the performance characteristics of this sector and involve such issues as cost and time of product to market, as well as the anaemic growth of new therapeutic drugs reaching the consumer[4].

DeMasi and colleagues estimated that the cost of developing a new drug in 1987 was ~$231 million[5]. A number of studies since 2000, have suggested that this cost has significantly increased and ranges anywhere from $868 million to a staggering $1.7 billion[6]. Furthermore, each successful drug still takes on average ~10-15 years to meander through the stringent and laborious procedures of research, development and federal regulatory oversight before entering the marketplace[2].

In 1938 the USA Food, Drug and Cosmetic Act was enacted and it heralded the advent of the 'new drug application' (NDA) as well as the 'new molecular entity' (NME). These two filing documents along with 'NDAs received' have subsequently served as productivity indicators of the industry. **Figure 1** details the number of NDAs received, NDAs approved and NMEs administered by the US Food & Drug Administration from 1950 through 2006[7]. It is interesting to note that since the 1950s there has been a steady downward trend of NDAs approved. During the 1950s the yearly total (exception: 1952) has always exceeded 220, and often surpassed 320 approvals. Since 1962 (exceptions: 1967, 1984, 1996 and 1997), annual approvals have not exceeded 120. In the case of NMEs, approvals reached a zenith of 56 in 1996, and a record low of five in 1969 (see **Figure 1**). Even with the advent of Biologic License Applications included in the NMEs figures from 2004 onwards, the profile of productivity for the industry over the past 50-plus years has been on a downward spiral.

The Pharmaceutical Research and Manufacturers of America (PhRMA) reported recently that its members had spent $43 billion on Research and Development (R&D) in 2006. This reflects a ~7.8% increase from 2005 when the total budget was $40 billion, and is in sharp contrast to 1980 when only $2 billion was spent by US-based pharmaceutical companies affiliated with PhRMA (see **Figure 2**)[8]. However, this trend of ever increasing R&D costs does not appear to have halted the continued perceived decline in productivity. For

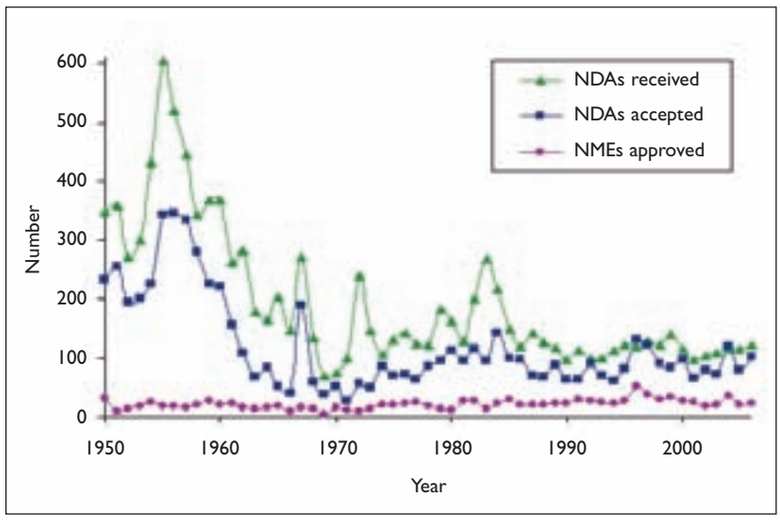

Figure 1: Productivity indicators for the US pharmaceutical industry over the past 56 years. The number of New Drug Applications (NDAs) received and accepted, as well as New Molecular Entities (NMEs) approved, by the US FDA from 1950-2006[7]

example, the number of NMEs reached a peak in the mid-1990s (53 in 1996) and has declined by more than a factor of two to 22 in 2006 (see **Figure 1**). In addition, the number of compounds reaching late stage clinical trials has decreased during this same time period. According to the FDA critical path initiative, the number of phase I compounds that will ultimately be marketed has dropped from 14% to 8% over a 15-year time period[9]. Additionally, the number of drugs that fail after reaching the costly phase III clinical trial stage has increased from 20% to 50% over a 10-year timespan[9]. Analysis of the various metrics indicates an industry that has been struggling for a period of time with issues of spiralling costs, inefficiencies and lack of productivity. This has provoked serious debate and discussion about the need for substantive remedies to alleviate the situation.

Technology – a solution?

The consulting company Accenture published a report in 2000, entitled 'High Performance Drug Discovery: An Operating Model for a New Era'[10]. It covered "…the current state of research performance and critical success factors for drug discovery in the pharmaceutical industry". It opined that "simply increasing R&D spending does not appear to be the answer to the industry's pipeline challenges". In addition, it noted that in 1980 the average R&D expenditure of US pharmaceutical companies was only ~ 8.9% of global sales, whereas in 2000 R&D costs as compared to a percentage of global sales had almost doubled to 16.1%. This is shown in more detail in **Figure 2**. The Accenture authors proposed that pharmaceutical company performance and productivity could be enhanced by focusing on six key strategic areas. It is also interesting to note that four of the six proposals invoked optimal use of new and/or integrated technologies. The six suggested foci were:-

1 **Operational optimisation of R&D –** The discovery operating model should align more closely with the research strategy. In particular it proposed that it is important to integrate new scientific and information technologies into the discovery process.
2 **Prioritisation and decision-making –** The authors noted that it is important to expedite decision making and replace the top-down management process with multidisciplinary teams complete with empowered team leaders.
3 **Information and knowledge –** It was argued that the pharmaceutical industry was actually in the knowledge business. Therefore it was important to embed new integrated technology platforms in the R&D process to connect "disparate data, information and technology".
4 **Genomics and other technologies –** Companies must integrate the new technology platforms in genomics, proteomics and other technologies to improve all process along the Drug Discovery and Development (DDD) pipeline.
5 **Economies of scale –** Companies needed to re-evaluate the 'bigger is better' model. Critical mass could be achieved by alliance partnerships and virtualisation of research.
6 **Partnership and alliances** – Such an approach allows companies to take advantage of innovative and emerging new technologies and integrate them into existing platforms.

More recently, Bains has argued that inappropriate use of science and technology contributes significantly to the ballooning cost, in time and dollars, of the DDD process[11]. He also made the salient point that poor management decisions concerning borderline projects are also a major contributing component. Subsequently, Naylor has asserted that pharmaceutical managers and scientists must have accurate, reproducible and interpretable data, in order to make such unambiguous and decisive decisions[12]. He declared that it is imperative that new computational, informatic and knowledge management technologies are acquired and adopted in order to facilitate this process.

This torrent of advice and recommendations has induced further investment in technology by

the pharmaceutical industry. It has introduced a plethora of innovative scientific and information technology tools and platforms over the past quarter of a century. The list includes computational chemistry, PCR, high throughput screening, combinatorial libraries, high throughput genetics, biomarkers, target validation tools, chemical genetics, predictive toxicology, omic-analyses, imaging, systems biology, high-content screening, biostatistics, bioinformatic and knowledge assembly capability. The swirling interactions of scientific and information tools and technologies have produced an avalanche of new data, and an expectation of enhanced efficiency and productivity.

Unfortunately, the productivity bonanza has not materialised. Since the Accenture report was published in 2000, the number of NDAs received and approved as well as NMEs granted has remained relatively constant as seen in **Figure 2**. In 2000 the number of NDAs received (115) and approved (98), as well as NMEs granted (27) were very similar to those reported in 2006. In the past year, 123 NDAs were received and 101 were approved, and 22 NMEs made it to the market. In addition, since 2000 the R&D spending of US pharmaceutical companies remained at or above 16% of global sales, as shown in **Figure 2**. Indeed in 2006, this figure increased to 17.5% of global sales, a notable upward swing of almost 9% as compared to 2000. Pharmaceutical companies are spending more money than ever before on R&D as well as new technologies, but this has not been matched by a concomitant increase in productivity. Why has this occurred? Has technology failed the pharmaceutical industry?

Technology evaluation and valuation

There has been unrelenting pressure on scientists, managers and executives within the pharmaceutical industry over the past two decades. The well documented issues of limited productivity, coupled with cyclical downsizing and disruptive mergers and acquisitions have created a silo mentality. Individual managers are expected to make rapid decisions on issues such as the introduction and implementation of 'critical' new technologies. It has been predicted[10] that this should have facilitated an increase in both efficiency and productivity for the sector/silo that the manager was overseeing. However, such a confluence of circumstances has led to a situation where the manager is often isolated, and unaware of the complexities associated with technology development and implementation cycles.

The Technology Development Cycle[13] typically consists of:

1 Technology research – usually carried out within a university or early stage technology or biotechnology company.
2 Application demonstrator leading to an architecture standard.
3 Industrial prototype leading to an adoption standard.
4 Marketable product.

This global pipeline of technologies is a complicated mishmash of 'products' at various stages of developmental maturity, and the rush to acquire them is often fraught with difficulty. This often results in the consideration and adoption of technologies that are traversing any part of the Technology Development Cycle.

Over the past 20 years, the Technology Development Cycle time has decreased and led to a plethora of new, innovative and potentially disruptive technologies. In addition, the decision as to what technologies should be adopted has been compounded by the Technology Hype Cycle[14]. Fenn and co-workers at the Gartner Group have described the enthusiasm that often greets new technologies and the subsequent disenchantment that follows. The Technology Hype Cycle[14] is shown in **Figure 3** and consists of the following five stages.

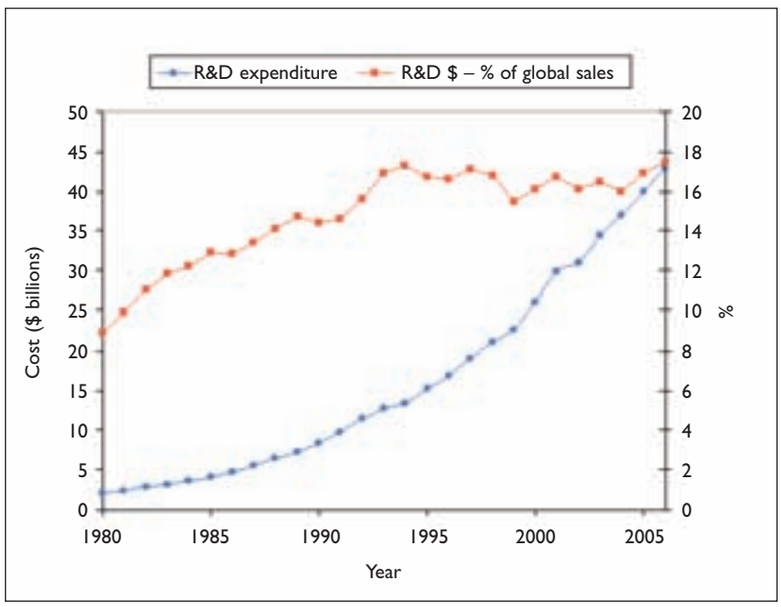

Figure 2: Increasing cost of doing R&D in the US pharmaceutical industry. The left hand y-axis shows the increased R&D spending by US based pharmaceutical companies in US dollars (billions) spent per annum[8]. The right hand y-axis charts the total R&D US dollars spent as a percentage of global sales of US Pharmaceutical companies during the period 1980-2006

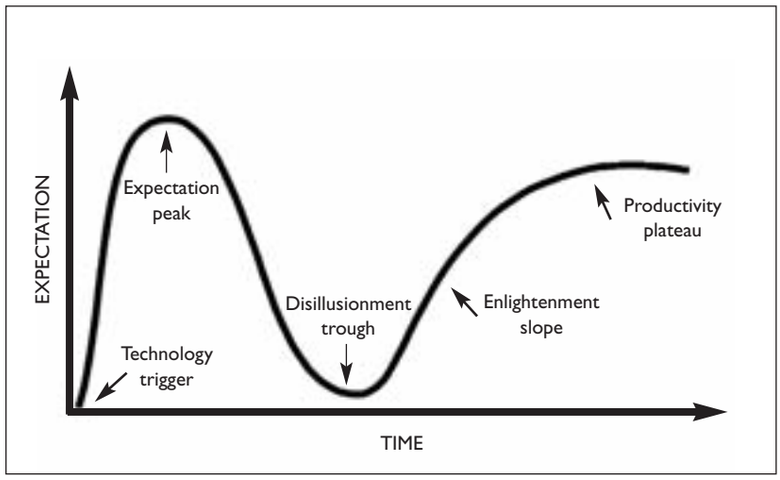

Figure 3: Technology Hype Cycle. Such cycles map the general response to new technologies as a function of time[14]

1 **Technology trigger –** the product launch produces excitement and general interest.

2 **Peak of inflated expectations –** a 'frenzy of publicity' generates over-enthusiastic assessment and unrealistic expectations.

3 **Trough of disillusionment –** expectations have not been met, and advocates and general interested parties abandon the technology.

4 **Slope of enlightenment –** some businesses continue to evaluate and develop the technology and determine limitations as well as realistic and practical applications of the technology.

5 **Plateau of productivity –** benefits of the technology are demonstrated and the technology becomes stable evolving through further improved generations.

Scientists and management are often caught up in the throes of the Hype Cycle. There are significant pressures to adopt such hyped technologies in order to remain competitive with other pharmaceutical companies. Also, this is compounded by the psychological factor of not missing the one technology that may affect that paradigm shift that everyone is seeking. Paradoxically, there is also the possibility that a promising new technology can be prematurely abandoned if the technology is in the 'Trough of disillusionment' stage. In either scenario, it is critically important that the decision process of adoption and/or abandonment of the technology is predicated on objective assessment of whether it meets the needs of the scientific team and the questions being posed by that team. Hence, it is important for any pharmaceutical management team to be acutely aware of the Hype Cycle and its potential impact on shaping the decision making process concerning any key technology.

Finally, any evaluation and value determination of technology must also include an awareness of the classical Technology Assimilation[15] and Technology Innovation Adoption S-Curves[16]. These concepts have been combined into a single amalgamated figure as shown in **Figure 4**. The assimilation of technologies is determined by a simple set of criteria. Initially, individuals experiment with the technology, in a classic 'kicking the tyres' type scenario. Subsequently, the technology is assessed for its efficiency and convenience factors followed by its effectiveness in carrying out a task or producing quality data output. Ultimately, the technology is assimilated into constant use if it provides an unprecedented opportunity to carry out 'previously unthinkable' experiments or insight into solving a complex set of problems. The Technology Innovation Adoption S-Curve has been previously described in considerable detail by a number of authors[16,17]. It is initially characterised by a very small number of innovators (1-3% of adopters), who over a period of time (typically years) invent and champion the technology. Depending on a variety of factors, additional cohorts of individuals will ultimately adopt the technology and they include, early adopters (~13-15%), opinion leaders, early (30-35%) and late majority (30-35%) adopters and the laggards (12-16%)[16]. Assessing the status of a technology and where it is on the adoption curve is not a trivial matter. For example, the television was invented in 1926, but it was not until the 1960s, 40 years later, that the laggards finally adopted this now ubiquitous technology. In the case of the Internet, which was invented in 1975, it is currently only in the 'early majority' phase of adoption. Often the cycle of technology adoption can take decades for successful technologies to reach levels of widespread acceptance, and in the majority of cases a technology is ultimately abandoned.

It is clear that the evaluation and valuation of technologies is not a simple process. Many factors have to be considered including the status of the technology in the Technology Development, and the Technology Hype Cycles as well as the Technology Assimilation and Technology Innovation Adoption S-Curves. Scientists and managers have to make pressure-ladened decisions about the implementation and adoption of technologies at various levels of maturity in an often time-constrained manner. Under such circumstances it is not surprising that errors of judgment are made resulting in the acquisition and/or adoption of technologies that are either not yet mature, or simply unsuitable.

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Future considerations and conclusions

It is clear that the indiscriminant introduction of technologies into the DDD process is not the panacea for lackluster or falling productivity. As scientists and managers continue to struggle with this issue, it is possibly useful to consider the following factors in determining the adoption and role of specific technologies:-

1 **Timing and maturity of technology –** As noted in detail above, managers are faced with a complex set of parameters as they consider whether or not to introduce a new technology into their silo of the DDD process. Often a technology is adopted without a complete understanding of where it resides in the Technology Development and Hype Cycles (**Figure 3**) and Technology Assimilation and Innovation Adoption S-Curves (**Figure 4**). For example, how does a manager decide when to invest in a technology using the Innovation Adoption S-Curve (**Figure 4**)? In order not to lose competitive advantage many managers invest in very early stage technologies. However, rather than investing in a single technology, it may be more prudent to make smaller investments in a larger pool of competing technologies in order to ascertain which is likely to provide the superior output. The optimal time to invest in a technology and simultaneously minimise risk is at the early phase of the 'early majority' Adoption curve point (**Figure 4**). This can be additionally advantageous since it is possible to leapfrog to later generations of the technology that are more stable and productive compared to other less mature technologies. Hence in any decision making process, timing and the maturity of a technology are critical components to consider. Managers should resist the external influences described in the Cycle of Hype (**Figure 3**) and maintain an objective stance on evaluating the potential of any particular technology. It is clear that technologies are useful in the DDD process; however it is important that a better understanding of the development times of new technologies and how they mature will be factored into how they will be meaningfully utilised in the future. The willingness of the industry to simply embrace new and untried

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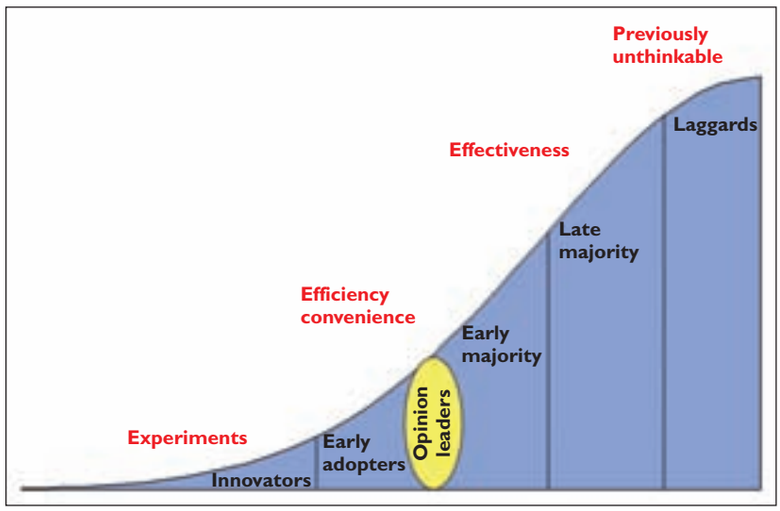

Figure 4: A combination of a classical Technology Assimilation Curve[15] (stages shown in red) and a Technology Innovation Adoption S-Curve[16] (stages shown in black) shown as a function of time

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technologies with the outlay of millions of development dollars has to stop.

2 **Importance of the scientific question –** Technologies are critical components in either providing or interpreting data (see below). However, the determination and significance of the actual biological or chemical question(s) is of paramount importance. Technologies should not be a substitute for poorly thought out science. Such technologies have to be evaluated in terms of how they serve the problem solving issues of the biologists/chemists/clinicians driving the DDD process. Technology implementation should not be about higher throughput, and massive data generation, but a means to provide insight and mechanistic understanding of the biology and pharmacology under investigation.

3 **Technologies and data interpretation –** Many of the technologies introduced into the DDD process over the past quarter of a century have increasingly produced a surfeit of data. Unfortunately, this has not led to new insight into the DDD process, but possibly confounded investigators. Managers and scientists are inundated each day with polybytes of data and information. They are ill-equipped to analyse such content, and efficiently utilise it in key decision-making processes. Most of the data and information remains unfiltered, unprocessed and unused. The ability to transform:

Data➛Information➛Knowledge➛Decision Making

is particularly limited, since they lack many of the appropriate tools. As a consequence many elements of decision-making along the DDD process need to be addressed in the near future. Informatic infrastructure and bioinformatics capability needs to be more encompassing and should be an integral part of any DDD process. In addition the formation of knowledge-management groups should be a staple of the industry. The development of technologies and databases to ensure better decision making will be critical to the success of the industry.

4 **Usefulness of technology –** At every level of the Technology Development Cycle, innovative and potentially useful technologies are being invented, developed and commercialised in universities, biotechnology, technology and commercial instrumentation companies worldwide. In addition, many of the technologies now used in the DDD process have found some use in facilitating the production of new therapeutic entities. However, technology has proved to be neither the bane nor the bonanza to the pharmaceutical industry. It has been overhyped as a possible cure for the industry's productivity woes. In part this has been due to a misunderstanding of the complexities of introducing new technologies into the workplace. Technology has not failed the pharmaceutical industry; it has produced ever more complex and massive data sets. The inability to efficiently mine these data sets and create new knowledge has hampered productivity efforts. Bains[11] has asserted that if scientists and managers can be more efficient in decision making along the DDD process then the cost of bringing a drug to market can be cut in half! That would be a dramatic boost to productivity and efficiency and technophiles would truly be able to assert that technology was a bonanza to the pharmaceutical industry. DDW

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Dr Stephen Naylor *is Chairman and CEO of Predictive Physiology and Medicine Inc (PPM), a personalised medicine company based in Bloomington, Indiana, USA. PPM provides 'Health and Wellness Management Tools' that lead to informed decision-making in predictive and preventative medicine as well as the general health and well-being of the consumer.*

Adam Culbertson *is an Analytical Research Scientist at PPM.*

Dr Stephen J. Valentine *is Executive Vice President for Science and Technology at PPM.*